Reasonable Drugs

Making Decisions with Ambiguous Knowledge

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For my grandparents

– inspiring role models, each in their own way

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Stockholm November 9, 2006

Ebba B:dotter Sjögren

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ACRONYMS

ATC	Anatomical Therapeutic Chemical Classification System
Apoteket	National Corporation of Swedish Pharmacies
EMEA	European Medicines Agency
LFN	Pharmaceutical Benefits Board
MPA	Medical Products Agency
SEK	Swedish krona
SPC	Summary of Product Characteristics

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Diagrams

1. KNOWLEDGE-BASED DECISION-MAKING

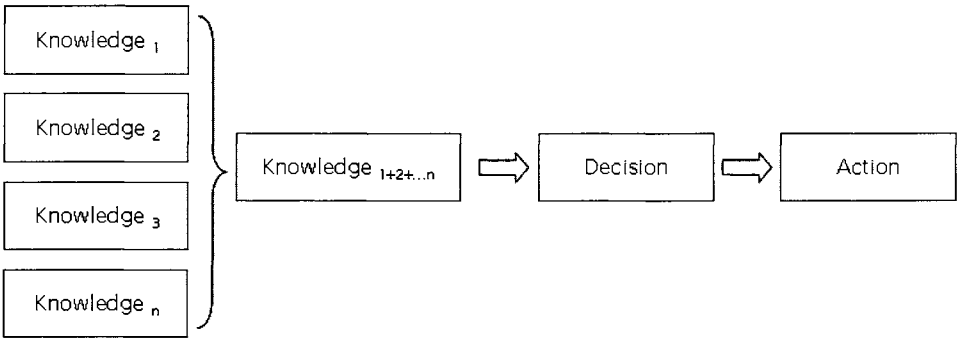
More knowledge, better decisions?

This study is about how organizations make decisions. In particular, it is about how organizations make decisions with knowledge – especially scientific knowledge; that is to say, factual claims about the world which make reference to systematic inquiry. The study takes its point of departure in a widespread notion that decisions should be based on the 'facts of the matter'. Many normative theories see this as a means of ensuring that 'good' choices are made about future courses of action. Making knowledge-based decisions is considered to be particularly important when deciding purportedly technical issues, or matters that can have varied and far-reaching implications for many people.

Organizing experts as advisors or, indeed, decision-makers are two common ways of taking knowledge into account in decision-making processes. Often it is more than one kind of expertise that is considered relevant to take into consideration. Knowledge from different areas is thought to provide a more comprehensive and qualitatively better understanding of the matter being decided on. In other words, the *cumulative* knowledge from many sources is considered better for ensuring good choices than knowledge from any single source. However, this assumes that knowledge claims from different areas of expertise are in agreement with one another. Only then will more and more knowledge provide an increasingly detailed and informed characterization of the matter being decided on, such that the choice of future action becomes

increasingly clear. If knowledge claims do *not* agree, it presumes that they at least are *coherent*. That is to say, that they refer to a shared, objective reality and therefore 'agree on what they disagree about' (see Diagram 1, below).

***Diagram 1**: A rational model of knowledge-based decision-making*



Adapted from Fernler and Helgesson 2006, 37, Figure 2.

However, the assumption that different areas of expertise are coherent has been frequently questioned. Though they may share a topic of inquiry – as in the case of economics and marketing, which both claim to study the functioning of markets – differences in basic assumptions about the world have been described to preclude interchange (cf. Kuhn 1996 [1962]).

That different disciplines, when taken together, disagree is perhaps less problematic in settings where there is no clear expectation of synthesis. Academia, for example, has a long tradition of upholding differences through with the separate organization of departments, courses, conferences, and publications. Incoherence between multiple sources of knowledge is arguably more problematic when they are to provide basis for *decision-making*. This would seem to be a relatively common concern:

Take the example of climate change. This is a topic which engages expertise from a variety of disciplines including biology, meteorology, botany, archeology and marine biology, to name a few. Individually, each of these areas claim extensive knowledge about matters related to climate change. But, when *taken together*, what is known and whether this is relevant for solving problems

attributed to climate change, has recurrently been a matter of extensive debate (cf. Jasanoff and Wynne 1998; Yearly 2005, 171). In the case of climate change, the 'facts of the matter' have not provided a coherent basis for making choices about future actions. The multiple sources of (scientific) knowledge are *ambiguous*.

To characterize knowledge as ambiguous in this way is different from saying that there is a lack of knowledge, or uncertainty about what is known. The term is used in reference to situations where multiple knowledge claims do not 'add up' to a coherent account of the world.[1] Instead, there is an incoherent 'unknown'.

It is my argument that many organizations may face having to deal with ambiguous knowledge when trying to make decisions. In this book, I focus on one example of such an organization: *Läkemedelsförmånsnämnden* (the Pharmaceutical Benefits Board, henceforth 'LFN' or 'the Agency'), a governmental agency tasked with deciding which prescription pharmaceutical use should be subsidized in Sweden.[2] Specifically, I discuss findings from my study of how the Agency works to decide whether individual pharmaceuticals fulfill the criteria for subsidy set out in its governing legislation: that the drug has a "reasonable cost of use ... from medical, humanitarian and socio-economic perspectives" (Act (SFS 2002:160) on Pharmaceutical Benefits, section 15). Using the example of LFN, I look to answer the broader question of how organizations make decisions with ambiguous knowledge.

Ambiguity and choice – revisited

As I will elaborate on in the next chapter, my interest in how organizations make decisions with ambiguous knowledge brings into question basic

[1] To borrow from March (1994, 178): "Ambiguous situations are situations that cannot be coded precisely into mutually exhaustive and exclusive categories....Uncertainty...refers to imprecision in estimates of future consequences conditional on present actions".

[2] I have chosen to use the term 'subsidy' to characterize LFN's work, rather than 'reimbursement' (which is also widely used to describe pharmaceutical benefits schemes) since

assumptions about the coherence and objectivity of knowledge – in particular scientific knowledge – that underpin many well-known and wide-spread theories of organizational decision-making.

Normative theories of organizational choice, which take a point of departure in the assumed rationality of actors, assume that decision-making requires coherent knowledge. A decision is only possible if the decision-maker knows about choice alternatives and their future consequences. An *optimal* choice about future action is only possible if the decision-maker has perfect knowledge about all possible choice alternatives, their future consequences and the decision-maker's preferences as regards these future outcomes. Given such knowledge, however, the optimal choice of future action is also given (van Neumann and Morgenstern 2004 [1944]).

Although applications of rational theories of organizational choice have recognized the possibility of imperfect information due to "the cost of search" (cf. Stigler 1961, 216), there is still an underlying idea about the possibility and desirability of *optimal* search. That there might be ambiguity of information is a temporary state caused by circumstances such as incorrect problem specification, false information, inadequate search or bias due to principle-agent problems (for various examples see Babe 1994). The assumption is that there are objective truths which should determine decision-makers choices. Thus, provided that the aforementioned problems with information collection and processing are addressed, there will be no *ambiguity* of knowledge – even though there may still be uncertainty.

The rational model of organizational choice has for more than fifty years been critiqued by scholars undertaking behavioral studies of organizational decision-making (cf. March and Simon 1958; Cyert and March 1963; March 1978). Studies of organizational decision-making *in practice* have questioned the aforementioned assumptions about organizations' perfect knowledge about future consequences and future preferences. Ambiguity – rather than something

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the Swedish public pharmaceutical benefits scheme is designed to lower the *direct cost* of drugs rather than *reimburse* pharmaceutical outlays (see pp. 77-8 of this volume)

pathological and temporary – is characterized as a common property of organizational activity (in line with Garfinkel's (1967) treatment). In particular, studies of decision-makers' use of knowledge conclude that it is not the neutral determinant of decision outcomes posited by the rational choice model. Knowledge can be used to legitimate decision-making processes *ex post* or influence the agenda for decision-making *ex ante*. However, I will argue that despite the treatment of knowledge as something flexible to various interpretations and uses, behavioral decision theory still assumes that the content of 'decision-able' knowledge is exogenous to decision-making proceses (cf. discussion about the similar 'taken-for-granted' knowledge base needed to set rules, Fernler and Helgesson 2006).

By avoiding the content of knowledge as a topic of inquiry, behavioral theories of decision-making skirt tricky questions related to epistemology. However, this position of 'indifferent relativism' provides a limited understanding of organizational decision-making where 'what is known' is expected to justify what is decided, but this knowledge is ambiguous. This study therefore asks the question of *how organizations deal with ambiguous knowledge when trying to make decisions*. To answer this question, I have undertaken a study of how the Swedish Pharmaceutical Benefits Board determines which prescription pharmaceuticals to include in the public pharmaceutical benefits scheme.

Knowledge-based decisions about 'reasonable' drugs

Prior to the creation of LFN in October 2002, all prescription pharmaceuticals in Sweden were "automatically subsidized" (The New Pharmaceutical Benefits Bill 2001, 1). Once a drug had been approved for use by the Swedish Medical Products Agency (or its European equivalent, EMEA), it was included in the public pharmaceutical benefits scheme. Since the inception of LFN, a pharmaceutical is not included unless the Agency has approved subsidy. Through its work, the Agency classifies prescription drugs into one of three categories: pharmaceuticals with approved subsidy (either with or without explicit restrictions on subsidized use) and those denied subsidy. How a

pharmaceutical is classified has potentially significant effects. More obviously: the denial of subsidy for a pharmaceuticals requires all out-patient use[3] to be paid for by patients. What determines which pharmaceuticals are to be subsidized?

According to the Agency's governing legislation, it is certain characteristics of a pharmaceutical's use that determines which category of subsidy the drug is placed in. LFN is instructed to grant subsidy to those drugs where:

> [T]he cost for using the pharmaceutical ... is reasonable from medical, humanitarian and socio-economic perspectives (Act (SFS 2002:160) on Pharmaceutical Benefits, section 15).

If a pharmaceutical has 'reasonable' medical, humanitarian and socio-economic characteristics, then LFN is to approve subsidy.[4] Conversely, if a pharmaceutical does not fulfill these criteria, the Agency should deny it subsidy. In special cases, LFN can combine the two outcomes and approve subsidy for restricted uses of a drug (Ibid., section 11). Regardless of which conclusion the Agency reaches as regards a pharmaceutical's subsidization status, it must publicly justify this outcome in a so-called decision justification document.

However, the legislation does not specify in detail what it means for a pharmaceutical to have a 'reasonable' cost of use. Although some clarification is provided in the legislative bill that was that was submitted to Parliament, this document explicitly states that the precise interpretation of the law is left to LFN as it "develops practice" (The New Pharmaceutical Benefits Bill 2001, 47). The onus is on LFN to make decisions that can be publicly justified as being in accordance with the Agency's governing legislation.

This study takes an interest in how LFN deals with multiple sources of knowledge about pharmaceuticals' characteristics. In particular, the focus is on how the Agency deals with situations where these multiple sources of knowledge

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[3] Out-patient treatment refers to medical services that are provided to patients who are not hospitalized. Pharmaceuticals can be prescribed for out-patient use but also provided on an in-patient basis, i.e. for patients that reside in the hospital during treatment.

[4] Throughout the book, I will use the term 'reasonable' in reference to the decision criteria for subsidy set out in the Act (SFS 2002:160) on Pharmaceutical Benefits, section 15.

are ambiguous. I have undertaken three studies of LFN's decision-making activities, two of which will be discussed in this book (see Sjögren forthcoming [2006] for a discussion of the third study). Using examples from these studies of LFN's work to determine whether drugs are 'reasonable' to subsidize, I will propose a model for how organizations deal with ambiguous knowledge when making decisions.

Outline of the book

Before discussing my findings, the next chapter (Chapter 2) positions the study in relation to earlier research about ambiguity and knowledge in organizational decision-making. The starting point is behavioral studies of organizational decision-making, which characterize organizations as dealing with ambiguity between multiple preferences by separating them in time or space, and using expert knowledge to legitimate decisions *ex post*. I argue that these theories provide a limited understanding of how organizations make decisions when there is ambiguity between multiple sources of knowledge. This leads me to introduce ideas from science and technology studies (STS), where a core research topic is the construction of knowledge. This theoretical approach provides conceptual tools for talking about LFN's work to remove ambiguity and achieve coherence about pharmaceuticals' characteristics.

In Chapter 3 I discuss the design of my two studies and describe how I went about inquiring into LFN's efforts to make decisions about pharmaceuticals' subsidization status. In a first study, I investigated characteristics of 'reasonable' and 'unreasonable' drugs, as argued in the decision justification document issued by LFN over a period of two years. In a second, interview-based study, I followed two decision-making processes within LFN from their formal initiation in October 2003 until their completion sixteen and twenty-eight months later, respectively. The chapter also discusses methodological considerations that I made while planning and performing the two studies.

Chapter 4 gives a background to the studied organization, LFN. A particular focus is the Agency's mandate and organizational structure. The chapter also describes the creation of LFN against a backdrop of recent reform initiatives in the Swedish healthcare sector, and compares the Swedish system for determining pharmaceutical subsidy with that of other countries.

The next chapter (Chapter 5) presents findings from my reading of LFN's decision justification documents. I conclude that the Agency uses similar arguments when justifying different outcomes about drugs' subsidization status. Notably, both approvals and denials of subsidy are justified on the basis of comparisons of applicant drugs' characteristics with other, already subsidized, pharmaceuticals. An applicant pharmaceutical's similarity or difference, as compared to other pharmaceuticals, justifies whether it should be subsidized. However, *which* similarity or difference is characteristic of a 'reasonable' or 'unreasonable' drug varies – both as regards the definition of comparable properties, and the basis for delineating comparable pharmaceuticals. The decision justification documents also illustrate the many sources of knowledge that LFN has to consider when determining drugs' characteristics – and the presence of incoherence between sources.

The conclusions in Chapter 5 about the importance of comparisons serve as a backdrop to the second study, which is presented in Chapter 6. In the chapter, I give an account of LFN's work to determine the subsidization status of pharmaceuticals approved for the treatment of migraine and stomach-acid related disorders, respectively. The chapter is organized thematically and chronologically and focuses on situations where efforts were made to resolve ambiguity between multiple sources of knowledge when defining groups of comparable drugs, comparable treatment effects, and pharmaceuticals' price. I discuss how the Agency dealt with ambiguity between multiple sources of knowledge in the following two chapters.

In Chapter 7, I use examples from the previous chapter to characterize three methods by which LFN attempted to *remove ambiguity* about pharmaceuticals' characteristics. One method is privileging one source over other sources; achieving coherence by excluding all but one source of

knowledge. A second method is calibrating different sources of knowledge to one another using a common metric; removing ambiguity through the use of a standard format. The third method is mediating between multiple sources in an attempt to construct a composite object of knowledge.

In Chapter 8, I extend the analysis of LFN's work and outline two organizational responses to unsuccessful attempts at removing ambiguity between multiple sources of knowledge using the methods outlined in Chapter 7. One response is to *delay decision-making*, pending new efforts to remove ambiguity. A second response is to *make decisions delegating unresolved ambiguity* to others. This delegation of ambiguity, I argue, also involves the delegation of choices about future action to others.

In the concluding chapter (Chapter 9), I summarize the study's findings and propose a model for understanding how organizations deal with ambiguous knowledge when making decisions. The study's conclusions suggest a tendency for organizations to deal with ambiguity of knowledge by making decisions that leave open for many courses of action, rather than make choices about specific future actions. The chapter discusses these conclusions in relation to previous research about organizational decision-making with ambiguity, and touches on implications of the study's conclusions for the use of knowledge-based decision-making in practice.

2. TAKING A VIEW: THEORETICAL FRAMING AND ANALYTICAL CONCEPTS

This chapter gives a theoretical framing to the study. It also outlines specific analytical concepts that I will use to discuss how LFN dealt with ambiguity of knowledge about pharmaceuticals' characteristics. My overarching focus in the study is on organizational decision-making *in practice*. This chapter therefore takes its point of departure in the formative early work by Herbert Simon and James March (Simon 1967 [1957]), 1976 [1947]; March and Simon 1958). Their research has influenced scholars within many areas of the social sciences, including organization studies, economics and political science. In my study, I will specifically draw on research within what I term 'behavioral studies of organizational decision-making', or 'behavioral decision theory'.

In the first section of the chapter I discuss the genesis of behavioral decision theory, and how this has informed researchers' treatment of both ambiguity and knowledge in relation to organizational decision-making. It is my argument that while the content of knowledge – particularly scientific knowledge – is recognized as a potential source of ambiguity, it has not been considered analytically as such. This leaves a theoretical gap in the understanding of how ambiguity between multiple sources of (scientific) knowledge is dealt with in decision-making processes. In the second section of the chapter, I introduce ideas from science and technology studies with the purpose of assisting in bridging this gap.

Ambiguity and knowledge in organizational decision-making

From assumptions of perfect knowledge...

Decision-making has a long history of interest from organizational scholars, looking to understand and explain organizational behavior. A well-known and widely used theory about organizational decision-making is the rational choice model (von Neumann and Morgenstern 2004 [1944]; Arrow 1963 [1951]). This theory is premised on the basic assumption that decision-making determines (organizational) behavior through the choice of one future course of action to the exclusion of alternative actions. The theory of rational choice is a normative model for how to go about making decisions in order to make optimal choices. An underlying assumption is that decision-making processes lead to choices, and all choices result from decision-making processes (cf. Brunsson 2000).

The optimal choice in a particular situation is given by a rational actor's linear and sequential application of a consequential logic. In the first instance, all alternative courses of action are specified, and the future consequences of each alternative evaluated. The evaluation is done in relation to the decision-maker's known preferences for these future outcomes. Subsequent to this evaluation, the choice alternative is selected which is optimal given these preferences (cf. summary in Lindblom 1959). Since current and future preferences are supposed to be known, decision-making centers on collecting and processing information about choice alternatives and their future consequences. Once all possible choice alternatives and their possible consequences have been evaluated, the optimal choice of future action is given.

Behavioral studies of organizational decision-making are, from the outset, formulated in opposition to the rational choice model. Although the degree of critique varies, a basic contention is that the rational choice model has limited descriptive capacity. Organizational decision-making *in practice* does not readily adhere to its prescriptive tenets (Simon and March 1958; Cyert and March 1963). A focal point for this critique is the "two guesses" (March 1978, 589) regarding decision-makers' perfect knowledge about both future

consequences of choice alternatives, and future preferences. Both of these assumptions are characterized as difficult to sustain in practice:

The assumption about known future consequences is problematic since the future is *uncertain* (cf. Merton 1936). Hence, a decision-maker cannot know the exact future consequences of a chosen course of action. While there may be expectations about what *might* happen in the future, it is not perfect knowledge about what *will* happen. For this reason, it is difficult to compare the future consequences of choice alternatives. Even when attempting to make qualified guesses about the future, individuals are assumed to be incapable of more than *bounded* (Simon 1967 [1957]) or *limited* (March and Simon 1958, Lindblom 1959) rationality. In other words, they lack the capacity to anticipate all possible alternatives, and evaluate all available information. Hence, Simon argues:

> the capacity of the human mind for formulating and solving complex problems is very small compared with the size of the problems whose solution is required for objectively rational behavior in the real world - or even for a reasonable approximation to such objective rationality (Simon 1967 [1957], 198).

This limited capacity for rationality in face of complexity is an important reason why decision-makers construct simplified models of the world (Simon 1976 [1947], xxviii-xxx).

The assumption that decision-makers' have known, coherent and stable preferences is also characterized as difficult to sustain in practice.[5] Empirical studies routinely show preferences to be ambiguous in practice (March 1978). Preferences can be vague. For example, an organization may have a preference for 'satisfied customers'. Preferences can also include multiple objectives – some of which may be incoherent. The same organization may have a preference for 'satisfied customers', 'environmentally friendly production processes' and 'profitability'. Preferences can furthermore change over time. Vague, incoherent

[5] There are numerous terms used to characterize decision-makers 'desires', including preferences, goals, interests and tastes. For the sake of consistency, I will use preferences unless directly quoting from other sources.

and dynamic preferences complicate the choice of an optimal course of action. Not only is it uncertain what will be the future consequence of choice alternatives, it is also unclear what will be the preferences for the (uncertain) consequences.

It is against this backdrop that scholars have sought to develop descriptive theories based on studies of how organizations make decisions in practice. One focus has been on how organizations deal with ambiguity of preferences when making decisions.

...to theories about ambiguity of preferences ...

Behavioral studies of decision theory assume that decision-makers "find themselves in a more complex, less stable, and less understood world than that described by standard theories of organizational choice; they are placed in a world over which they often have only modest control" (March and Olsen 1976, 21). Studies of how organizations deal with ambiguity of preferences suggest that attempts are made to order preferences in various ways. One way is to order multiple preferences *in time*.

Cyert and March (1963, 166) propose that organizations respond to ambiguous preferences by paying "sequential attention to goals". Through the separation of preferences in time, individual choices can satisfice a few – if not all – preferences at one given time (see also March and Simon 1958; March 1978). This, according to Cyert and March (1963), makes it possible to manage the many groups with heterogeneous preferences that make up an organization. For although groups may reach agreement about certain preferences *in principle*, these preferences may not lend themselves to unambiguous realization through decision-making *in practice*.

An alternative to ordering preferences in time is to order them *in space*. Cyert and March (1963, 165) characterize *local rationality* as another means by

which organizations deal with ambiguous preferences.[6] This involves the separation of different preferences *in space*. A complex issue is divided into smaller issues, which are then left to a number of sub-units within the organization to decide. Each sub-unit can then seek to make a choice with a more limited set of problems, and a more limited set of preferences (at one time). For example, one division of an organization can be made responsible for making decisions to 'satisfy customers', while another is responsible for making decision about 'environmentally friendly production processes'. Although the difficulties with making rational choices about each of these matters remain, Cyert and March argue that a separation of preferences *in space* can decrease the risk for protracted conflict about how to realize multiple preferences in the same choice situation.

Other researchers similarly characterize how conflicts between preferences are avoided by organizing aspects of a larger problem into parallel decision-making processes that are kept as separate from one another as possible. In his study of the municipality of Stockholm attempts to buy a coal-fueled power plant, Jacobsson (1994) describes how three processes – one energy-political, one technical, and one environmental – were run in parallel with one another. Each process involved largely different participants and focused on different issues. Jacobsson notes that keeping the processes as separate as possible for one another was a means for proponents of the power plant purchase to avoid conflicts that would delay the completion of the decision-making process. Opponents of the proposed purchase, meanwhile, sought to connect the processes to one another and thereby illustrate an inadequate consideration of particular preferences (Ibid. 108-12; for further discussions of parallel processes see Sahlin-Anderssson 1986; Blomquist and Jacobsson 2002).

Separating talk, decisions and actions in both time *and* space is yet another way in which organizations are characterized to deal with ambiguous

[6] The authors describe sequential attention to goals as one means of achieving aggregate consistency if and when local rationality has been used as a means of making decisions. I have chosen to emphasize their thematic differences – separation in time and space, respectively – rather than their possible interrelationship.

preferences – and attendant rationalistic demands for coherent justification. Various studies illustrate how different parts of the same organization can be made responsible for engaging in talk, for making decision and for taking action – at different points in time (Brunsson 1989; Lawrence and Lorsch 1967; Oliver 1991).

For example, a senior executive can talk about environmental friendly purchasing, while the purchasing manager chooses a short-list of suppliers based on price comparisons, and the line manager places orders with the company that has products in stock and an attentive customer service representative. To make each of these activities *individually coherent* at one point in time is easier than making them *coherent with one another*, over time. But with different parts of an organization responsible for a particular set of activities, each part can also seek to justify these activities to different parts of the environment. In this way, the separation of talk, decision and action makes it possible for an organization to avoid overt conflict between both multiple organizational preferences *and* multiple environmental demands (cf. Meyer and Rowan 1977).

The aforementioned ways in which organizations are characterized to handle ambiguity of preferences relate to how decision-making processes are organized. Studies also highlight how organizations can reach vague outcomes in order to avoid conflict between ambiguous preferences. In her study of the construction of Stockholm's multi-purposes arena Globen, Kerstin Sahlin-Andersson (1989) characterizes the project process and its participants as loosely coupled to one another. Various groups worked simultaneously on the project, but not necessarily in collaboration. The groups had many co-existing definitions of the project which sometimes agreed, and sometimes conflicted with each other. The project had many, and changing, purposes. Being vague about the success, or completion, of the project allowed for *interpretational flexibility* as regards which future action(s) had been decided on. Being vague opened for the possibility of mobilizing diverse support for a decision on the basis of satisfying many preferences both within and outside of the organization (see also Baier, James and Saetren 1986), while hiding difficulties with adhering

to normative ideals about known, stable and coherent preferences, and the linear relationship between decision-making and action (Brunsson 1989).

Taken together, behavioral studies of organizational decision-making characterize numerous ways in which organizations deal with ambiguity of preferences by avoiding conflict between multiple preferences at *one* time, in *one* space. The aforementioned studies of how organizations deal with ambiguity of preferences question the assumption that actors are rational, and can make intentional choices of future courses of action. These studies highlight how decision-makers diverge from the assumptions of orderliness and intentionality that underpin the rational choice model. A related research trajectory centers on questioning assumptions in the rational choice model about the orderliness of *the environment* in which decision-making takes place.

Normative theories of organizational choice presume a coherent and objective reality that a (rational) actor can act on, and respond to (March 1994, 181; cf. March and Olsen 1976, 19). Scholars of behavioral decision theory question the assumed existence of such an objective, coherent and causal reality. One particular focus is the ambiguity of (organizational) history, also referred to as ambiguity of experience (cf. Cohen and March 1974). In opposition to the rational model's assumption that "what appeared to happen did happen", empirical studies illustrate how historical events can be interpreted in multiple, and changing, ways.

...ambiguity of history...

The interest in organizational history within behavioral studies of organizational decision-making is often couched in relation to questions about how organizations learn. The rational model of organizational choice assumes that organizations learn adaptively, by responding to environmental stimulus and drawing conclusions about causal links between chosen actions and (environmental) reactions. In opposition to this, March and others argue that nothing 'happens' to an organization independent of the individuals who interpret these happenings as relevant events. Events are not interpreted

objectively, and independent of a particular (organizational) setting. Records of actions and past events are often inaccurate, incomprehensive or irretrievable. Different parts of an organization perceive different "worlds" (March and Olsen 1975, 161).

With past events and the possible causality of organizational decision-making and action ambiguous, individuals draw on myths, illusions or ideology to understand the past and how it relates to the present and the future. This, according to Cohen and March (1974), means that managers can rewrite (the interpretation of) history by actively constructing meaning about disordered situations. Based on their study of university presidents, they outline a series of different 'strategies' whereby leader of "organized anarchies" can attempt to exercise influence. One such strategy is to control the written history of the organization. According to Cohen and March, "definitions of what is happening and what has happened become important tactical instruments.... Minutes should be written long enough after the event so as to legitimize the reality of forgetfulness.... The model of consistency is maintained by a creative resolution of uncertainty about the past" (1974, 215).

Developing a common meaning about the organization's past can serve to further reduce ambiguity by focusing attention on limited aspects of reality (Brunsson 1982, 42), and ordering future search for knowledge in connection with decision-making activities (Levitt and March 1988). This can facilitate decision-making. For example, Lindblom (1959) characterizes incremental decisions, which take previous decisions as a point of departure and a means of successively limiting comparison of consequences and preferences, as a practically effective means of making decisions and addressing many – if by no means all – preferences.

The treatment of organizational history in the aforementioned studies infers a significant degree of *interpretational flexibility* vis-à-vis the reality of the past. In the rational choice model, it is assumed that history shapes the future. Decision-makers respond to environmental signals, for example about the consequences of past choices, and this influences what choices are made about future actions. Behavioral decision theory, in contrast, proposes that

decision-making processes take part in shaping history. Instead of something exogenous to organizational decision-making processes, the reality of what happened in the past is endogenous to and influenced by these activities.

It is relevant to note, however, that the treatment of reality *of history* is not extended to other representations of reality. Of particular interest for the present study, there has been limited attention paid to science, despite the characterization that "history and science are formal attempts to provide causal stories about ambiguous events" (March 1994, 181). The use of information, more broadly, *has* been pursued. However, as I will argue further in the next section, this has been done in opposition to the assumption that information collection and processing is determinant of organizational choice. Specifically, information (which I will henceforth refer to as knowledge, in keeping with the chosen terminology of this study) is characterized as a means of legitimating decision outcomes *ex post* – and influencing decision-making processes *ex ante*.

...and knowledge as a resource to legitimate or influence decision-making processes

The analytical treatment of knowledge in behavioral decision theory, like that of preferences and history, can be understood in relation to an overarching critique of assumptions in the rational choice model. The rational choice model is deterministic as regards knowledge, specifically knowledge about preferences and consequences. In other words, according to the rational choice model of organizational decision-making the optimal choice is *given* by knowledge about future preferences for the future consequences of alternative courses of action. It is not surprising then, that behavioral studies of organizational decision-making have taken as topic how organizations use knowledge in practice – as compared to this rational ideal.

The specific assumption that Feldman and March (1981) question in their study is that knowledge from various sources is collected and then used by decision-makers to determine the outcome of decision-making processes. In

contrast to this assumption, the two authors find the "paradoxical situation" that information is collected and then disregarded by decision-makers:

> Organizational participants seem to find value in information that has no great decision relevance. They gather information and do not use it. They ask for reports and do not read them (Feldman and March 1981, 182)

Feldman and March attribute this 'un-rational' behavior to the symbolic role of information collection activities. Although rationality may be difficult to practice, the principle is an important value to espouse. Collecting information:

> ...symbolizes a commitment to rational choice. Displaying the symbol reaffirms the importance of this social value and signals personal and organizational competence (Ibid.).

Knowledge is a means of signaling procedural rationality and a commitment to substantive rationality (cf. March 1994, 2). In direct contrast to the rational choice model, then, knowledge is characterized as legitimating decision-making processes and their outcomes *ex post*, rather than determining these outcomes.

The conclusion that knowledge is used to legitimate the *output* of decision-making processes complements findings in studies that take issue with rationalistic assumptions about knowledge as a neutral *input* to decision-making processes. Notably, March (1988) argues that the interpretation of knowledge is influenced by *who* collects and presents it and *how* it is collected and presented. This conclusion mirrors findings in studies of the relationship between civil servants and politicians that illustrate how civil servants influence what decisions politicians' make about the actions civil servants should take (Brunsson and Jönsson 1979; Jacobsson 1986).

According to the rational choice model, it is the decision-maker who is knowledgeable about future consequences and future preferences. Those who are to take action based on the decision-makers choices are, in contrast, 'knowledge receivers'. The aforementioned studies explain the reversal of this sender-receiver model in part by civil servants' ability to frame relevant problems and solutions due to their greater knowledge about the matters being decided on (Ibid.; cf. Lipsky 1980).

That those with knowledge have the possibility of exercising influence can, according to Pfeffer, be explained by: "our belief that there is a right answer to most situations and that this answer can be uncovered by analysis and ... more information, means that those in control of the facts and the analysis can exercise substantial influence" (Pfeffer 1997, 247).

The idea that those in control of knowledge can exercise influence mirrors research by Kingdon (1995 [1986]) about the role of agenda-setting in decision-making processes. Particularly in conditions of crisis or formation, it is possible for "policy entrepreneurs" to frame the parameters of discussion by providing decision-makers with packaged combinations of problems, solutions and decision opportunities (Ibid., 122; see also example of organizational gatekeepers in innovation processes in Pettigrew 1972).[7] Other studies have similarly illustrated how 'technical' artifacts, such as accounting reports (Cohen and March 1974, 213) or investment calculations (Jansson 1992), can be strategically used to influence the choice of a particular course of action.

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In the rational choice model, knowledge is assumed to be something stable and neutral, which determines the (optimal) outcome of decision-making. In contrast, behavioral studies of organizational decision-making illustrate how knowledge is used to legitimate outcomes after they have been made; how knowledge is used strategically by actors in decision-making processes; how knowledge can be interpreted in different ways. In short:

> Students of ambiguity argue that information may not resolve misunderstandings of the world; that the 'real' world may itself be a product of social construction, thus not so much discovered as invented (March 1994, 179).

[7] Gaventa (1987) makes a similar, but more sinister, point in his application of Lukes (1974) three-dimensional view of power to principally discuss why certain forms of organizational oppression (he focuses on states' oppression of citizens) can continue without revolt. He notes that opponents can be *directly* excluded from participation in political (decision-making) processes. However, opposition can also be thwarted by framing the perceptions of what are relevant problems, solutions and preferences such that opposition cannot be articulated (Gaventa 1987, 38-42).

However, this overarching conclusion that there is *interpretational flexibility* as regards the contents of knowledge and its use raises several questions. Specifically, the notion of interpretational flexibility is not coherent with the underlying assumption of objectivity inferred by descriptors such as "biased information" (Brunsson 1985, 31; Cyert and March 1963)

More generally, it is questionable whether knowledge is a readily available resource to legitimate a particular decision outcome if it is ambiguous – at least not if there is an expectation of a coherent reality and 'a right answer' (as the previous quote from Pfeffer suggests). Nor is it obvious that interpretational flexibility is a readily available recourse for satisfying demands for coherent justification. While it may be possible to justify a particular decision based on a certain interpretation of reality, this interpretation could be challenged by other interpretations. This should be particularly problematic if the expectation is that decision-making outcomes be justified on the basis of scientific knowledge, since it is widely assumed that scientific knowledge is an objective representation of a coherent reality (Drori et al. 2003). As I will elaborate on in the next section, this suggests the relevance of posing further questions about *how* 'decision-able' knowledge is *constructed* to make 'justifiable' decisions.

A theoretical gap: ambiguity of (scientific) knowledge

Previous studies propose that organizations handle ambiguous preferences by separating them in time and/or space. Studies of the use of knowledge in organizational decision-making characterize knowledge as flexible to many and changing interpretations. Yet it is not immediately apparent that an organization can engage in 'strategies of avoidance'[8] if it is required to make decisions that can be justified on the basis of multiple sources of (scientific) knowledge. Nor it is it evident how the 'strategies of interpretation' can be extended to expert knowledge – particularly scientific knowledge, which is

[8] The term 'strategy' is used loosely. Studies vary as to the degree of intentionality ascribed to organizations. Some lean towards a more intentional view of organizational responses to ambiguity (cf. Meyer and Rowan 1977; Brunsson 1989), while others explicitly view them as unintended outcomes of organizational activities (Røvik 2000).

assumed to offer stable, causal accounts of reality (cf. March 1994, 181). To attribute knowledge a legitimating function in the justification of organizational decision-making, skirts the issue of how to make 'justifiable' decisions when there are many *legitimate* but together *incoherent* knowledge claims.

Taken together, behavioral decision theory has been 'indifferently relativist' vis-à-vis the contents of knowledge claims. Knowledge can *mean* different things, but an underlying assumption about the objectivity of knowledge has remained. My argument is that this approach provides a limited scope for discussing how decisions are made when there is ambiguity of (scientific) knowledge. To take this question seriously requires a theoretical approach that has the construction of knowledge as a topic of inquiry, and treats knowledge as an outcome. To this end, I will in the next section introduce ideas from science and technology studies (henceforth also 'STS'). This area of research, broadly speaking, centers around questions about how dichotomies such as the truth/falsity of knowledge, and the division between society/nature are constructed, changed, and maintained in practice.

My translation of concepts from STS into behavioral decision theory is supposed to engineer a shift towards a less 'indifferently relativist' stance to the contents of knowledge. This enterprise is not without risks. To date, behavioral studies of organizational decision-making have largely avoided tricky questions related to epistemology (much less ontology). For this reason, I will now briefly comment on how an 'STS approach' fits into the study's theoretical framing, before proceeding to outline specific concepts that will be used in my analysis of the empirical case.

My introduction of ideas from STS is premised on four circumstances: First, a similar research agenda. Behavioral studies of organizational decision-making pursue what can be termed an empirically-founded critique of the pervasive idea that organizations can and should make rational choices. Science and technology studies pursue a similar critique of another normative idea(l), that of objective science (and – by extension – functional technology). Second, a shared methodological focus. Both approaches take as a starting point the study of their respective phenomenon *in practice*. Third, a common analytical

position. Both behavioral decision theory and STS have a process-orientation vis-à-vis their respective topic of inquiry. It is the *processes* of decision-making and knowledge construction that are the analytical focus. Four, a relativist world view – at least at an epistemological level. Both decisions and knowledge are constructions; *achievements requiring effort*. Neither specific decisions nor particular knowledge are the sole or inherent outcome of decision-making processes or knowledge production.

Thus, although founded in different research traditions, it is my contention that the similarity in research agenda and shared methodological and analytical focus makes it possible to combine these two theoretical approaches *in principle*. In the next section, I discuss how concepts from STS will be used to extend behavioral studies of organizational decision-making *in practice*.

Theories about knowledge as outcome

Science and technology as social endeavors

The field of science and technology studies[9] (STS) draws on Kuhn's (1962) characterization of science as a succession of paradigms – socio-intellectual constructs that determine which types of knowledge claims are permissible – rather than an accumulation of discoveries, bringing us closer to an objective truth about reality.

An early trajectory within STS, called sociology of scientific knowledge (SSK), developed in opposition to the dominant 'received view' of science. This 'reviewed view' separates natural science from social science, on the assumption that Nature holds a unique truth and the current state of scientific knowledge is the best available representation of that truth. According to the received view, there are no social factors intervening between nature and its representation in scientific fact. Thus, there is no need to examine why scientists believe what

[9] Writing *the* history of STS is at odds with an overarching tenet that "things could have been otherwise" (Bijker 1995, 280). Nevertheless, it serves a practical purpose for situating the present study (cf. Latour 2005, 94)

they believe provided there is scientific proof. Scientific debate is legitimate if the evidence is incomplete or contradictory, but not after uncertainties are removed through applications of acknowledged scientific methods. For those individuals who continue to disagree with proven facts, it is assumed that there are psychological, cultural and social foundations for their adherence to scientifically disproved or unproven knowledge claims (cf. Merton 1973).

Bloor (1991 [1976]) proposes an alternative approach to this "sociology of error" (Ibid., 17; Woolgar 1988, 40). His point of departure is that sociology has a role in epistemology that is not limited to explaining the "pathology of beliefs" (Heese 1980, 32). Rather than conceptualizing knowledge as true and justified belief, Bloor (1991 [1976], 5) argues that knowledge should be treated as a "natural phenomenon". In other words, knowledge is that which people take to be knowledge (cf. Berger and Luckmann 1966). Since all representations of reality are mediated by social circumstances, it is this mediation which requires empirical investigation. Thus, scientific knowledge is to be studied *as a practice*, and in a manner that emphasizes the production of knowledge rather than its justification.

Two related directions of research following Bloor's proposed 'Strong Programme' are the historical and ethnographic study of scientific controversies.[10] In contradiction of the view that disputes over facts are resolved by the impersonal or "objective" rules of experimental procedure, extensive empirical studies of laboratories and other sites of scientific work characterize scientific knowledge as an outcome of collective consensus-making among groups of experts (Collins 1981, 1985; Collins and Pinch, 1979; Pickering 1984; Pinch 1986). A general argument is that the closure of a scientific controversy is not an independent outcome of rigorous testing, but a result also of pressures and constraints exerted by the surrounding community. These pressures and constraints include both the previously accepted knowledge of the community,

[10] Bloor was a member of what has since come to be termed the 'Edinburgh School', which emphasizes a historical approach to studying scientific controversy. In contrast, the 'Bath School' emphasizes the use of microsocial studies of scientific controversy in laboratories and other sites of scientific work.

but also the social/political interests that it embodies (Barnes 1977, Shapin and Schaffer 1985, MacKenzie 1981, Shapin 1979).[11]

An extension of the focus on social interests as causes for why scientific beliefs are held to be true, was the consideration of how artifacts such as laboratory equipment, machines and other measurement tools play a role in the construction of facts (Latour and Woolgar 1986 [1979]). This interest subsequently informed a critique of SSK for asymmetry in respect to social explanations; an over-reliance on human actors and social rules and conventions in settling scientific controversies.[12] The argument made by Bruno Latour, Michel Callon and others is that SSK explanations include "missing masses" (Latour 1992) – various non-human actors (so-called actants) – that should be included on an equal basis.

In extending symmetrical explanations to dichotomies such as that of nature/society, researchers within what came to be termed the actor-network (ANT) approach proposed a step-wise model characterizing the process of constructing facts. According to this 'translation model', a fact *becomes* through the successive mobilization and enrolment of allies, and the construction of an actor-network to support the fact-under-construction's world (Latour 1987, Callon 1986). An important aspect of this process of translation is that what 'the fact' *is* changes as it is moved from different sites and takes various forms:

> translation has both a geometric and a semiotic meaning. [It] is both the movement of an entity in time and space, as well as its translation with (sic) from one context to another - as in translating from one language to another, with the necessary transformation of meaning that this always implies (Gherardi and Nicolini 2005, 287).

[11] The SSK-argument that social interests play a role in closing scientific controversy is similar, but not analytically equivalent, to a "group politics approach" to scientific controversy (cf. Martin and Richards 1995, 511-2), where it is treated as any other form of politics involving a process of conflict and compromise between various groups bringing a diversity of resources – including science – to bear (Nelkin 1975, 1979; Greenberg 1967; cf. notion of 'public interest science' in von Hippel and Primack 1972; Primack and von Hippel 1974).

[12] This is a damning charge, given that one of four foundational methodological tenets of the Strong Programme is the symmetry principle, which holds that "the same type of causes would explain...true and false beliefs" (Bloor 1991 [1976], 5).

Over time and space, the successive translations become increasingly 'black-boxed' – invisible – as the network of supporting allies becomes increasingly stabilized. Only if the network fails, which it can do at any time, does the work needed to construct a fact once again become visible – and more clearly contestable. However, the failure or success of a fact is an outcome of the changing stability and durability of the network of allies supporting it rather than a consequence of the claim's inherent properties (Latour 1996; 1991).

Scholars within ANT and SSK both treat facts as the outcome of social endeavors (albeit in different ways as regards the epistemological and ontological status of these outcomes). This insight would seem to be the same position as that inferred by a 'generic' relativist approach that is widespread within the social sciences. The difference lies in how this view is commonly not extended beyond 'social' objects such as culture, leadership or – indeed – decision-making. The overarching point of the STS stance, as I treat it in this study, is its relativist stance vis-à-vis things which are 'natural givens', such as gravity, mathematics – death and furniture (cf. Edwards, Ashmore and Potter 1995). Or, as in the present case, pharmaceuticals' characteristics.

Following this brief background on some central themes in STS, I will now proceed by focusing on studies that have studied science in 'organized' settings such as policy-making and judicial process. It is relevant to note that while many studies have been undertaken of organizational decision-making processes, this 'organizational' aspect has typically not been emphasized (perhaps since STS researchers do not take organizations to be – inherently – interesting). Given the present study's interest in the use of scientific knowledge in organizational decision-making, however, the next section will discuss studies of (scientific) knowledge *to advise* decision-makers. The subsequent section will move to consider studies of attempts at achieving coherence in organizational practice.

Expert advice in decision-making processes

The role of 'expert advisor' is entrenched in many decision-making processes, particularly those related to policy-making. Studying expert advisors has a long

tradition in many disciplines. While the approaches taken to this broad topic vary considerably, one point of differentiation of relevance to the present study is between researchers who emphasize the importance of experts "speaking truth to power" (i.e. policy-makers), and those that are more critical to the capacity of experts to speak truth and the possibility and desirability that policy-makers listen to it (for an overview see Haas 2004; Jasanoff and Wynne 1998). Whereas the former approach is typically focused on developing techniques for improving the means by which experts engage in policy-making, the latter takes an interest in what expert advisors *do* – rather than what they should do. The latter approach is characteristic of 'STS-informed studies' of expert advisors.

In her study of several American policy-making processes, Sheila Jasanoff (1990) concludes that scientists engage in adaptation and negotiation over what is true knowledge. In other words, the activities of experts are not fundamentally different from those of other participants in these processes. Various other studies similarly conclude that 'science' is not an objective, value-neutral resource for closing conflicts when 'the facts of the matter' are in question. Since different scientific arguments are evoked by different parties, they do not automatically lead to the resolution of conflicts since a burden of proof for a given policy is not available separate from the setting in which the knowledge claims are evoked (see also Hilgartner 2000). Agreement on what is evidence is needed before 'the evidence' is determined. Thus, conflicts over knowledge claims tend to be particularly common and severe in situations were 'what counts' is in question (Espeland and Stevens 1998, 332). Without incentives to reach agreement about what is 'true', this can lead to on-going disagreement over 'technical' details – and delay or lack of closure (Collingridge and Reeve 1986).

These studies of science advisors characterize the construction of scientific advice as a situated outcome, rather than something separate from and external to policy-making processes. Studies highlight the difficulty for scientific advisors to provide decision-makers with coherent 'facts', since there are no simple criteria for resolving incoherence between knowledge claims through generic appeals to 'objectivity' and 'impartiality'. In a similar vein, studies of the use of

scientific evidence in court illustrate how 'the facts of the matter' become *deconstructed* in judicial proceedings.

In his study of the (in)famous O. J. Simpson trial, Lynch (1998) shows how submitted DNA evidence – and the experts and the practices through which this evidence was produced – was undermined through testimony that emphasized the practical contingencies and sources of uncertainty in the production of this knowledge. Various other studies similarly illustrate how evidence is deconstructed in judicial proceedings when divergence of scientific practice from an ideal characterization of the procedures of neutral and objective science are put forth (Smith and Wynne 1989; Jasanoff 1995, 2005; Swanson 2005; Edmond 2002). Oteri, Weinberg, and Pinales (1982), in an early treatment, characterize a series of methods by which an expert's authority can be thrown into doubt. These include challenges to the specific relevance of the expert's qualifications; identification of variations in methods, and practical considerations in choice of methodology, for example cost, ease and speed (as opposed to accuracy). In a mirror of these findings regarding the deconstruction of scientific advice through failure of methods and procedures, Cole (1998) argues that latent fingerprint examiners were successful in making fingerprint identifications 'matters of fact' through their articulation of standard rules of method and practice.

As in the case of scientific advisors, the studies of scientists in court point to difficulties in (re)moving scientific facts from the circumstances of production, such that 'the evidence' speaks for itself. The substantive stability of evidence rests on procedural agreement about its format and the procedures for its production. Bringing the practice of knowledge production into question is a way to undermine the truthfulness of knowledge claims.

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Studies of scientific advisors work in various organizational decision-making processes suggest that they often fail to provide decision-makers with coherent knowledge on which to base their decisions, or are undermined in their efforts to do so. Multiple sources of expert knowledge can remain largely unrelated to

one another when organized to advise decision-making processes, with different knowledge claims sustained in separate "epistemic communities" (Haas 1989, 1992; cf. Knorr-Cetina 1981, 1999).[13]

However, the conclusion that multiple knowledge claims – and the practices in which these claims are produced – remain separate and incoherent from one another without shared procedures or methods, is in part challenged by scholars who propose that multiple sources of practice *can* be coordinated – through their shared use of certain objects.

Objects as a means of achieving coherence ...

Star and Griesemer (1989) propose that coordination between various social worlds can be achieved through different groups shared use – but different interpretations – of so-called "boundary objects". These objects:

> have different meanings in different social worlds but their structure is common enough to more than one world to make them recognisable, a means of translation. The creation and management of boundary objects is a key process in developing and maintaining coherence across intersecting social worlds (Star and Griesemer 1989, 393).

The authors use the term 'boundary object' to characterize how objects such as a standardized form for specimen reporting linked professional biologists with amateur naturalists, conservationists, and trappers in the creation and maintenance of Berkeley's Museum of Vertebrate Zoology. The standardized form served as a means of creating coherence between individuals within diverse social worlds "with commitments to activities and interpretations different than those across the border" (Geiryn 1995, 414). This was possible

[13] "An epistemic community is a network of professional with recognized expertise and competence in a particular domain and an authoritative claim to policy-relevant knowledge within that domain or issue-area. Although an epistemic community may consist of professionals from a variety of disciplines and backgrounds, they have (1) a shared set of normative and principled beliefs, which provide a value-based rationale for the social action of community members, (2) shared causal beliefs ... (3) shared notions of validity ... and (4) a common policy enterprise" (Haas 1992, 3)

because the same form – the 'boundary object' – was used in different practices, where it was attributed a variety of different meanings.

However, a boundary object's capacity to give rise to coherence is premised on the assumption that there *are* certain characteristics that are sustainable in different sites. In other words, there cannot be *complete* interpretational flexibility as regards a boundary object's characteristics. The notion of boundary objects further presumes that there is no conflict between multiple, incoherent perspectives on the object – precisely because of their separation in space and/or time. If there are demands for a common and coherent meaning and characterization of a boundary object *in one site*, then arguably it can not fulfill its coordinating function between multiple sites since the incoherence between different perspectives would be a source of conflict.

I have previously argued that decision-making processes are one situation where there may be expectations of a coherent reality. (In the specific case of LFN, it is precisely the expectation that the Agency reach a conclusion about a pharmaceutical's subsidization status based on a combined consideration of the drug's medical, humanitarian and socio-economics characteristics of use). The notion of 'boundary object' does not readily provide a conceptual framework for understanding how incoherent interpretations in one site are dealt with. In the next section, I will therefore go on to discuss studies that seek to characterize *how* ambiguities between multiple sources of knowledge are handled through attempts to *remove ambiguity* or *sustain ambiguity* (by moving it elsewhere).

...or embodying incoherence

In her study of how diagnosis and treatment decisions are made for patients who have (or do not have) arteriosclerosis, Mol (2002) characterizes ways in which multiple characterizations of what this illness *is* are related to one another in practice.[14] Her point of departure is that incoherent characterizations

[14] Since the topic of Mol's study is precisely what arteriosclerosis 'is' it is difficult to give a definition of 'arteriosclerosis'. However, in the interest of clarity rather than methodological purity, it can be characterized as a condition in which fatty materials collect along the walls of

of 'the same' object cannot co-exist in one practice. She is therefore interested in what happens when there are *clashes* between different *versions* of objects that arise from their *enactment* in different *practices*. (These are her words. In line with the framing of this study, I will discuss Mol in terms of how ambiguities between multiple sources of knowledge are dealt with when making decisions).

The focus on incoherence between multiple sources of knowledge about an object follows from an emphasis on practice:

> If practices are foregrounded there is no longer a single passive object in the middle, waiting to be seen from the point of view of seemingly endless series of perspectives (Mol 2002, 4)

In contrast with the epistemological notion of boundary objects, which coordinates between multiple practices through differences in understanding, Mol's point is that different practices (and the representations of objects they product, in the form of diagrams, texts, measurements and so on) do not simply give different perspectives of an object.[15] They create different *referents* that do not necessary converge. In other words, 'an object' is not a single entity but a multiplicity of objects which need to be re-arranged and re-aligned before they can be – and be acted on – as a unitary object with clear characteristics. Thus, it is the "ontological politics" (Mol 1999) whereby incoherence between referents of multiple practices is played out that is of primary interest.

In this study, I will lean towards emphasizing the politics that Mol alludes to more than their ontology. For although Mol does not emphasize it, the 'unsustainable' ambiguity between multiple sources which she refers to in her study of arteriosclerosis typically arises in situations where *decisions* are to be made about treatments, the need for new tests and so on. It is my argument that *the need to make decisions* brings incoherence between multiple, ambiguous sources of knowledge about arteriosclerosis into being.

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arteries so that they thicken and harden. This can lead to a blockage of an artery and a heart attack or stroke.

[15] An interesting parallel argument is made by March (1981, 570): that organizations create their own environments by the way they interpret *and behave* in a confusing world.

Based on her observations of incoherence between multiple sources, Mol characterizes two overarching methods for attempting to remove ambiguity about an object's characteristics: *addition* and *calibration*.

Addition is used in reference to 'adding up' multiple characterizations into a coherent object. It can be achieved in one of two ways. The first is when multiple sources of knowledge *coincide*, and characterize an object in 'the same' way (Mol 2002, 61). In her study, Mol describes how "the anamnesis, a physical examination, pressure measurements, and duplex Doppler scan. They jointly back up a single diagnosis" (Ibid., 57). In this case, the various sources of knowledge supported one another. As there was no visible incoherence between them, no additional effort was needed to relate the sources with one another.

Adding up visibly incoherent sources of knowledge is characterized as requiring greater effort. Mol describes how such ambiguity can be removed by *privileging* one version over another, since "two diverging signs cannot have a single object as their common source" (Ibid., 62). To illustrate this point, Mol uses the example of a patient's complaints about symptoms and the laboratory's findings:

> [W]here two facts contradict each other, one may be accorded more weight than the other. In the case of clinical complaints and pressure measurements, a hierarchy with the lab on top looks likes this. If Mr. Somers has complaints but his pressures are all right, then he is in trouble, but such trouble does not have a vascular origin. The question of where the pain comes from must be asked again (Ibid., 63)

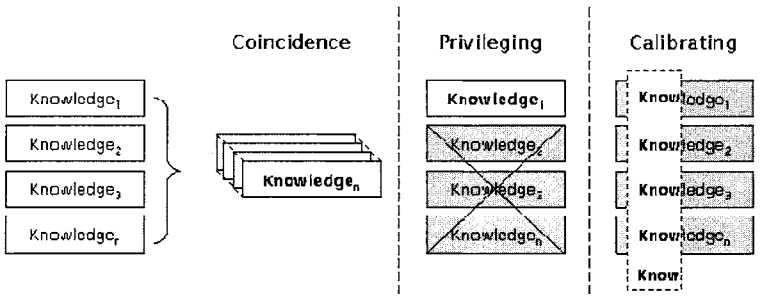
By privileging the laboratory measurements of arteriosclerosis and excluding the patient's account of his symptoms, it was possible to achieve coherence between the two sources.

An alternative method for attempting to remove ambiguity is to standardize different sources through *calibration*. Calibration hinges on the establishment of an agreed on common metric (what Mol terms a "common measure", Ibid., 84). The example used to illustrate this method of removing ambiguity was the efforts made to make two diagnostic methods coherent with

one another. Mol describes work to develop cut-off points that linked measurements on one scale with measurements on the other (Ibid., 76-77). Once there was such a "translation rule" (Ibid., 78), then the two sources could be related to one another. The use of one diagnostic method could even stand in for the other.

The three methods of removing incoherence outlined by Mol are translated into the current study's framework in the diagram below:

***Diagram 2**: Methods of removing ambiguity between incoherent sources of knowledge (based on Mol 2002)*



Mol's typology provides a starting point for distinguishing between different ways of *removing* ambiguity between multiple sources of knowledge when making decisions. However, Mol does not elaborate on what happens if attempts at removing ambiguity fail. The underlying assumption is that attempts *must* succeed, since ambiguity is ontologically unsustainable in one practice.[16]

Although recent studies of regulatory processes (involving decision-making about rules) empirically support the notion that local ambiguity is left behind when standardized characterizations of objects are made to travel in time and space (MacKenzie 1990; Helgesson and Fernler 2006; Helgesson 2006), there are other studies that describe efforts to deal with ambiguity by delegating its resolution to others.

[16] The heading 'One reality wins' (Mol 2002, 55) is illustrative of this point.

In his study of the regulation of a so-called non-lethal weapon (a spray), Rappert (2001) discusses how the recommendations for use of this technology issued by police headquarters made no definitive characterization of the technology's properties. Specifically, ambiguity about *when* the spray had 'appropriate' characteristics was *delegated* (Rappert refers to this as deferral) to individual policemen. Rappert argues that the delegation of ambiguity about when the spray is appropriate to use also delegates the responsibility for deciding to use the spray to others than those formulating recommendations for the technology's use. What Rappert's study suggests is that ambiguity is sustainable when making *certain* decisions – namely those where the resolution of ambiguities is left to other parties.

Concepts going forward

In this chapter I have argued that previous studies of organizational decision-making have considered other sources of ambiguity than (scientific) knowledge, notably preferences and organizational history. When dealing with ambiguity of preferences, organizations are characterized to employ various 'strategies of avoidance'. Notably, these strategies involve the separation of incoherent preferences in time and space, in order to avoiding conflicts in *one* time or in *one* space.

As regards the use of knowledge in decision-making, I have argued that theories of organizational decision-making take one of two approaches. In the rational choice model, it is knowledge about future outcomes and future preferences which *determines* what is the optimal choice. In contrast, behavioral studies of organizational decision-making characterize knowledge either as a means of legitimating decision-making processes or as a resource for particular groups to influence what outcomes are reached. There are few – if any – links between the contents of knowledge and the outcome of decision-making processes. My conclusion is that neither approach provides analytical leverage for understanding how LFN works to determine whether prescription pharmaceuticals have characteristics that make them 'reasonable' to subsidize.

In an attempt to bridge a gap in the theoretical treatment of multiple, legitimate sources of knowledge, I introduced ideas from the science and technology studies (STS). Specifically, I have highlighted studies within STS that have developed concepts for characterizing how ambiguity between multiple sources of knowledge is *removed* and *delegated.* I will elaborate on these concepts in my forthcoming analysis.

3. A GOOD ACCOUNT? RESEARCH DESIGN AND METHODOLOGY

Managing pharmaceutical spending is a 'hot' topic for healthcare financiers and service providers, irrespective of how healthcare services are funded. In recent years, numerous initiatives have been launched in a variety of countries in an effort to increase control of 'who gets what treatment at whose expense' (cf. Jost 2005; Ham and Robert 2003). LFN is one example of such an initiative. The societal and financial importance of the organization's work in a Swedish context is itself a reason for studying the organization. However, my decision to study LFN was primarily premised on circumstances that make the Agency an example of organizational decision-making with ambiguous knowledge.

The foremost circumstance was the legal requirement that LFN "make decisions" (Act (SFS 2002:160) on Pharmaceutical Benefits, section 7), in combination with various restrictions on *when* the Agency make decisions, *how* the Agency makes decisions, and *which* decisions the Agency makes.

As will be elaborated on in Chapter 4, LFN is required to reach a conclusion about a pharmaceutical's subsidization status within a certain period of time. In the case of pharmaceuticals that have received marketing authorization after the Agency's creation in October 2002, this time period is 180 days from the time an application for subsidy is submitted (Ordinance 2002:687, section 9). As regards those products that were subsidized prior to the Agency's creation, LFN was initially expected to complete its review of these

drugs' subsidization status in five years (SOU 2000:86, 312). This time plan was subsequently revised to six years (LFN 2006d, 25).

When evaluating pharmaceuticals' subsidization status, LFN is instructed to approve subsidy for those pharmaceuticals that have "a reasonable cost of use ... from humanitarian, medical and socio-economic perspectives" (Act (SFS 2002:160) on Pharmaceutical Benefits, section 15). The Agency is also encouraged to adopt "a broad approach" (The New Pharmaceutical Benefits Bill 2001, 46), to make use of other governmental agencies with activities within the healthcare sector, and to consider health economic calculations as a "valuable decision tool" (Ibid.).

When the Agency has reached a conclusion about a pharmaceutical's subsidization status, LFN must publish a decision justification document which gives the grounds for this conclusion. The decision justification document then serves as the basis for an eventual appeal to the administrative courts by the pharmaceutical company marketing the drug in question (Act (SFS 2002:160) on Pharmaceutical Benefits, section 26).

As regards which conclusions the Agency can reach about a drug's subsidization status, LFN is restricted to one of three outcomes: denying subsidy or approving subsidy (with or without explicit restrictions).

The requirement that LFN make decisions on the basis of multiple characteristics of pharmaceutical use, in combination with the need for the Agency to publicly justify its conclusions about pharmaceutical subsidy are two circumstances that led me to anticipate that the organization would face situations where there was ambiguity about what a pharmaceutical's characteristics were, and whether these characteristics were 'reasonable'[17].

There were also several methodological reasons for my decision to study LFN. When I initiated the study in 2003, the Agency was a relatively new organization. It was also an organization with a new task, at least in a Swedish

[17] The reader is reminded that I use 'reasonable' in reference to the Agency's legal decision criteria.

context. This "new and difficult task" (The New Pharmaceutical Benefits Bill 2001, 47), was cited by legislators as a reason for giving LFN imprecise instructions which the Agency was to interpret as it developed practice. In choosing to study LFN, I was able follow an organization that was still developing organizational routines. This was particularly relevant in the second study, in which I followed the Agency's two pilot projects for the product assortment review[18]. These two projects were the first reviews undertaken by LFN. Studying these groups contributed in a positive way to my study. Firstly, because situations where there was ambiguity of knowledge were visible in a way that might change as the Agency develops routines for dealing with incoherence between multiple sources of knowledge. Secondly, since my informants were reflexive about their work. *How* they went about evaluating these drugs was of importance – also for them.

Having decided to study LFN, I went on to limit my study to how ambiguity between multiple sources of knowledge about pharmaceuticals' characteristics was dealt with in the organization's decision-making processes. This delimitation was in line with my interest in understanding how organizations deal with ambiguity between multiple, *concurrent* sources of knowledge. It also meant that I could use an empirical definition of ambiguity. In other words, that there was ambiguous knowledge was *not* a consequence of my highlighting incoherence between different sources of knowledge. That the 'dosage' in a clinical study of a pharmaceutical's effect differed from the 'dosage' prescribed to patients in clinical practice was not a situation with ambiguous knowledge *unless it was treated as such in the Agency's practice.* However, a further consequence of the chosen delimitation is that I have systematically privileged LFN over other possible sources of knowledge about the process of deciding pharmaceutical subsidy in Sweden.

[18] As discussed in greater detail in Chapter 4, LFN is instructed to evaluate the subsidization status of all pharmaceuticals that were included in the public pharmaceutical benefits scheme when the Agency was created in October 2002. I refer to this evaluation as the 'product assortment review'.

So far in this chapter, I have discussed *why* I chose to study LFN. The next two sections describe *how* I followed LFN's decision-making activities in the two studies that are presented in subsequent chapters.

Design and methodology of the 'outcome study'

As mentioned earlier in this chapter, the Agency's governing legislation does not specify in detail what it means for a pharmaceutical to have a 'reasonable' cost. This left to LFN to determine as it "develops practice" (The New Pharmaceutical Benefits Bill 2001, 47). The work to determine whether a pharmaceutical was 'reasonable' to subsidize is where I anticipated the organization to face situations of ambiguity between multiple sources of knowledge about the drug's characteristics. It was therefore relevant to understand the practice LFN developed *ex post*. (This, in turn, served as a background to my second study, in which I followed two of the Agency's decision-making processes over time). In the following sections I will discuss *what* I studied and *how* I went about performing this study.

What?

In my first study (henceforth also referred to as 'the outcome study'), I inquired into how LFN knows whether a drug is 'reasonable' to subsidize through a study of LFN 'developed practice' – as expressed in the decision justification documents issued by the Agency during its first two years of operations.[19] By analyzing the contents of these documents, I sought to understand what characterizes a drug as 'reasonable' or 'unreasonable' to subsidize.

LFN's governing legislation places the onus on the Agency to make decisions that can be justified as being in accordance with the governing legislation. A further purpose of the outcome study was to inquire into what constitutes 'decision-able' justifications – as expressed in the Agency's attempts to provide justifications of its conclusions.

LFN issues a decision justification document for ever decision it makes about a pharmaceutical's subsidization status. These documents are the way LFN publicly communicates the grounds for its conclusions. They are also the basis for any eventual appeals. The contents of the documents can therefore be expected to be of importance to LFN, expressing *for the Agency* justifiable decisions. Since each decision about a pharmaceutical's subsidization status leads to the issuance of a decision justification document, the documents are also a common means for studying LFN's decision-making.

Not all of the decision justification documents issued by LFN from its inception in October 2002 until the end of 2004 were included in the outcome study. To maximize similarity and facilitate comparisons, I chose to include only those decision justification documents concerning individual, original pharmaceuticals.[20] Documents justifying LFN decisions about general changes in the sales marginal for the National Corporation of Swedish Pharmacies were excluded, as were decisions about generic competitors to subsidized pharmaceuticals and decisions about medical-technical products. In total, ninety-four justification documents were included in the study.

It was also of methodological importance to have variation in the empirical material, since this made it possible to consider the contents of individual documents in relation to other documents (Denk 2002, 47-8, 90-2). Of particular importance was the ability to compare the justification of drugs that had been denied and approved subsidy, respectively. This would allow for the possibility of comparisons between the characterization of 'reasonable' and 'unreasonable' pharmaceuticals.

Of the ninety-four justification documents, LFN classified seventy-three (approximately 78%) as approval of subsidy, fourteen (approximately 15%) as

[19] LFN was created on October 1 2002, but the Agency issued its first decision justification documents at the end of January 2003.

[20] 'Original' is a term used to describe a patented pharmaceutical; it is 'the first' drug of its kind. An original pharmaceutical can face competition from 'generic' pharmaceuticals. Generic pharmaceuticals contain the same active substances as an original pharmaceutical. Generic competition commonly emerges when the patents for the original pharmaceutical's active

denial of subsidy and seven (approximately 7%) as approval of subsidy with restrictions. Of the seventy-three documents that the Agency classified as approval of subsidy, six approved subsidy *for a restricted period of time.* Since restriction in time was mentioned as one of several possible ways in which LFN could limit subsidy of pharmaceuticals (The New Pharmaceutical Benefits Bill 2001, 39-40), I chose to change the classification of these documents from LFN's 'approval of subsidy' to 'approval of subsidy *with restrictions*'.[21]

How?

My analysis of the ninety-four decision justification documents involved three-stages, whereby I iteratively classified and thematically organized the contents of the included decision justification documents.

In the first stage, each document was coded by the date of decision and the applicant pharmaceutical's subsidization status, name, route of administration, and medical condition(s) for which the applicant pharmaceutical was approved to treat.

The second stage, which was reiterated between two and four times per document, involved the classification of each document's arguments. A particular focus was the contents of the section of each decision justification document entitled 'Grounds for decision'.[22] Excerpts were tagged with descriptors such as 'serious condition of patients', 'no treatment alternative', and 'same price as already subsidized pharmaceutical'. These descriptors were coded and grouped thematically. For example: the category 'product variant' was created by combining tags about 'new route of administration', 'new formula', 'new strength', and 'new package size' (see p. 219 for an illustration).

substance(s) expires. When the patent(s) expires, the original pharmaceutical producer no longer has the sole right to produce and sell or license production for the active substance.

[21] The pharmaceuticals classified as 'approval of subsidy with restrictions' and 'denial of subsidy' are listed in Appendix A (section A2, p. 220).

[22] A more detailed overview of the contents of decision justification documents, and extended excerpts from two decision justification documents, can be found in Chapter 5 (see pp. 94-9 of this volume).

In the third stage, I organized groups of descriptors in relation to decision outcome. This grouping resulted in a characterization of arguments for decisions about 'reasonable' and 'unreasonable' drugs that is presented in greater detail in Chapter 5.

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What can my reading of LFN's decision justification documents say about how Agency's deals with ambiguity of knowledge? Following the ideas of Wittgenstein (1953) concerning the interpretability of text, I do not view documents in general, and LFN's decision justification documents in particular, as objective sources of truth about the processes they may describe. However, the documents *are* relevant in relation to their authorship and provenance (cf. Hammersley and Atkinson 1995). These are part of there contents, rather than a source of 'invisible' biases in the material (Merriam 1994, 118-9).

The decision justification documents in the outcome study were how the studied organization publicly justified these decision outcomes. In the present study, I use them to highlight types of justifications and characterizations of drugs that LFN needs to achieve in order to have 'justifiable' outcomes about 'reasonable' (or 'unreasonable') drugs. These findings form a basis for my second study, in which I followed two of LFN's decision-making processes.

Design and methodology of the 'process study'

In the outcome study, my focus was on how 'reasonable' drugs were characterized in the formal justifications of decisions. In the second study (henceforth also 'the process study'), I focused on the process leading up to the issuance of decision justification documents. I did this by following the on-going work to evaluate the subsidization status of pharmaceuticals in the two pilot cases of LFN's evaluation of the existing product assortment.[23] The two groups, comprising pharmaceuticals approved for treating migraine and stomach-acid

[23] As described further in Chapter 4, the Agency's formal task includes an evaluation of the subsidization status of those pharmaceuticals which were subsidized prior to LFN's inception. The initiation of this work was publicly announced in October 2003 (LFN 2003a).

disorder (henceforth 'the migraine group' and 'the stomach-acid group'), were initiated in October 2003. Through interviews with project members and members of the Agency Board, I followed the work within these two groups until their completion sixteen and twenty-seven months later, respectively.

Unlike the document-based outcome study, the process study involved negotiation of access and management of field relations over time. I found the negotiation of access to be an on-going process. As others have noted, it did not end with the formal approval of my undertaking the study, and had significant influence on how the study was designed and performed (Hammersley and Atkinson 1995). In the following discussion I will focus in particular on the consequences that negotiation of access and the management of field relations had on my choice of research methods and analytical focus.

A particularly influential event followed the Board of LFN having agreed in principle to take part in my study. This approval was a result of my having made written contact with LFN's Director-General and submitted a description of my study.[24] This project description, with minor changes, was then sent to the Chairman of the Board and to all Board members.[25] However, what my study entailed *in practice* became a matter for further debate. My intention had been to undertake interviews, and perhaps also take part as a participant observer at Board meetings. After a first set of interviews, project members in the migraine and stomach-acid group also suggested that I also take part in their internal meetings as a participant observer. However, my request to sit in on both Board meetings and project meetings was denied. In a telephone conversation with the Agency's chief counsel, it was explained that my participation could negatively influence the working environment for project members and potentially compromise classified company information.

One consequence of my failure to negotiate access was that I came to use interviews as my primary method for following the work in the migraine and

[24] For the project description (in Swedish), see Appendix A (section A1)

stomach-acid groups. A second consequence was that my analytical focus centered on efforts to deal with ambiguity between multiple sources of *measurements* of pharmaceuticals' characteristics and *classifications* of drugs properties. Had I undertaken participant observations of the Board's meetings, notably, the relevant analytical concepts would perhaps have been drawn more from theories about the development of consensus between experts (cf. discussion of 'controversy studies' on pp. 40-2 of this volume). As a consequence of using interviews, I came to focus more on the achievement of coherence between multiple sources of knowledge rather than consensus among multiple decision-making experts (see further discussion in *Comments on research design*, below).

Using interviews to study the two processes also had several methodological advantages, as compared to participant observation. Previous studies of organizational decision-making suggest that decision-making takes place in other settings than formal meetings (cf. Kingdon 1986). By interviewing project members and Board members over time, I could follow work that took place outside of meetings, and long before any formal decisions were made about drugs in the migraine and stomach-acid groups. In the next two sections, I discuss how I performed interviews and managed field relations.

Performing interviews

With whom?

A first issue was the identification and selection of informants. As I had chosen to limit my study to LFN and to the organization's two pilot projects of the product assortment review, there were a limited number of potential informants. The identification of potential informants was also simplified by circumstances surrounding LFN's product assortment review. When the two therapy groups were named as pilot project groups, three individuals from the

[25] It was further decided that any individual's participation was subject to personal consent. In the first contact with potential informants, the aforementioned project description and an introductory letter was sent together with the request for interview.

Agency were assigned as members of each project group (LFN 2003c, d). Information about current members of LFN's Board was also publicly available. One informant was also identified through a "snowball sample"; informants mentioned that they considered this individual to be relevant for me to talk to. The final selection of informants and, more importantly, the number of interviews performed with each informant, was determined by my analytical focus and theoretical interest in how organizations deal with ambiguity between multiple sources of knowledge:

Over the course of twenty-eight months, I performed fifty-seven interviews with twelve individuals: four members of the two pilot projects, six members of the Agency's Board and two employees of LFN (one of whom was the Agency's Director-General).[26] As my focus was on the on-going review of the migraine and stomach-acid groups, fourty-two of these interviews were performed with the project manager and health economist in the migraine and stomach-acid groups, respectively. I spoke with each of these individuals between nine and thirteen times from the initiation of the two groups in October 2003 until their completion in February 2005 (migraine) and January 2006 (stomach-acid).

Interview lasted between fourty-five and ninety minutes, with an average of approximately one hour. All interviews were recorded; the first seven with a tape recorder and the remainder with a digital voice recorder (except for one interview, where the digital recorder was unavailable). The interviews were subsequently transcribed by the author. Transcriptions were not verbatim and encompassed on average of 70% of the total interview time.

When?

It was my intention when planning the process study to perform multiple interviews with the same informants over time. This was also how I performed the study in practice. However, over time I changed *when* I spoke to informants. At the outset, I used a structured approach to scheduling interviews and spoke with informants after what I thought might be 'notable' events. For example, I

[26] For a list of informants (roles and names) and interview dates, see Appendix A (section A3).

interviewed project members at the start of the project, upon the formal appointment of seconded experts and in conjunction with the Board decision to proceed from an initial evaluation of the whole group of pharmaceuticals to an individual evaluation of specific drugs.[27] Over time, however, I developed a less rigid view of when it was relevant to speak with my informants. I found that the issues that I was interested in – how the project group dealt with ambiguous knowledge about pharmaceuticals' characteristics – were on-going concerns in the two projects over long periods of time.

How?

When performing interviews I sought to use a dialogue approach, based around on a semi-structured interview format with open-ended questions.[28] With the exception of two Board members, informants typically did not receive questions prior to interview – although certain questions were asked in repeated interviews.

My use of a less structured interview format was informed by previous studies which suggest that dialogue-styled interviews provide more relevant responses and improved cooperation from informants that are used to reasoning about and reflecting on their own activities (Zuckerman 1972; Aberbach et al. 1975; Melbourn 1979, 26-7).

The use of open-ended interview questions was also methodologically appropriate, since the two decision-making processes that I followed were not complete until the end of my study. Using semi-structured questions, which opened for discussions of a wide range of issues and activities, was a means of dealing with my own – and informants – lack of foresight. It was my experience that events gained relevance over time. For example, a Board meeting in June

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[27] The formal work plan for LFN's evaluation of the existing product assortment that was issued at the initation of the migraine and stomach-acid groups specified a two-state process. In Phase 1, the Agency was to evaluate characteristics of the entire group of pharmaceuticals. Provided that all of the drugs were *not* considered to be reasonable to approve subsidy without further investigation, a Phase 2 evaluation of individual pharmaceuticals' characteristics would be undertaken (LFN 2003b)

[28] For examples of interview questions, see Appendix A (section A3).

2005 *became* when an important principle position was formulated. This was important almost one year later when this principle was subsequently reversed towards the end of the stomach-acid group review. At the time of this meeting, informants had focused more on what were the *then* 'key issues'. While it was not always a successful strategy to use semi-structured interviews, as the previous example suggests, it was an attempt to take into consideration the chronology of the study.

My choice of interview questions was also informed by a desire to avoid rationalized answers about the informant's activities. Previous studies suggest that informants tend to to ascribe rationality to past events and actions (Merriam 1994). Since I was interested in situations where multiple sources of knowledge did not 'add up' to coherent characterizations of a drug's properties, the elicitation of rationalized accounts would have made it difficult to inquiry into how such ambiguity was dealt with. One strategy I employed was to ask informants to be specific when discussing activities in the two project groups, in order to avoid eliciting general opinions. I also made efforts to leave the causal analysis of events out of interviews, by asking questions about activities rather than explanations of events.

In addition to these considerations, I found it important to formulate 'appropriate' open-ended questions and follow-on questions. Since I talked with same informants over a longer period of time, I sought to perform 'ethnographically informed' interviews. This meant that I tried to be sensitive to how my position vis-à-vis informants developed over time. My experience for interviewing informants was that there was a certain acceptance of my ignorance. The position of "ignorant stranger" (Hammersley and Atkinson 1995) or "acceptable incompetent" (Lofland and Lofland 1995, 56) was mostly advantageous, since there also was a willingness to help me learn more about the matters I was asking about. However, informants' expectations about my knowledge increased over time. Towards the end of the two pilot projects, I was at times met with remarks such as "you know, that study". Implicitly, I was supposed to know these (by then) taken-for-granted references to various articles and other sources of knowledge about pharmaceuticals characteristics.

In certain cases, particularly when talking about health economic modeling, I struggled with the need to be 'smart enough'. To indicate a complete lack of understanding of certain basic health economic concepts would arguably have prevented my informants from talking about their work. Since it was in the details of constructing calculations that ambiguities between different sources were visible, this would have been problematic. Yet precisely because I wanted to elicite detailed accounts of this work, I could not appear to understand everything. My strategy was to initially mention that I was knowledgeable about certain concepts, and then test my understanding by asking questions about whether I had understood correctly after informants had spoken about their on-going work. My asking such 'clarification questions' elicited various responses, ranging from simple confirmations to further explanations.

Notwithstanding these efforts, the difficulty of maintaining analytical distance over time is well-known in ethnographic studies (cf. Grint and Woolgar 1997). In my study, this difficulty may have contributed to my being less sensitive to new instances of ambiguous knowledge, since I was familiar with 'how things were done' – and specifically which were the controversies about pharmaceuticals' characteristics.

Using open-ended questions also had disadvantages. Not defining the relevant or reasonable characteristics of pharmaceuticals ahead of time served as an important methodological tool for inquiring into *how* LFN sought to determine precisely these things. To have made assumptions about what was important and appropriate to consider would have limited the inquiry to whether the Agency adhered to these assumptions. However, the use of open-ended questions made it impossible to define the scope of my inquiry prior to undertaking the study. The use of open-ended questions also meant there were no pre-determined categories with which to organize informants. As will be discussed further, below, crafting a presentation and analysis of the empirical material was a time-consuming and iterative process.

Exiting the field

My exit from the field was less formalized than my entry. There was also a separation in time between when I stopped interviewing informants, and they were asked to review my written accounts of their activities.

The first stage of exit occurred soon after the completion of the each of the two pilot groups in February 2005 (migraine) and January 2006 (stomach-acid). "Final interviews" with informants were performed after the release of the decision justification documents and group reports, albeit with the caveat that additional contact was possible for the purpose of asking follow-up questions or requesting clarification.

A second stage of exit was based on my agreement with informants that they had the right to review accounts of their work, and comment on desired changes. This emic feedback was explicitly limited to the empirical accounts, and premised on the understanding that my informants could not be fully anonymous. There were few of them, and it was impossible to make the studied organization anonymous. Thus, while individual informants had given their 'informed consent' at the initiation of the process study, this consent was re-negotiated in practice when individuals read material that I had written about them. At no time were requests made for material changes. However, in the presentation of the process study, I have chosen to refer to informants by their formal position rather than by name.

As suggested by Merriam (1994, 178), my analysis was made subject to etic feedback by academic colleagues in seminars and through authoring and presenting various conference papers, working papers, and book chapters during the course of my research work (cf. Lagrelius and Sjögren 2004; Sjögren 2005, 2006; Sjögren and Helgesson forthcoming [2007])

Analysis: an iterative choreography

My analysis of material in the process study was an iterative process, which commenced long before the completion of either project group. This iteration

was, on the one hand, methodological. Which interview questions I posed, and what issues I focused on, changed over time in response to earlier interviews. The iteration was also analytical. In this, the study followed an abductive logic (Alvesson and Sköldberg 1994) where the empirical material developed in dialectic with an emerging conceptual framework.

An iterative analysis was in part a necessary consequence of my undertaking a study of a real-time process (as discussed in the previous section). In this, my lack of foresight in the research project mirrored the lack of foresight in the studied processes. In Chapter 6, where I present material from the process study, participants did not know from the outset about pharmaceuticals' characteristics; this was an outcome of the decision-making process. In a parallel argument: there was nothing inherently relevant in what my informants told me. Relevance was an outcome of a research process involving ordering work (cf. Law 1994).

That the present text reads as a linear and intentional account of the research process has presentational advantages, but does not account for the emergence of my analysis. Much effort went into choreographing the empirical account in Chapter 6. In this work, my efforts centered on organizing a plot with sequential and thematic coherence (Czarniawska 1998, 2; Janesick 2000, 389). When organizing informants' responses, I ordered them both chronologically and thematically. A first thematic organization centered on activities in the two processes, such as that the definition of treatment effect, or the delineation of comparable pharmaceuticals. A second thematic organization took its point of departure in the analytical concepts outlined in Chapter 2.

Comments on research design

The outcome and process studies have a common focus on LFN's efforts to determine whether pharmaceuticals' characteristics make them 'reasonable' to subsidize. Both studies also have ambiguity between multiple sources of knowledge about drugs' characteristics as a common focus. Methodologically, the interest in ambiguous knowledge led me to focus on instances of

controversy over knowledge claims when identifying and organizing my empirical material.

Controversy versus ambiguity

In both the outcome and process study, my focus was on instances where there was problematic incoherence between multiple sources of knowledge about pharmaceuticals' characteristics. Focusing on controversy has a long history in social studies of science and technology (Collins 1981). It is described as a useful methodological tool for visualization the construction of knowledge and the "interpretative flexibility" of facts (Pinch and Bijker 1984, 27).

Controversy, as treated in earlier studies of the social construction of knowledge (see pp. 40-2 of this volume), referred to disagreements over the truthfulness of a knowledge claim. Ambiguity, in the present study, refers to incoherence between multiple knowledge claims. Incoherence may not always be controversial. My focusing on controversy therefore has methodological advantages, but also limitations. It is questionable to what extent less controversial instances of ambiguity are included in the study. I have sought to address this problem with a comparative design in both studies. In certain cases, it was therefore possible to highlight a lack of controversy in one process, through a comparison with a visible controversy over incoherent sources of knowledge in another (for examples, see pp. 119-21, 162 of this volume)

Position in time and space

Where the outcome and process studies differ is in their position *in time* vis-à-vis the Agency's decision-making. The outcome study focuses on decisions that have been made already. The process study, in contrast, follows the work to make decisions. The shift in time between the two studies serves a methodological purpose:

The first study's analysis of the Agency's decision justification documents from a two-year time period is both temporally and spatially removed from the activities that the documents are said to account for. Using documents limits and standardizes the material included in the study. Notably, the potentially

'messy' process of determining pharmaceuticals' characteristics, making comparisons and authoring documents are invisible.

The second study, where I followed the work to make decisions in the two pilot projects of the Agency's product assortment review, is designed to be spatially and temporally closer to this 'mess'. My purpose in studying how LFN deals with ambiguous knowledge *over time* was to shift the focus away from a static view of both decision and knowledge as outcomes. However, the design limits the study to things that were important to informants at a *certain* time, in a specific situation (namely in interviews with the author). Matters which were not brought up in this setting are not present in the study.

The spatial and temporal distance to the decision-making processes which the use of interviews nevertheless entails has consequences for the kind of material included in the study and the analysis that I have been able to perform. In line with the previous discussion about consequences of my failure to negotiate access through participant observation, interviews gave limited insight into possible conflicts *within LFN*. Differences between members of the Board, or between Board and Bureau were seldom discussed. If and when such matters were brought up, these comments were heavily edited. More often than not, informants stated that their comments were personal and not something that I could include in my study. Whether there are power struggles within the Board is not something that I can discuss within the framework of the present study. As noted previously in this chapter, this aspect of the design of the process study is also a core reason for why it was less relevant to use theoretical concepts from the sociology of scientific knowledge (SSK) regarding the achievement of consensus among experts.

A further consequence of the outcome and process studies' design, specifically the delimitation to study LFN, is that there is no extensive consideration made of what happens *after* the Agency has made its decisions. The study's overarching focus on the decision-making process – from the perspective of a decision-making organization. A third study, in which I have analyzed the argumentation in four cases that were appealed to and ruled on by

the administrative courts, is not included in this book *in extenso*, although some findings will be discussed in Chapter 8 (see also Sjögren forthcoming [2006]).

Reflections on quality

The theoretical approach of this study would suggest that it is not possible or relevant to judge the quality of my research outcome without considering my research practice. Nor is it possible to objectively judge whether or not I have made a good account of LFN and its work. Any judgment of quality hinges on the extent to which I am deemed to have acted appropriately. Yet there are multiple sources of knowledge about what is 'good' research practice. I will endeavor to mediate between some of them.

One way to evaluate qualitative studies is to use three notions formulated within the natural sciences during the Enlightenment: validity, generalizability and reliability. Briefly, these concepts refer to whether the outcome of research work are representative for the phenomenon that has been studied and whether the same findings would result from others studying the same phenomenon – either in the specific setting or in other settings. The use of these measures for evaluating research within the social sciences has been frequently criticized. One general argument has been that the concepts do not provide a meaningful way to discuss whether or not a qualitative study offers a 'good' account since qualitative studies systematically fail to conform to these espoused ideals. The limited capacity for studies within the social sciences to conform to these ideals has been linked to *what* is studied (open systems) and *how* these inquiries are undertaken (inductively). My purpose here is not to engage in this long-standing debate. Rather, I conclude in line with Ratcliffe (1983) that *in practice* there is no universal way to achieve even the aforementioned ideals in the natural science. What is 'valid', notably, has varied over time; it "is not a commodity that can be purchased with techniques" (Brinberg and McGrath 1985, 13).

Social scientists have proposed numerous alternative criteria of 'good' research. Weber (1922 [1983]) suggests that research should be evaluated based

on its practicality; whether it is relevant and applicable in practice. This stands in contrast with Czarniawska's (1998) notion of 'good' research as defined also by the esthetics of narratives. This, in turn, differs from Brunsson's (1981) definition of 'good' research findings are those concepts that gain wide usage and are open for flexible interpretations in different settings, as defined by practitioners, on the one hand, and academic colleagues, on the other hand. Maxell (1996, 89-90) argues that a general principle to support a credible account is to be transparent and reflective with regard to one's own process. Informants are identified as one source of credibility. A complementary strategy to such emic reviews, suggested by Merriam (1994, 178), is to have colleagues undertake horizontal evaluations of work-in-progress.

A shared problem with applying the aforementioned criteria to the present study is that they all ascribe quality to research processes, rather than research outcomes. It is difficult to measure processes *ex post*. There is also a certain problem with time; whether research findings are practical, useful or flexible are difficult to judge at the time when findings are presented. I therefore note that the present research work was undertaken in an organized, academic setting where my work has been subject to various forms of formal and informal scrutiny. In addition, I have sought emic feedback on my work. In this chapter, I have described the design and execution of my two studies, and reflected on consequences of various methodological choices for my research process and its outcome. It is based on this procedural adequacy that I can claim to have made a substantively adequate account – as defined by multiple sources of knowledge about 'good' research.

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As a final comment on the design of the study, I will reflect on some consequences of moving away from what I in Chapter 2 referred to as behavioral decision theory's 'indifferent relativism' vis-à-vis knowledge – in particular scientific knowledge. This characterization was used to justify my introduction of conceptual tools from science and technology studies. However, I also noted that an indifferent relativism had the advantage of avoiding tricky questions about epistemology. Having stepped into such territory, it behooves me to

comment on some of these concerns. My point of departure in this discussion is Woolgar's (1988) characterization of three "methodological horrors", and his conclusion that research which takes an anti-essentialist view of knowledge must also reflect on the consequences of this approach for the outcome of research work.

Woolgar terms the three horrors of an anti-essentialist approach: inconcludability, indexicality and reflexivity (Ibid., 30-9). The first of these refer to the inconclusiveness of the relationship between representations and objects being represented. As exemplified by Garfinkel's (1967) 'breeching experiments', it is always possible to ask for additional clarification; each representation that may be evoked to clarify refers to and is explained by yet other representations. The second horror – indexicality – refers to the mutual interdependence between the representation and the object represented (Woolgar 1993, 33). Representations of any kind have meaning in relation to the activities in which they are situated. Thus, models of an empirical system based on different theories cannot be differentiated as more or less 'real' *on empirical grounds* (cf. Woolgar and Lynch 1990). The third horror – reflexivity – refers to the cross-reference between representation and knowledge about the object. The represented determines features of the representation, and the representation in turn determines features of the object being represented. Neither can be analyzed separate from the other.

The aforementioned problems are difficult to resolve in principle. But *in practice*, the concerns can be addressed by making visible the ordering work undertaken as part of the research process. Notably, the theoretical framing of the present study is an outcome of ordering work. From a starting point in behavioral studies of organizational decision-making, I have argued that the introduction of concepts from science and technology studies will allow for the contents of (scientific) knowledge claims to be treated analytically. In attempting to achieve coherence between these two approaches, the author notes that she has *calibrated* certain characteristics of STS to fit into a 'decision theory' format, and also *privileged* certain characteristics of decision theory, notably its terminology. This aligns with the primary purpose of the study: to

address a claimed gap in how behavioral theories of organizational decision-making treat ambiguity of knowledge. A possible alternative purpose – for example, to make STS studies more sensitive to the organizing and organization of knowledge construction processes – has been left aside as a consequence of how I have sought to achieve coherence between multiple sources of theory.

4. MONEY AND MEDICATION: PHARMACEUTICAL SUBSIDY IN SWEDEN

The development, production, distribution, and use of pharmaceuticals have been topics of considerable debate in recent years. One could say that the only small thing about prescription drugs is their physical size:

Pharmaceuticals embody big promises to individuals and societies of sought-after relief from the burdens of ill health.

Pharmaceuticals are also big business; developed and marketed by big corporations, for whom they generate substantial profits. One estimate of the global market for drugs in 2005 was 602 billion USD (approximately 472 billion Euro[29]), measured in volume of sales[30] (IMS Health 2006a). During the same year, the single largest selling drug in the world accounted for 12.9 billion USD in sales (approximately 10 billion Euro). The number of so-called 'blockbuster pharmaceuticals', with sales exceeding one billion-dollar per annum, was estimated at 94 in 2006 as compared with 36 in 2000 (IMS Health 2006b).

Conversely, pharmaceuticals constitute a sizeable cost for healthcare service financiers. In a recent report, the Organisation for Economic Co-

[29] For consistency rather than accuracy, all currency conversions are based on interbank rates from November 1 2006.

[30] The estimated sales figure includes direct and indirect pharmaceutical purchases of prescription and certain over-the-counter drugs from wholesalers and manufacturers, at manufacturer prices (IMS Health 2006a, b).

operation and Development (OECD) estimated that spending (in real prices) on prescription and over-the-corner pharmaceuticals in its member countries had increased by an average of 32% between 1998 and 2003 (OECD 2005, 74-6). In Sweden, statistics from *Socialstyrelsen* (the National Board on Health and Welfare) showed the annual costs for the public pharmaceutical subsidy rising between 0 and 14% per year between 1986 and 2004, with an average annual increase of 5% (Socialstyrelsen 2005, 14). The cost of pharmaceuticals as a percentage of total healthcare expenditure also rose from just over 8% in 1990 to 13.4% in 2004 (Socialstyrelse 1995; Socialstyrelsen 2006, 11)

Concern expressed over increased pharmaceutical spending has fuelled debates about *who* should receive *what* pharmaceutical treatment, at *which* cost and *whose* expense. Taken together, the aforementioned questions assume an air of being "the Ultimate Question[s] of Life, the Universe and Everything" (Adams 1982). Even with a more modest view, the ethical and financial stakes involved in deciding these matters are considerable.

Various solutions have been proposed to manage access to pharmaceutical treatment, and increase control of pharmaceutical spending. One initiative, which has been adopted in several countries with publicly financed healthcare services, has been the creation of healthcare technology assessment organizations (see examples in Jost 2005). LFN is one example of such an organization.

In the remainder of this chapter, I will situate my study of the Pharmaceutical Benefits Board. In the next two sections I will give some background on the public pharmaceutical benefits scheme in Sweden, and describe where decisions are made about pharmaceutical use in a Swedish context. The following sections will describe the creation of LFN, its governing legislation and organizational structure.

From 1955 to today: a brief history of pharmaceutical benefits in Sweden

Sweden provides its residents with a comprehensive, publicly financed system of health insurance. Since 1955, this health insurance coverage has included a pharmaceutical benefits scheme. Before then, the financing of out-patient prescription medication was largely a private concern. While the state regulated the pricing of drugs, it did so as a third party. Today, the state has a significant fiscal responsibility for prescription pharmaceutical use. In 2004, the annual cost of the public pharmaceutical benefits scheme was approximately 18.5 billion SEK (approximately 2 billion Euro).

The public pharmaceutical benefits scheme, and the social insurance system as a whole, is designed to minimize private expenses in connection with illness. In the current scheme, a patient pays the full cost of prescription pharmaceuticals up to 900 SEK (approximately 98 Euro).[31] A graduated subsidy then reduces the patient's direct cost for prescription medication so that (s)he never pays more than 1800 SEK (approximately 195 Euro) in a twelve-month period. When a patient has paid this maximum amount, a free pass is issued which exempts him/her from further costs for prescription drugs during the remainder of the twelve-month period. The cost of the pharmaceutical subsidy is billed to patients' resident county council by the state-owned National Corporation of Swedish Pharmacies (henceforth Apoteket), which holds a legally sanctioned monopoly on the distribution of pharmaceuticals in Sweden.

The current pharmaceutical benefits scheme differs from that originally introduced in 1955 in several ways.[32] An aspect that has varied over time, and which is of importance to the studied organization's task of determining the subsidization status of drugs, is on what basis prescription pharmaceuticals

[31] All over-the-counter medications are paid for by the individual patient, unless they are provided on a prescription basis under conditions outlined in the Act (SFS 2002:160) on Pharmaceutical Benefits, section 18.

[32] Aspects of the public pharmaceutical benefits scheme that have varied over time, but which will not be a focus in this study, include: *who* is provided with subsidized pharmaceuticals; *what level* of subsidy is offered; and *where* the fiscal responsibility for subsidy is placed.

have been included or excluded from the pharmaceutical benefits scheme. Initially, the subsidization of a drug was determined by the medical condition(s) it was approved to treat. *Medicinalstyrelsen*, a precursor to the National Board of Health and Welfare, was responsible for deciding which medical conditions should be granted subsidized pharmaceutical treatment. Whether an individual patient's pharmaceutical use was subsidized then depended on the diagnosis set by the treating medical professional. The diagnosis-based system for deciding subsidy was later abandoned in favor of a product-based system, which was in place at the time of LFN's creation. The overarching principle of a product-based system is that subsidy is decided by product: either a pharmaceutical is approved subsidy or it is not. Although the Agency has the discretionary right to limit subsidy of a drug to particular forms of use (Act (SFS 2002:160) on Pharmaceutical Benefits, section 11), LFN is only supposed to use this right restrictively (The New Pharmaceutical Benefits Bill 2001, 37, 39).

A second aspect of the pharmaceutical benefits scheme which has varied over time is which party has determined the subsidization status of pharmaceuticals. Most recently prior to the creation of LFN in October 2002, a drug was included in the pharmaceutical benefits scheme once an application for price had been approved by *Rikförsäkringsverket* (the National Social Insurance Board). However, according to the legislative bill submitted to Parliament prior to the passage of the law creating LFN, the mandate of the National Social Insurance Board was to set prices, not undertake systematic evaluations of drugs' subsidization status (The New Pharmaceutical Benefits Bill 2001, 28-9). This meant that prescription pharmaceutical were "automatically"approved subsidy (Ibid.). Since the creation of LFN, a pharmaceutical is not subsidized unless it has been approved subsidy by the Agency. However, although LFN decides the subsidization status of drugs, there are many other parties that make decisions about prescription pharmaceuticals' use and financing.

Decision-making about pharmaceutical use

For a prescription pharmaceutical to be legally available for use in Sweden, it must have been granted marketing authorization by the Medical Products Agency (MPA), a Swedish governmental agency under the aegis of the Ministry of Health and Social Affairs, or the European Medicines Agency (EMEA).[33] An important criterion for granting a pharmaceutical marketing authorization is that the treatment benefits of the drug stand in reasonable proportion to the side-effects of treatment.[34] When the MPA (or EMEA) authorizes the use of a pharmaceutical, the conditions for marketing authorization are set out in the drug's Summary of Product Characteristics (SPC). The SPC is an official documentation of the product's properties. It includes information such as which medical conditions a drug is approved to treat, and the pharmaceutical's approved treatment dosages. The SPC is issued in conjunction with approval of marketing authorization, and can be updated over time.

Once a pharmaceutical has been approved marketing authorization for use in Sweden, it can be prescribed to patients by medical practitioners. For the drug to be available *with subsidy*, however, an application for subsidy must be submitted to LFN for consideration. There is no requirement that a pharmaceutical with marketing approval be evaluated by the Agency; the approval of marketing authorization is separate from the approval of subsidy.

There is a similar separation between LFN's evaluation of a pharmaceutical's subsidization status and the prescription of a drug in medical practice. This separation is both organizational and financial. The Agency is not responsible for providing patients with pharmaceutical-based treatment. Nor

[33] Marketing authorization is needed when a new pharmaceutical is introduced. Applications for marketing authorization must also be submitted if changes are desired in the SPC of authorized drugs, such as the inclusion of a new approved treatment area or a change in treatment dosage (Medical Products Agency 2005).

[34] In certain cases, a pharmaceutical may not be approved *general* marketing authorization and instead be granted licensed approval. More information about licensed approval can be found in Chapter 6 (see p. 96 of this volume).

does LFN have budgetary responsibility for pharmaceutical spending. Both of these matters are the responsibility of the regional county councils.[35]

At the county council level, there are various initiatives to influence which pharmaceuticals are prescribed by medical practitioners. By law, every county council is required to have a so-called pharmaceutical committee (Act (SFS 1996:1157) on Pharmaceutical Committees). The pharmaceutical committee is tasked with providing local recommendations to medical practitioner about which pharmaceuticals they should prescribe in order to ensure a "dependable and rational pharmaceutical use" (Ibid., section 3). In the capital city of Stockholm, for example, the County Council Pharmaceutical Committee issues lists of recommended drugs for treating common medical conditions to both medical practitioners and patients (Stockholms läns landsting 2006).

However, the choice of pharmaceutical treatment for an individual patient is made by his/her treating medical practitioner. Legislation grants licensed medical practitioners, in particular physicians, significant autonomy regarding treatment choice. The Healthcare and Work Act (SFS 1998:531) grants a medical professional the right to "free prescription". That is to say, (s)he can prescribe any pharmaceutical treatment that (s)he sees fit, provided that it is based on "scientific findings and clinical practice" (SOU 1999, 10). The right to free prescription allows healthcare practitioners to prescribe pharmaceuticals for medical conditions other than those for which a drug has received marketing authorization, and in other dosages than those approved by the MPA or recommended by manufacturers or third parties. Prescription which differs from the conditions of marketing authorization for a drug is referred to as *off-label prescription*.

When a medical practitioner prescribes a pharmaceutical to an individual patient, it is in certain cases also possible for him/her to decide whether the

[35] The twenty-one county councils finance the majority of healthcare services directly through an income tax levied on all county residents who are in paid employment. A majority of healthcare services are also provided directly by the county council. Privately owned and operated healthcare service providers can also be awarded contracts for service provision, but these

patient should receive the drug with subsidy by indicating this on the prescription form. Provided that the pharmaceutical in question has been approved for subsidy by LFN (with or without explicit restrictions), then the patient will receive this drug with subsidy when the prescription is filled. If the prescription form is not marked in this way, then the patient must pay the full cost of the pharmaceutical out-of-pocket. Equally, if LFN has denied subsidy for a particular drug, then this is coded into Apoteket's product database. Patients holding prescriptions for drugs that have been denied subsidy must then pay the full cost themselves – even if their prescription indicates that they should have subsidized treatment. Apoteket does not oversee or enforce compliance with the restrictions set by LFN for the subsidization of certain drugs. Whether a patient fulfills the explicit restrictions for subsidy set out by LFN is not evaluated by Apoteket's personnel.

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LFN is one of many organizations in the healthcare sector that makes decisions about pharmaceutical use. Specifically, the creation of LFN is the most recent reform of the pharmaceutical benefits scheme. The scope of this reform, and the Agency's mandate and organization, are discussed in the next section.

New legislation and a new organization

The Swedish parliament passed the Act (SFS 2002:160) on Pharmaceutical Benefits into law on December 13 2001. This new legislation led to the creation of LFN, which began its operations on October 1 2002. The task of this new organization was to decide which prescription drugs should be included in the public pharmaceutical benefits scheme.

LFN's creation followed long-standing debates about problems attributed to increases in pharmaceutical spending (SOU 2000, 13). A few months before the Act creating LFN was passed into law, the Cabinet had taken the widely publicized – and subsequently also heavily criticized – decision to exclude two

services remain publicly funded (Government Offices of Sweden, Organisation and resources of

pharmaceuticals from the public pharmaceutical benefits system. The two drugs were Viagra, a pharmaceutical approved for treatment of male impotence, and Xenical, a drug approved for treatment of obesity (see Junker 2003 for a more detailed account). This unprecedented decision on the part of the Cabinet was justified on the grounds that the two drugs were being prescribed inappropriately in large volumes by medical practitioners. Patients who wished to continue to have their use of these pharmaceuticals subsidized were required to submit applications for exemption to the Cabinet for consideration. The exclusion of the two drugs from subsidy was subsequently reversed, in part due to practical and administrative difficulties with managing the many applications for exemption. Concurrently, legislation was passed that created LFN.

According to the New Pharmaceutical Benefits Bill (2001), submitted to Parliament prior to the passage of this new legislation, the primary purpose with creating LFN was to change the existing practice of "automatically" subsidizing all prescription pharmaceuticals with marketing authorization (Ibid., 1). A systematic oversight of drugs' subsidization status, undertaken by experts, was intended to improve the efficiency of resource use in the healthcare sector. In particular, the introduction of economic efficiency criteria for evaluating pharmaceuticals' subsidization status was a necessary step to realize the goal of "ensur[ing] a rational and cost effective public use of medicinal products" (Ordinance 2002:719, section 1). By law, LFN is to approve subsidy for those pharmaceuticals where:

> [T]he cost of using the pharmaceutical ... is reasonable from medical, humanitarian and socio-economic perspectives
>
> [and] there are no other available drugs or treatment methods which ... can be judged as significantly more suitable for the purpose

If the criteria for subsidy are fulfilled, then LFN should approve subsidy without restrictions.[36] If a drug does not fulfill the decision criteria, the Agency should

the health service, 2005).

[36] Subsidy 'without restrictions' is something of a misnomer, since there *are* restrictions on subsidization of such drugs. Specifically, a pharmaceutical is only supposed to be subsidized for treatment of medical conditions for which it has been approved by the Medical Products Agency

deny subsidy for the drug in question. A denial of subsidy means that there are no exceptions for when subsidy is allowed; all out-patient treatment using the pharmaceutical must be paid by the patient. A third alternative is for the Agency to approve subsidy for restricted uses of the drug. Which restrictions can be set is discretionary: LFN can "under particular circumstances" (Act (SFS 2002:160) on Pharmaceutical Benefits, section 11) choose to include a pharmaceutical in the public benefit for certain areas of use. However, as mentioned earlier in this chapter, LFN is explicitly instructed to be restrictive in doing so, in order to uphold the principle of a product-based subsidization system.

LFN evaluates the subsidization of two kinds of pharmaceuticals: those granted marketing authorization after the inception of LFN, and those drugs (more than 2000 in total) that were included in the public pharmaceutical benefits scheme prior to LFN's creation. Although the criteria for subsidy are the same for both kinds of pharmaceuticals, there are different requirements as to when the Agency reach a conclusion about their subsidization status.

In the case of pharmaceuticals that have received marketing authorization after the Agency's creation, this time period is 180 days from the time an application for subsidy is submitted (Ordinance 2002:687, section 9). These drugs can only be prescribed without subsidy until LFN has reached a conclusion about their subsidization status. As regards the pharmaceuticals which were subsidized prior to the Agency's creation, they remain subsidized until the Agency has reviewed their subsidization status. LFN initiated its first reviews of these drugs in October 2003. In its annual report for 2005, LFN tentatively predicted that the entire product assortment review would be completed in 2009/2010 (LFN 2006d, 25).

Once LFN has made a decision about a pharmaceutical's future subsidization status, the law grants the pharmaceutical company marketing the

(MPA). In LFN's first two decision justification documents, the Agency clarified this interpretation of its governing legislation when it denied subsidy for two pharmaceuticals on the grounds that the applications for subsidy concerned usage which was not approved by the MPA (Autonativ 2003-01-30, Robinul 2003-01-30).

drug in question the right to appeal the decision to the administrative courts within three weeks (Ordinance 2002:687, section 20). In the first instance, the decision can be appealed to the Stockholm County Administrative Court (henceforth also referred to as 'the lower court'). A decision by the lower court can subsequently be appealed to the Stockholm Court of Appeals ('the appellant court') and then, if right of appeal is granted, to the Supreme Administrative Court ('the highest court'). The courts have the mandate to judge whether LFN has acted in accordance with its governing legislation when making decisions about pharmaceuticals' subsidization status. But what does that mean?

The Agency is instructed to approve subsidy when a pharmaceuticals' medical, humanitarian and socio-economic characteristics are 'reasonable'. However, the law does not specify what characterizes a 'reasonable' drug. In particular, there is no exact description of what characteristics take 'medical, humanitarian or socio-economic perspectives' into consideration.

Some clarification is provided in the legislative bill submitted to Parliament. However, this document repeatedly states that imprecise instructions are necessary because of the Agency's new and complicated task (The New Pharmaceutical Benefits Bill 2001, 43, 47). LFN is explicitly given the job of building practice as it gains greater experience (Ibid., 36, 39, 43, 47).

When building practice, LFN is instructed to adopt "a broad approach" (Ibid., 46), and take into consideration the three principles of priority-setting that were approved by Parliament in 1997 (Ibid., 26, 44), namely:

1. Equal human value: all people have an equal right to life and health
2. Need solidarity: those with greatest need of treatment should have priority over those with lesser need
3. Cost-effectiveness: the benefit of treatment must be reasonable in relation to the cost of treatment

Please note that I will refer to all decision justification documents by the name of the drug and the date of the decision. For all referenced justification documents, see p. 216 of this volume.

As in the case of the criteria for subsidy, there are no detailed instructions about what it means in practice to take into consideration the aforementioned principles. However, the Agency is encouraged to use health economic techniques for evaluating drugs since:

> Increasingly health economic analyses are used to evaluate whether a treatment can be considered cost-effectiven. This scientific discipline is still developing. However, the development is dynamic and there is reason to assume that health economic analyses can increasingly constitute a valuable decision tool for the Board (Ibid., 46).

As efforts to calculate cost-effectiveness will be one focus in the forthcoming presentation of the process study in Chapter 6, the next section gives a short introduction to health economics techniques for evaluating pharmaceuticals.

Health economics at a glance[37]

LFN is encouraged to use health economic techniques to evaluate drugs' cost-effectiveness, and instructed to evalaute whether a pharmaceutical has a 'reasonable' cost of use from a 'socio-economic perspective'. This codification of a health economic perspective in healthcare policy is a new phenomenon in Sweden. Even in a broader perspective, the use of health economics has grown from modest beginnings some 30-40 years ago to become increasingly entrenched into healthcare policy-making.

The various tools developed for health economic evaluations are typically policy oriented, and are often presented as methods to assist decision-making within health care. One fairly simple technique is to compare the costs of different treatments that are seen to produce identical effects. A so-called cost-minimization analysis answers the question of what is the less costly treatment for gaining a given effect. This evaluation relies on both the measurement of treatment effect, and the equivalence of the compared drugs as regards this measurement, having already been established in some way, for example through clinical trials. The technique makes rather narrow comparisons. It can,

[37] The section is based on material in (Sjögren and Helgesson forthcoming [2007]).

at most, differentiate between the costs of using pharmaceuticals that have identical treatment effects.

Several other techniques can go beyond differentiating between the cost of treatments with identical treatment effects. A cost-effectiveness analysis, for instance, compares the cost per effect of treatments using a common scale for measuring treatment effect. Then it is possible to determine which of the compared treatments has the lowest cost per defined effect unit. This is *the* cost-effective treatment. Like the aforementioned cost-minimization analysis, a cost-effectiveness analysis can be used to compare different treatments that from a clinical perspective are deemed similar, and used for treating the same medical condition. However, a cost-effectiveness analysis can also be used for comparing treatments of different medical conditions – provided the treatment effects are expressed using the same scale (cf. SOU 2000, 82-3). If the effectof a kidney transplantation and a heart surgery are both expressed in terms of *life-years saved,* they are comparable.[38]

Quality-adjusted life-year (QALY), is a unit of measurement created within health economics to further extend the ability to forge comparisons between medically disparate treatments. Coined in the 1970s, but with a genealogy stretching further back, this metric embodies the idea of having a unit of measurement that allows for comparison among very different treatments (Drummond et al. 1997). The core idea is to take into consideration the effect of treatment in terms of both life *quantity* and life *quality*. A critical step in calculating QALY is to rank different states of health and illness from a scale of 0 (defined as death) and 1 (defined as perfect health).[39] Having made a ranking of different states of health and illness, it is possible to compare treatments

[38] Example from Drummond et al. 1997, 13.

[39] An illustrative example: being severely depressed might be given a QALY value of 0.6. A one-time treatment which removed this depression and made the individual otherwise perfectly healthy, would have a positive effect of 0.4 QALY (the difference of moving from 0.6 to 1). If this treatment cost €500, the cost per QALY would be the cost of the treatment, divided by the increase in QALY for the patient's remaining life expectancy (=€500/(0.4 QALY*remaining life years)). For a further elaboration of QALYs and how they are assessed, see (Drummond et al. 1997) or the discussion in chapter 5 of (Ashmore, Mulkay, and Pinch 1989).

which are considered very different in medical terms using this standardized metric.

The vantage point of a QALY-based calculation is therefore broader than a comparison based on medical effect measurements, since the former is not limited to comparing treatments of patients with the same medical condition. A cost-effectiveness calculation using QALYs can render comparable treatments that in clinical practice are not classified as comparable. Treatments which are different in the clinical sense can (in theory) be equivalent in terms of cost per QALY. This way of measuring similarity and difference opens for intervention in medical practice based on 'non-medical' characterizations of pharmaceuticals.[40]

LFN: Organization and outcomes

The LFN is made up of two parts: the Board and the Bureau. These two entities have different structures, members and formal roles.

The Board formally makes decisions about pharmaceuticals' subsidization status. It has eleven members appointed by the Government on personal mandates.[41] The selection of Board members is supposed to be done in such a manner that their combined expertise reflects different interest groups within the healthcare sector (Ordinance 2002:719, section 8). Present members include practicing general physicians, health economists, medical specialists, a medical ethisist, individuals with experience from patient organizations and county council health administrators.

The Bureau, meanwhile, undertakes evaluations of pharmaceuticals to support the Board in its decision-making. These evaluations are made in accordance with the Board's instructions, and the results are presented to the Board for consideration. The Bureau also authors the decision justification

[40] The use of health economics, in general, and QALY, in particular, has been extensively debated. For a discussion 'from within', see (Nord 1999). For an external critique, see for example (Nussbaum and Sen 1993).

[41] This means that the Board members do not formally represent any organization, professional group or political party.

documents which justify the Board's decision outcomes.[42] The Bureau employs approximately thirty individuals, many of whom hold doctorates in pharmacy or health economics.

The annual budget in 2005 for LFN as a whole was approximately 55 million SEK (approximately 6 million Euro). As mentioned earlier, the organization has no financial responsibility for pharmaceutical spending. Nor is LFN instructed to fulfill specific targets as regards changing the level of pharmaceutical spending.

Sweden in an international comparison

Thus far in this chapter, I have situated LFN in the Swedish healthcare system. In this section, I briefly compare the Swedish system with how other countries' regulate pharmaceutical subsidy. This comparison is by no means exhaustive, but rather illustrative of how a common concern with controlling pharmaceutical spending has been dealt with in a variety of ways.

Swedish healthcare sector has undergone many reforms in recent decades. Many of these reforms were inspired by ideas about introducing particular forms of business-like practices in public organizations as a way of making resource allocation more efficient (Forssell and Jansson 2000; Hood 1995). The creation of LFN can be seen to address a further question of who should have access to what treatment *at whose cost*. To systematically evaluate the public financial responsibility for healthcare services and use this as a means to control access to treatment is a relatively recent phenomenon in Sweden.[43] Several other countries with publicly financed healthcare systems – such as Great Britain, Italy, Australia and New Zealand – have central organizations which undertake evaluations of pharmaceuticals' subsidization status. These organizations have similar, but not identical, mandates to LFN.

[42] Information about decision justification documents can be found in Chapter 5 (pp. 94-9).

[43] Until recently, a lack of treatment options rather than a lack of economic resources has been described as the primary bottle neck in many areas of the healthcare sector (Granqvist 1990).

A Swedish public inqiry undertaken prior to the creation of LFN highlighted differences and similarities in: how evaluations were organized; the level of fiscal responsibility given to the evaluating organizations, particularly as regards budgetary control of pharmaceutical spending; the scope of evaluation; the status of decisions about coverage; and the means of overseeing and enforcing compliance with the evaluating organization's conclusions (cf. SOU 2000, 117-43). A more recent comparison of eight countries, including Great Britain, Germany, the Netherlands, Australia and USA points to considerable variation in how healthcare coverage – including pharmaceutical reimbursement – is determined (Jost 2005). The study concludes that while *the principle* of increasing the efficiency of resource allocation and securing quality of services is shared, there is considerable variation as to how this principle is sought in practice.[44]

How is the Swedish system for regulating pharmaceutical subsidy similar to or different from that of other countries? One point of similarity is the separation between decisions about subsidy and budgetary responsibility for pharmaceutical spending. LFN is responsible for decisions related to pharmaceuticals' subsidization status, but has no budgetary responsibility for pharmaceutical spending. Nor is LFN instructed to take budget restrictions into consideration when deciding whether a pharmaceutical fulfils the criteria for subsidy. This appears fairly common in an international comparison (Jost 2005). In the Netherlands, for example, it is the Ministry of Health, Welfare and Sport that makes the final decision as regards a drug's subsidization status, based on advice from expert bodies (Carino and Rutten 2005, 146). One exception to this separation between coverage decisions and budgetary responsible is New Zealand, where the organization that decides pharmaceuticals' subsidy (The Pharmaceutical Management Agency,

[44] Early studies of attempts to implement explicit controls on treatment access in other courties – particularly in publicly funded healthcare systems – similarly suggest that principle agreement about the advantages of systematic evaluation of treatment content and regulation of treatment access is not matched by shared views on *who* should do this and *how* it should be done *in practice*. In particular, studies note consistent problems in achieving acceptance for and compliance to explicit restrictions (see Ham 1997; Sassi 2002; Ham and Robert 2003).

PHARMAC) is also fiscally responsible for these decisions, since it manages the purchasing of hospital pharmaceuticals on behalf of District Health Boards (PHARMAC 2006a). In other words, an additional criterion for approving subsidy for a drug is that its decisions can be met within the given budget restriction (PHARMAC 2006b). Combining decision-making about pharmaceutical coverage with budgetary responsibility for pharmaceutical spending is also done in the United States, where private insurance companies both determine coverage and pay for treatment.

Where LFN differs from many other organizations with similar tasks is in the breadth of evaluatory scope. LFN is instructed to take a broad, 'societal' view when evaluating drugs' characteristics. This contrasts with organizations such as the British National Institute of Clinical Excellence (NICE), which is instructed to consider pharmaceuticals' costs and effects from the perspective of the National Health Service, NHS (SOU 2000, 133). Other consequences, such as costs for geriatric care or untreated patients' productivity loss, are not included in these organizations' evaluations.

LFN's broad scope is reflected in the composition of the Agency's Board. Members include medical specialists, health economists, county council senior civil servants and individuals with experience from patient organizations. Many organizations are primarily concerned with the *medical* effectiveness of pharmaceuticals: "whether the technology in fact works, or, in some countries, whether it is more effective than existing technologies available to the same patients" (Jost 2005, 257). LFN, as well as the aforementioned NICE, are formally required to consider both medical *and* economic characteristics of pharmaceuticals. Only in a few cases, notably Australia, is there a strict application of cost-effectiveness (SOU 2000, 138).

Another source of variation between organizations is in the status of their decisions, and how compliance is overseen and enforced. Unlike many other organizations (such as British NICE), LFN's outcomes are not recommendations. Notably, when the Agency denies a pharmaceutical subsidy then this outcome is coded into the product database of Apoteket. As Apoteket holds a monopoly on pharmaceutical distribution in Sweden, this means that

patients cannot receive the drug without paying for it, even if (s)he holds a prescription stating otherwise. However, there is no similar system for overseeing compliance with the restrictions implicit or explicit in LFN's approval of subsidy. Many other countries review prescription behavior at the level of individual medical practitioners. This is not done in Sweden (cf. SOU 2000, 20).

Taken together, it is difficult to draw any general conclusions about how the regulation of pharmaceutical subsidy is organized in various countries. LFN is both similar to and different from how other countries (through different organizational constellations) determine which pharmaceuticals are included in reimbursement systems. However, it is not *the organization* of LFN that is the topic of the present study. It is how the Agency goes about making decisions about pharmaceutical study *in practice*. In this chapter, I have described LFN as one of many organizations that makes decisions about pharmaceutical use and financing in Sweden. However, the Agency's specific mandate – to systematically evaluate the subsidization status of prescription pharmaceuticals drugs – is new in the Swedish context, as is the explicit instruction to consider a 'socio-economic perspective' of pharmaceutical use. LFN's new task has been a justification for giving the organization a broad mandate to develop practice. It is to this practice that I turn in the next chapter (Chapter 5), and present findings from the outcome study in order to answer the question: what characterizes a 'reasonable' drug?

5. WHAT IS A 'REASONABLE' DRUG? A LOOK AT DECISION JUSTIFICATIONS

How does LFN know whether a drug should be subsidized? The Agency's governing legislation does not specify in detail what it means for a pharmaceutical to have a "reasonable cost ... from medical, humanitarian and socio-economic perspectives" (Act (SFS 2002:160) on Pharmaceutical Benefits etc, section 15). As mentioned previously, this is left to LFN to determine as it "develops practice" (The New Pharmaceutical Benefits Bill 2001, 47).

In this chapter, I will focus on LFN's 'developed practice' – as expressed in the decision justification documents issued by the Agency during its first two years of operations.[45] An analysis of the contents of these documents informs a discussion of how LFN characterizes a drug as 'reasonable'[46] or 'unreasonable' to subsidize. Since LFN's governing legislation places the onus on the Agency to make decisions that can be justified as being in accordance with the governing legislation, the chapter also gives a characterization of what constitutes 'decision-able' justifications (as expressed in these documents).

Before I go on to discuss in greater detail the arguments used by LFN to justify approval or denial of subsidy, I will give an overview of the documents

[45] See Chapter 3 (pp. 56-9 of this volume) for a more detailed description of how the study was performed.

[46] The reader is reminded that I use the term 'reasonable' in reference to the wording of the decision criteria for subsidy set out in LFN's governing legislation.

included in the study and also consider two examples of decision justification documents. These examples are illustrative of what a 'decision justification document' is. Both the overview and the examples are intended to provide a background to the subsequent thematic discussion of arguments used by LFN to justify different outcomes about pharmaceutical subsidy.

Decision justification documents: overview and examples

LFN issued ninety-four decision justification documents (henceforth also 'decision documents' or 'justification documents') concerning individual prescription pharmaceuticals during its first two years of operations.

A clear majority of these documents (sixty-seven, or approximately 70%) involved the approval of subsidy. An addition thirteen documents (approximately 14%) approved subsidy *for restricted uses* of the pharmaceutical in question.[47] The remaining fourteen documents (approximately 15%) denied the applicant pharmaceutical subsidy.[48] In two cases, which I discuss in greater detail later in the chapter, LFN first denied subsidy and subsequently reversed this decision and approved subsidy for both drugs.

The distribution of outcomes for LFN's first two years is summarized in Diagram 3 and Table 1, below. In the interest of comparison, I have included all decision justification documents concerning individual pharmaceuticals issued by the Agency prior to November 2 2006.

[47] See Chapter 3 (p. 58) for a discussion about my classification of these documents.

[48] These documents concerned a total of twelve pharmaceuticals. In the case of two drugs, the Agency twice denied them subsidy (Xyzal 2004-09-02, 2004-11-09; Levitra 2004-04-13, 2004-09-01).

As noted previously, I refer to all decision justification documents by the name of the drug and the date of the decision. For all referenced decision justification documents, see p. 226 of this volume.

***Diagram 3**: Distribution of decision outcomes per year (# of documents)*

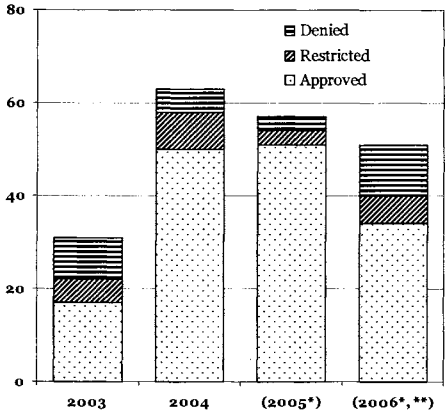


***Table 1**: Distribution of outcomes per year (%)*

	Approved subsidy (%)	Restricted subsidy	Denied subsidy
2003	55%	16%	29%
2004	79%	13%	8%
(2005*)	89%	5%	5%
(2006*,**)	67%	12%	22%
Total	**75%**	**11%**	**14%**

** According to classification on LFN homepage, ** Until of November 2 2006*

In addition to the variation in outcome, the justification documents concerned pharmaceuticals' approved for treatment of a variety of medical conditions. The most common *specific* medical conditions included: erectile dysfunction/male impotence (6 documents[49]), HIV (5) and diabetes (4). Other recurrent medical conditions included Parkinson's disease (3 documents), in-vitro fertilization treatment (3) and asthma (3). The Agency also evaluated pharmaceuticals approved for treatment for various kinds of cancer (6 documents), several antibiotics (5) and a variety of cardiovascular conditions such as high blood pressure and high cholesterol.

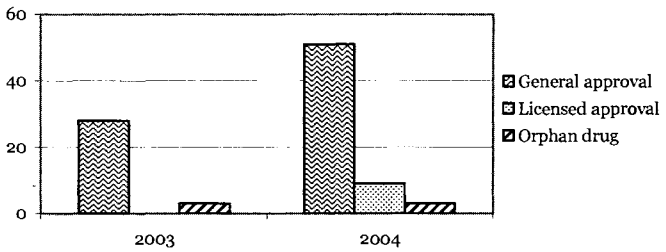
[49] The six documents concerned five pharmaceuticals. One drug was evaluated twice within the studied time period (Levitra 2004-04-06, 2004-09-01)

The ninety-four decision justification documents also varied as regard the market status of the evaluated pharmaceuticals. A majority of the drugs had been approved general marketing authorization by the Medical Products Agency (or its European equivalent, EMEA). A few drugs were also available on licensed prescription. Licensed pharmaceuticals are drugs which have been denied general marketing authorization. This can happen if a drug has considerable side effects of treatment. In such cases, the pharmaceutical can still be available for prescription, subject to the Medical Products Agency's approval of its use in individual cases (Medical Products Agency 2005).

In addition to licensed drugs, LFN also evaluated the subsidization status of a smaller number of so-called orphan drugs. Orphan drugs are pharmaceuticals used in the treatment of rare diseases. Legislation in many countries grants orphan drugs special status in order to encourage research and development. Sweden, as a member of the European Union, has regulation that places lower requirements on the scope and contents of clinical trials concerning orphan drugs than for other medications (Regulation (EC) No 141/2000).

During the studied time period, LFN issued six decisions documents concerning the subsidization status of orphan drugs (approximately 6%) and nine concerning licensed pharmaceuticals (approximately 10%, see Diagram 4)

***Diagram 4**: Market status of pharmaceuticals evaluated by LFN 2002-2004 (# of documents)*



Although the decision justification documents also varied as regards their contents, they typically had a common structure.

Each document included an introduction of the case – the pharmaceutical under evaluation, the application terms put forth by the pharmaceutical company – and a presentation of the Agency's evaluation findings. Every decision justification document also included a specific section with the grounds for LFN's conclusions as regards the drug's subsidization status (in bold, see Table 2).

***Table 2**: Structure of decision justification documents*

Heading		**Contents**
Swedish	*English*	
Saken	Case	The matter at hand, typically "Application concerning pharmaceutical benefits scheme"
Beslut	Outcome	Summary of subsidization status and pharmaceutical price
Ansökan	Application	Summary of application for subsidy, including treatment areas and proposed pharmaceutical price
Utredning i ärendet	Inquiry into case	Summary of LFN's evaluation
Skäl till beslut	**Grounds for decision**	**Reasons for LFN's conclusion about subsidization status**
Hur man överklagar	How to appeal	Description of how to appeal decisions
-	-	A list of the Board members that took part in the decision

Although the structure of the ninety-four decision justification was similar, the length of documents varied. Many documents – particularly those justifying an approval of subsidy – comprised two or three pages. Decisions approving restricted subsidy, or denying subsidy altogether, were typically a few pages longer. A smaller number of decision documents were longer still, numbering up to ten pages.

Extended excerpts of two decision justification documents issued by LFN prior to December 31 2004 can be found in Appendix C (see pp. 227-30 of this volume).[50] The first document justifies the approval of subsidy for Keppra, a

[50] Both documents are presented in their original language, Swedish.

drug approved for the treatment of epilepsy. The second document justifies the denial of subsidy for Niferex, an iron supplement. The two documents are included as examples of the kind of justifications given by LFN in these documents. Although the arguments themselves are not representative for all documents, they are an example of the kind of material referred to in the remainder of the chapter. Extended sections of the two documents' 'Reasons for decision' are presented below: [51]

In the case of Keppra, the approval of subsidy is justified on the basis of the drug's route of administration, which makes it the sole treatment alterantive for certain groups of patients. This lack of treatment alternatives makes the requested price acceptable (emphasis added):

> Keppra tablets are already included in the public pharmaceutical benefits scheme. The price the applicant firm has demanded for Keppra oral solution would make the difference in treatment cost in relation to the tablet-based treatment considerable. Other drugs used in the treatment of epilepsy do not constitute a general alternative to Kepra (sic), which has characteristics that differ from other pharmaceuticals. Keppra administered via oral solution is therefore a prerequisite for certain patients to receive adequate treatment, and the cost of treatment must be evaluated in light of this. The increased cost which a switch from tablet to oral solution will result in cannot be expected to considerably change the cost-effectiveness of the pharmaceutical as a whole.
>
> Taken together, the Board finds the conditions set out in section 15 of the Act on pharmaceutical benefits etc. fulfilled such that Keppra oral solution shall be included in the public pharmaceutical benefits scheme at the demanded price. The application is approved.

The denial of subsidy for Niferex, in contrast, hinges on the drug's unacceptably high cost in relation to treatment alteratnives (emphasis added):

> The price comparison which can be made show that the demanded price involves an increased cost of treatment in relation to

[51] The cited paragraphs in each document are highlighted with a bolded box in Appendix C.

> comparable pharmaceuticals. The applicant form has not shown that this increased cost of treatment is combined with corresponding health economic benefits. Nor does the cost seem to be otherwise reasonable. The conclusion is therefore that Niferex does not fulfill the criteria for subsidy in section 15 of the Act on pharmaceutical benefits etc. The application is therefore denied.

The two decision justification documents concerning Keppra and Niferex illustrate the kind of material that will be used in the remainder of the chapter. In the following sections, I will thematically discuss how LFN justified whether a drug was 'reasonable' or 'unreasonable' to subsidize.

Reasonable - when compared to other drugs

The sixty-seven documents that concerned decisions to approve subsidy, were justified on the basis of one of two arguments: the applicant pharmaceutical's *difference* as compared to other pharmaceuticals, *or* the drug's *similarity* as compared to one or more drugs that were already included in the public pharmaceutical benefits scheme.

'Different' from other pharmaceuticals

There were certain characteristics that made a pharmaceutical different from other drugs in a way that made it 'reasonable' to subsidize.

One such characteristic was if the pharmaceutical had a 'special' market status. During the studied time period, LFN approved subsidy for all drugs that were available through licensed prescription *or* classified as orphan drugs. A recurrent argument put forth by LFN for why it was reasonable to approve subsidy for orphan drugs was that they by definition treated a small number of patients with serious medical conditions (cf. Onsenal 2004-07-01, 4). In the case of licensed pharmaceuticals, the limitation placed on access to the drugs in question was taken to indicate that those patients who *did* get prescribed the drug were cost-effective to treat. The following justification was used more or

less verbatim in all the decision documents concerning licensed pharmaceuticals:

> License is only granted if a patient has not received satisfactory treatment with [generally] approved pharmaceuticals. This restriction means that the use of such a drug can be assumed to be cost-effective for those who are prescribed it (Valoid 2004-02-17, 2).

A pharmaceutical could also have differences in effect that made it 'reasonable' to subsidize, because there were no or few comparable treatments. In the case of the drug Keppra, which I used earlier as an example of a decision justification document, the difference in *route of administration* (an oral solution, compared with tablets) in combination with the pharmaceutical's *different treatment mechanism* as compared to other drugs made it 'reasonable' to subsidize despite a 60% higher cost of treatment (Keppra 2004-09-01, 2).

The approval of subsidy for two pharmaceutical-based treatments of male impotence was justified on the grounds that the product's route of administration ensured that only patients with severe forms of this condition received treatment (Caverject 2003-05-15; Bondil 2003-05-15). These two drugs' route of administration (injection) made them incomparable with three other tablet-based treatments of the same medical condition. As I will discuss further, below, these three tablet-based treatments were denied subsidy on the grounds that the smaller number of patients with severe forms of male impotence (who fulfilled the criteria for receiving subsidized treatment) could not be reliably identified in medical practice.

In summary, characteristics such as a pharmaceutical's market status, route of administration and/or the severity of patients treated with the drug could differentiate a drug from other pharmaceuticals in a way that made it 'reasonable' to subsidize. The argument that a pharmaceutical be granted subsidy due to its difference – or even its incomparability – with other drugs contrasts with the justification of approved subsidy for a pharmaceutical on the grounds that it was 'the same' as one or more pharmaceuticals that were already included in the pharmaceutical benefits scheme.

'The same' as other pharmaceuticals

One basis for justifying the approval of subsidy was if a drug was *a variant* of a pharmaceutical that was already included in the pharmaceutical benefits scheme.[52] A product variant could have a different route of administration, but still be 'the same' as an already subsidized drug: [53]

> Glivec coated tablets have are therapeutically identical to Glivec hard capsules, which are included in the public pharmaceutical benefits scheme. The two variants differ only as regards their route of administration. The prices the applicant firm demands are per mg the same as the price for the capsules which are currently subsidized. (Glivec 2004-04-23, 2)

LFN also approved applications for subsidy for a number of pharmaceuticals with a different route of administration and a higher treatment cost on the grounds that the difference in price was 'the same' as the price differential between already subsidized pharmaceuticals:

> Atarax tablets are previously included in the public pharmaceutical benefits scheme....The price the applicant firm demands for Atarax oral drops will make the cost of treatment in comparison to the tablet-based treatment considerably higher. In light of the differences between other comparable drugs' oral-based administration and tablets the difference for Atarax is one that can be deemed acceptable (Atarax 2004-05-25, 2).

The previous examples illustrate how pharmaceuticals were 'reasonable' to subsidize if they were variants of an already subsidized (brand of) pharmaceutical. Differences in route of administration or in the cost of treatment were, in these cases, not relevant grounds for differentiating between the pharmaceuticals' subsidization status. This contrasts with examples in the

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[52] In a few cases, the decision to approve subsidy for a drug was qualified with an explicit note that LFN would be reviewing the subsidization status of *all* pharmaceuticals within the particular therapy group in time. However, in these cases the pharmaceuticals in question was approved subsidy pending this review (e.g. Glucosine 2003-06-30, 2; Vesicare 2004-12-20, 5).

[53] For other examples see Zyrlex 2004-03-16; Procren Depot 2004-02-19; Ovitrelle 2003-12-18.

previous section, where a pharmaceutical's route of administration – when combined with differences in active substance – was a characteristic that could differentiate it from other drugs and make it 'reasonable' to subsidize because of this difference.

Drugs that were not variants of already subsidized pharmaceuticals could also approved subsidy by virtue of having the same or better characteristics as other drugs. In several of these cases, there was reasoning about *which* drugs were relevant comparisons and how a variety of characteristics compared in relation to these pharmaceuticals. Examples of reasoned judgments include a pharmaceutical that had the same treatment effect and a lower direct price than an already subsidized product, but had a more difficult and costly route of administration (Menopur 2004-12-21, 3). Another example was a drug that commanded a higher *direct* price but had a lower cost of administration than a variant of the same drug (Bondromat 2004-06-30, 3). In a third case, where the application for subsidy concerned a drug that included two active substances, it was argued that the pharmaceutical should be compared with these different drugs. There was also reasoning about the value of providing the two substances together in one pharmaceutical (Teveten Comp 2004-10-25). These examples illustrate how LFN justified outcomes based on a consideration of multiple characteristics – as compared to various drugs.

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A crude classification of decision justification documents using the aforementioned forms of difference and similarity is summarized in Table 3.

Table 3: *Justifications for approval of subsidy (# of documents and % of total)*

	No. of documents	% of documents
Special status	14*	21%
Difference of effect	11**	16%
Product variant	37	55%
Reasoned	15	22%

* of these, six *also* product variant

** of these, four *also* product variant

Both justifications are based on a characterization of applicant pharmaceuticals' characteristics as compared with other drugs. However, whether *a particular* characteristic such as route of administration, price or treatment effect was a basis for delineating difference or similarity varied.

The following section will elaborate on both the importance of comparisons when justifying decisions to *deny* a pharmaceutical subsidy and the variation in which pharmaceuticals' characteristics were the basis for delineating similarity and difference.

Unreasonable - when compared to other drugs

Although close to 85% of all decision justification documents issued by LFN prior to the end of 2004 involved the approval of subsidy (in 70% without restrictions, in 14% of the cases with restrictions), the Agency also concluded that certain drugs did not fulfill the criteria for subsidy due to *unacceptable differences* in effect or cost. LFN also denied subsidy for drugs due to *irrelevant comparisons* with other drugs.

Unacceptable differences

In four of the fourteen documents denying subsidy, the Agency justified the denial of subsidy on the grounds that the drugs had too high a cost of treatment as compared to already subsidized pharmaceuticals. This was a primary justification for the denial of subsidy for the iron supplement Niferex, which I used as an example earlier in the chapter, and Totelle, a pharmaceutical approved for the treatment of menopausal symptoms (Totelle 2003-11-06, 4). Similarly, the Agency's justified the denial of subsidy for a pharmaceutical approved for treatment of ADHD on the grounds that the product had 'the same' treatment effect as another drug, but twice the price (Concerta 2003-03-24, 3).[54] A lack of "statistically significant" differences in treatment effect as

[54] As discussed further below, LFN subsequently reversed this decision, on the grounds that the 'comparable' drug was not a relevant comparison (see pp. 109-10 of this volume).

compared to other drugs was also used to justify the denial of subsidy for Cerazette, a birth-control pill (Cerazette 2003-03-27, 2).[55]

These justifications for denying subsidy referred to pharmaceuticals characteristics' as compared to already subsidized drugs. However, what constituted an 'unreasonable' difference in treatment cost relative treatment effect was contested in certain cases. Although LFN Board members seldom wrote minority positions, several of these concerned whether differences in cost were acceptable and the cost of treatment was reasonable.[56] For example, in a minority position concerning the aforementioned drug Totelle, one Board member argued that the price of the drug was not unacceptably high since the *relative* cost difference was large, but the difference in *absolute* cost was small:

> According to the evaluation the demanded price will increase the cost of treatment with 25% compared with [Product A], 64% compared with [Product B] and 100% compared with [Product C]. The absolute difference in daily cost would only be 50 öre, 1,1 SEK and 1,5 SEK, respectively. The total cost ... would be 3 SEK per day, which I consider to be a low price if the treatment is effective (Totelle 2003-11-06, 4).

A second justification for the denial of subsidy for a drug centered not only on a pharmaceutical's unacceptable difference in treatment cost and treatment effect relative other pharmaceuticals, but on the definition of 'comparable' drugs and 'comparable' characteristics.

Irrelevant comparisons

Irrelevant comparisons were cited as grounds for denying subsidy in twelve of the fourteen decision justification documents.

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[55] As discussed further below, this decision was later reversed by the Agency on the grounds that there were statistically significant differences in treatment effect (see pp. 110-1 of this volume).

[56] Individual Board members or groups of Board members wrote 'minority opinions', in which they expressed disagreement with the Board's outcome, in seven of the ninety-four documents. In one minority position, concerning the denial of subsidy for a pharmaceutical approved for treatment of male impotence, LFN's lack of a precise definition of 'reasonable' cost was explicitly highlighted (Viagra 2003-03-26, 5)

In the aforementioned case of Totelle, the drug had an unacceptably high treatment cost in part since the claimed treatment benefits which were cited in the application for subsidy were not "clinically relevant", according to LFN. In other words, while there *were* differences between the applicant pharmaceutical and other drugs, these differences where not grounds for accepting the difference in cost of treatment (Totelle 2003-11-06, 3).

In the case of one pharmaceutical, LFN twice denied it subsidy during the studied time period. Both decisions were justified on the grounds that the claims made in the application for subsidy of the pharmaceutical were based on irrelevant comparisons. In its first decision justification document, the Agency argued that it was incorrect of the applicant company to compare the pharmaceutical with no treatment since there *were* pharmaceutical-based treatment alternatives with different active substances (Xyzal 2004-09-02). The second decision document, in which the Agency confirmed its previous decision to deny the pharmaceutical subsidy, argued that the second application for subsidy did not use the most relevant comparable drug. The Agency contended that the relevant comparison was one between the applicant drug and a more commonly used, and less expensive, pharmaceutical than the one used in the application for subsidy (Xyzal 2004-11-09, 3-4). When the applicant pharmaceutical (Xyzal) was compared with the 'comparable' drug defined in the application for subsidy it was cheaper. But Xyzal was more expensive that the 'comparable' drug as defined by LFN.

LFN also deemed certain comparisons of pharmaceuticals' treatment effects and costs to be irrelevant due to their having been measured on different patient groups. In the justification document concerning Elidel (a cream for treating eczema), LFN argued that the application for subsidy cited health economic results based on clinical studies of other patients than for those whom the company had applied for subsidy (Elidel 2004-05-28, 4).[57] Similarly, the Agency argued that two pharmaceuticals approved for the treatment of male

impotence that had been approved subsidy were irrelevant comparisons for three other drugs. Although the medical condition that the products were approved to treat were 'the same', the pharmaceuticals were not comparable since they were not used by 'the same' patients (Levitra 2004-09-01, 5).

An irrelevant definition of pharmaceutical use was grounds for LFN not evaluating the subsidization status of pharmaceuticals in the first place. In its first two decision justification documents, LFN turned down the application for subsidy of two drugs for areas of use that was not approved by the Medical Products Agency (Autonativ 2003-01-30; Robinul 2003-01-30). In another decision justification document, LFN denied a pharmaceutical subsidy on the grounds that a comparison of the applicant pharmaceutical's treatment cost using the treatment doses in the Medical Product Agency's approval documents showed the drug to be more costly than the comparable product (Flutide 2003-02-17, 1-2).

All in all, LFN justified denial of subsidy in twelve of fourteen decision justification documents based on 'irrelevant comparisons'. Irrelevance was attributed to: comparison of irrelevant characteristics, definition of irrelevant comparable drugs, incomparable or irrelevant patient groups, and irrelevant types of use (i.e. treatment areas that were not approved by the Medical Products Agency or EMEA).

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The preceding two sections illustrate how LFN justified the approval and denial of subsidy on the basis of whether the pharmaceutical had a 'reasonable' cost of use – for all patients. In a few cases, the Agency concluded that it was 'reasonable' to approve subsidy for restricted uses of a drug. In the next section, I will point to the importance of feasibility when justifying these outcomes.

[57] On June 29 2005, LFN reversed the denial of subsidy for Elidel following the submission of a new application for subsidy that cited changes to the Medical Product Agency's approved treatment areas for the drug (Elidel 2005-06-29).

Reasonable – but also feasible – restrictions

Thirteen of the ninety-four decision justification documents issued by LFN prior to December 31 2004 approved subsidy for the pharmaceutical in question *with restrictions*. What were grounds for such restrictions? During the studied time period, the Agency defined restricted use in three ways: with specific values of *clinical measurements*, based on diagnosis of certain *medical condition*(s) and for a limited *period of time*.

In the six documents where LFN approved subsidy for a certain period of time, this restriction was justified on the grounds that the applicant companies needed additional time to submit new information about pharmaceuticals characteristics. With this new information, it would be possible for the Agency to evaluate whether or not the pharmaceuticals in question had a 'reasonable' cost of use in practice (Yentreve 2004-11-10, 4; Zyban 2004-09-28, 5; Risperdal Consta 2004-04-20, 3-4; Rapitva 2004-12-21, 4).

In the remaining seven cases, the Agency restricted subsidy to certain patients on the basis of clinical measurements or medical conditions. In the case of Xenical and Reductil, two drugs approved for the treatment of obesity, the measurement-based restrictions were based on specific values of height/weight ratios (Xenical 2003-06-04, Reductil 2003-06-30). The measurement-based restrictions for subsidy of Forsteo, a pharmaceutical approved for use in treatment of osteoporosis, referred to a combination of bone-mass calculations and previous instances of bone breakage (Forsteo 2003-12-22, 1). In those cases where subsidy was restricted to patients with certain medical conditions, these conditions included diabetes 1 (Levemir 2004-10-12, 1), established heart disease or diabetes 2 (Ezetrol 2003-06-26, 3), and a "lack of achieved treatment goals" with the first-hand treatment alternative (Crestor 2003-06-26, 3).

When approving restricted subsidy to particular uses of a pharmaceutical, it was emphasized that there must be no question as to *who* belonged to the subsidized group of patients. Using "objectively verifiable findings", such as measurements of height, weight and mass could ensure the correct identification of these patients (Forsteo 2003-12-19, 6). The *inability* to define

which patients were 'reasonable' to treat was grounds for denying subsidy for all patients. This argument was used to justify the denial of subsidy for three pharmaceuticals approved for the treatment of male impotence (Viagra, Cialis and Levitra):

In one decision justification document, the Agency argued that the medical studies cited in the application for subsidy "neither showed that the product was generally cost-effective nor showed for which particular patient groups the drug was cost-effective" (Viagra 2003-03-26, 4; emphasis added). Critically, the Agency judged it unclear whether a proposed diagnostic tool for determining the severity of a patient's condition was useful in a clinical setting (Cialis 2003-05-14, 4), or used by medical practitioners (Levitra 2004-04-06, 6). A lack of feasible means for identifying 'reasonable' patients justified the denial of subsidy since: "the existence of a small group of individuals with a well founded need does not justify ... a general subsidization of these pharmaceuticals from a societal perspective" (Ibid., 5).

In summary, the Agency's justifications of approval of restricted subsidy highlight how the characteristics on which restrictions on subsidy were based needed to define differences between groups of patients in a way that was coherent with and feasible in clinical practice. As in the previous examples of approved and denied subsidy, there was variation in *which* characteristics and *what* comparisons were relevant for judging whether a particular drug fulfilled the criteria for subsidy

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The three previous sections illustrate the importance of comparisons for LFN's justification – regardless of outcome. In the next section, the focus will shift to how the Agency's characterization of a pharmaceutical's properties, and its delineation of comparisons, related to how different sources characterized the drug in question.

Comparisons and characteristics – as defined by whom?

The Agency routinely justified outcomes regarding pharmaceutical subsidy by referring to characteristics of the evaluated pharmaceutical in relation to other drugs. This section will show how LFN's characterizations of pharmaceuticals' properties were made in relation to how other parties characterized the drugs in question. The importance of other parties as sources of knowledge about pharmaceuticals' characteristics is first illustrated by two cases where LFN reversed its decisions to deny subsidy for these drugs.

Changed comparisons, changed outcomes

The first reversal concerned Concerta, a pharmaceutical approved for treatment of attention deficit hyperactivity disorder (ADHD). The second reversal was made as regards the subsidization status of Cerazette, a birth-control pill. In both cases, a denial of subsidy was changed to an approval of subsidy. Both reversals were justified on the basis of changed delineations of comparisons, and pharmaceuticals characteristics.

In the Agency's first decision document concerning Concerta, a product was characterized as the 'primary treatment' for the same medical condition that Concerta was approved to treat (Concerta 2003-03-24, 2). Since Concerta did not give additional treatment benefits in comparison with this 'primary treatment', it was denied subsidy.

LFN's denial of subsidy for Concerta was subsequently appealed to the Stockholm County Administrative Court. The Agency's second decision justification document (Concerta 2003-06-10), described that the appeal rested on the claim that the comparison between Concerta and the aforementioned 'primary treatment' was not relevant since the latter drug was only available through licensed prescription. As part of the appeals process, the Medical Products Agency was requested to comment on the availability and use of this product. The Medical Products Agency statement, as accounted in LFN's second decision justification document, was that "there is ... an important principle difference between approved and un-approved pharmaceuticals. Licensed

products can not be considered to be equally available as approved pharmaceuticals" (Ibid., 2). This statement from the Medical Products Agency led LFN to conclude that "the lack of other available pharmaceutical treatment means the treatment with Concerta is considered cost-effective" (Ibid., 3). The initial denial of subsidy for Concerta was justified with the product's unacceptably large difference in cost as compared with another drug. The subsequent approval of subsidy was justified the basis of a lack of comparable treatments. Concerta's difference as compared to other pharmaceuticals made it 'reasonable' to subsidize.

LFN's second reversal, concerning the birth-control pill Cerazette, was precipitated by changes in the Medical Products Agency's characterization of the drug. The initial decision to deny Cerazette subsidy was justified on the grounds that a comparison between the applicant pharmaceutical and another drug did not show a "statistically significant difference" in treatment effect. Furthermore, "[t]he Medical Products Agency's [SPC] for Cerazette also shows that the numerical difference in pregnancy frequency between the two products is not statistically significant" (Cerazette 2003-03-27, 2). For these reasons, Cerazette was judged to have an unacceptable difference in cost.

As in the case of Concerta, LFN's denial of subsidy for Cerazette was appealed. However, this appeal was withdrawn before any ruling was made and a new application for subsidy submitted to LFN. In a second decision (Cerazette 2004-08-30), the Agency approved subsidy for the drug. The changed decision outcome was justified by changes in Cerazette's Summary of Product Characteristics (SPC). Previously Cerazette had not had statistically significant differences in treatment effect compared to other drugs. However, the SPC had been changed following the submission of new clinical studies. These studies showed Cerazette to be cost-effective compared to certain birth-control pills. Whether Cerazette was cost-effective *in practice* depended on which kind of pharmaceutical it replaced in specific cases (Cerazette 2004-08-30, 4-5). However, the Agency judged Cerazette to be was 'reasonable' to subsidize pending a review of all birth-control pills in the product assortment review.

The examples of Concerta and Cerazette illustrate the importance of comparisons *and* the importance of other sources of knowledge for LFN's decisions about pharmaceutical subsidy. Specifically, the two cases illustrate the importance of a particular source (the Medical Products Agency) for determining pharmaceuticals' properties and defining relevant comparisons. In the next section, I will discuss the presence of multiple sources of knowledge about pharmaceuticals' characteristics. In certain cases, there could be alternative ways of characterizing and comparing pharmaceuticals. Different sources of knowledge did not consistently characterize pharmaceuticals in the same way. And LFN did not consistently use any one source as the relevant source of knowledge about the properties of drugs.

Many sources of knowledge

LFN referred to various sources, such as the Medical Products Agency, medical practitioners and clinical studies when justifying outcomes. But different sources could disagree about pharmaceuticals' characteristics. Notably, none of the aforementioned sources were consistently used by LFN as the relevant source of knowledge about which characteristics, and what comparisons, were relevant for determining whether a drug fulfilled the criteria for subsidy.

Take the example of the Medical Products Agency. As previously mentioned, LFN's first two denials of subsidy were justified on the grounds that the Agency's governing legislation did not grant it mandate to approve subsidy for pharmaceutical usage that fell outside of the Medical Product Agency's approved treatment areas (Autonativ 2003-01-30; Robinul 2003-01-30). In other words, pharmaceutical use that was not formally approved by the Medical Products Agency was not a relevant characteristic, even it was a characteristic of 'pharmaceutical use' as defined by the product's use in medical practice.

Similarly, LFN denied a pharmaceutical subsidy on the grounds that the application for subsidy used another treatment dose than that defined by the Medical Product Agency's marketing authorization. A comparison with the approved doses showed the drug to be more costly than a comparable product

(Flutide 2003-02-17, 1-2). In this case, it had been arguied in the application for subsidy that the approved doses were an irrelevant basis for comparison, since the pharmaceutical was used differently in medical practice. But this was not accepted by LFN. The Medical Products Agency was the appropriate source of knowledge about pharmaceutical treatment dose.

In the previous two examples, the Medical Products Agency was the relevant source of knowledge about certain pharmaceutical characteristics. This was not always the case. In two cases, LFN's approved restricted subsidy for a pharmaceutical based on criteria that differed from the approved treatment areas for these two drugs.[58] The Agency justified the difference by referring to how other countries had restricted subsidy, and citing experiences from clinical medical practice (Xenical 2003-06-04, 5; Reductil 2003-06-04, 2). In another justification document, it was noted that the Medical Products Agency's conclusion that a particular drug was a valuable treatment alternative for certain patients did not automatically mean that LFN should approve subsidy of the drug. The reason for this was that the Agency was tasked with taking more characteristics into consideration:

> In addition to the Medical Products Agency's medical evaluation LFN has ... to make a judgment based on a broad perspective where aspects such as need and cost-effectiveness are included (Elidel 2004-05-28, 3).

Taking additional characteristics into consideration led LFN to draw the conclusion that this drug was to be denied subsidy.

In the aforementioned case, then, the Medical Products Agency could not 'stand in' for LFN's own evaluation. In other cases, however, other sources were considered adequate proxies for the Agency's own evaluation of whether a pharmaceutical was 'reasonable' to subsidize. Notably, a pharmaceutical's status

[58] The two drugs, Xenical and Reductil, are both approved for treatment of obesity. Specifically, they are approved for treatment of patients with a Body Mass Index (BMI = weight/height^2) over 30. or BMI over 28 in the case of patients with diabetes (Medical Products Agency 1998a). LFN's approval of subsidy restricted subsidy of the drugs to patients with BMI over 35 or BMI over 28, in the case of patients with diabetes.

as licensed or orphan drug was consistently taken to mean that treatment with this drug should be subsidized. In these cases, medical practitioners, together with the Medical Products Agency who oversaw access to licensed drugs, were assumed to identify those patients that were 'reasonable' to treat with subsidized pharmaceuticals.

In summary, LFN's justification documents included many references to various sources of knowledge about pharmaceutical characteristics. However, a *particular* source of knowledge could be considered relevant in one case, but not in another. Different sources could also disagree as regards individual characteristics – or suggest that different properties or comparisons were appropriate grounds for evaluating a pharmaceutical.

'Reasonable' drugs - and 'decision-able' justifications

A first conclusion of this chapter is that LFN's justification of outcomes hinges on comparisons of pharmaceuticals' characteristics. A critical matter is whether a pharmaceutical is *different from* or *the same as* drugs already included in the public pharmaceutical benefits scheme.

However, a second conclusion is that *which* particular characteristics and comparisons are grounds for justifying a certain outcome varies. Both relevant and irrelevant similarities and differences can relate to characteristics such as: availability, patients treated, treatment effect, route of administration and cost of treatment. In the decision justification documents discussed in this chapter, characteristics such as treatment effect, route of administration or cost of treatment were relevant differences in certain cases, but irrelevant in others. Only licensed marketing authorization or orphan drug status consistently led to the approval of subsidy (in one case, Duodopa 2004-01-23, with a time-based restriction).

A third conclusion is that the relevance of individual characteristics, the basis for comparison and the conclusions about subsidy can be contested. There are multiple sources of relevant knowledge about pharmaceuticals' characteristics. These parties do not always give coherent accounts of drugs'

properties. An individual drug's properties can also change, as illustrated by the two cases where LFN reversed earlier decisions to deny the pharmaceuticals in question subsidy.

Taken together, the present chapter gives a (somewhat facetious) answer to the question of when a drug is 'reasonable' to subsidize: a pharmaceutical is 'reasonable' to subsidize when relevant pharmaceutical characteristics are compared with relevant comparable drugs – as defined by relevant sources of knowledge – and show the drug to be (relevantly) different or similar to these pharmaceuticals. The point, I will stress, is that *what* is a 'relevant characteristic' and a 'relevant comparison' can be ambiguous in some – if far from all – cases. Yet to make a 'decision-able' justification it is precisely such a comparison that LFN must achieve. In the following chapter (Chapter 6) I will present findings from my study of LFN's work will the evaluation of two groups of drugs approved for the migraine and stomach-acid related disorders, respectively. Based on findings in this chapter, the focus in this account is on:

1. How are relevant characteristics of pharmaceuticals determined?
2. How are relevant comparisons defined?
3. How is ambiguity between multiple sources of knowledge dealt with?

6. 'SHOOTING A MOVING TARGET WHILE IN MOTION': EVALUATING SUBSIDY OF PHARMACEUTICALS IN USE

LFN announced the outcome of its second pilot project for the product assortment review on January 19 2006. Nearly two and half years after the official start in October 2003, the evaluation of the stomach-acid group was complete. (The outcome of the first group, concerning pharmaceuticals for the treatment of migraine, had been published in February 2005).

On the day of the public announcement, I sent an email to an informant in which I congratulated him on finishing the review. He responded (excerpt, my translation):

> It's easy to explain why we're [excluding] certain pharmaceuticals: If two drugs are equally good then one cannot cost twice as much as the other one.
>
> To think that such a simple decision could be made so complicated.

This chapter is about the twenty-seven months of 'complications' that preceded LFN's completion of the stomach-acid and migraine groups.

In the chapter I give a thematic account of efforts to evaluate whether these various pharmaceuticals fulfilled the criteria for subsidy. I describe attempts to define comparable drugs, calculate and compare pharmaceuticals' cost-effectiveness, draw conclusions on the basis of the Agency's evaluations,

and author appropriate decision justification documents. Throughout, the focus is on instances where the evaluation of pharmaceuticals' characteristics was complicated by ambiguity between multiple sources of knowledge. Together, these examples serve to illustrate the efforts needed to make 'simple' statements such as that about equally good drugs having significant differences in cost.

Before we start off, two methodological comments. First, a reminder to the reader of the study's descriptive approach. My purpose is not to pass judgment on the merits of LFN's evaluation of the migraine and stomach-acid groups, but use the Agency's work as an example with which to develop an understanding of how organizations deal with ambiguous knowledge in decision-making processes. I have neither methodological nor theoretical grounds for saying whether the Agency's activities are appropriate or not. The material in the chapter is empirically founded on what informants recounted to me and what was written in various documents. Thus, when I write that there *is* incoherence between different sources, for example, I seek neither to confirm nor disprove this statement.

Second, although the study has a descriptive approach my presentation in this chapter is by necessity a simplified and selective story about the work in the migraine and stomach-acid groups. Specifically, the interest in how ambiguous knowledge between multiple sources is dealt with has led to an emphasis of certain occurrences, and an exclusion of others.[59] In this, my attempts to write a coherent and linear account of the Agency's work based on an abundant empirical material has certain similarities with efforts to determine definitive knowledge about pharmaceuticals' characteristics from multiple sources of knowledge about pharmaceuticals' characteristics and appropriate use. Both are outcomes of ordering work.

A final note on presentation: due to the many references in this chapter, I have chosen to footnote all sources in the interest of legibility.

[59] For a description of how the study was performed see pp. 59-67. For a of controversy as a basis for selection see p. 68.

Starting out

LFN officially kicked off its review of the existing pharmaceutical assortment on October 20 2003, with the announcement of its two designated pilot groups: pharmaceuticals for the treatment of migraine and stomach-acid related disorders, respectively.[60] In an accompanying document, the choice of these two pilot cases was explained with their being: "sufficiently extensive, sufficiently complex and different enough to test work methods, organization and so on".[61] The possibility of developing the Agency's process was important since "the review of medicines eligible for reimbursement is dealt with only very summarily in the preliminary work for the new Act".[62] At the time of the two project groups' initiation, the Agency's Director-General described their work as "a pioneer effort"[63]; elaborating on the need for the first groups to take time to develop and improve specific routines for subsequent reviews as this was important for establishing LFN's credibility with county councils, pharmaceutical companies, patients and taxpayers.

Although the practicalities of undertaking the review process were not set-out in detail, there was certainty about the intended outcome of the assortment review:

> When the [product assortment] review is completed then Sweden shall subsidize the best and most effective pharmaceuticals at the best possible price. We will have sorted out those drugs which do not provide enough benefit in relation to what they cost. But this does not mean that we only should have cheap pharmaceuticals ... If a

[60] LFN 2003a. Concurrently, LFN issued documents that listed the pharmaceuticals included in the two groups, see Appendix B (section B1 and B2, pp. 237-8). The members of both project group were also published. In each case, the group comprised two pharmacists and a health economist from the Agency's Bureau (LFN 2003c, d).

[61] LFN 2003b, 2.

[62] LFN 2005b, 6.

[63] Interview LFN Director-General, October 24 2003.

> drug has positive effects on health and life quality, then we are willing to pay for it.[64]

The initial plan for the review process outlined a two-phase process that would be completed by the end of 2004.[65] In the first phase, each group of pharmaceuticals would be evaluated as a whole, and the findings from this evaluation presented to the Board. At this stage, the Board could decide to approve subsidy for all the pharmaceuticals, if the evaluation showed the entire group of pharmaceuticals to fulfill the criteria for subsidy. Alternatively, the Board could decide to proceed to a second phase of evaluation. Once the second phase was initiated, each pharmaceutical would be evaluated more closely in comparison to other drugs in the same group. At the completion of the second phase, it was up to the Board to determine the subsidization status for each drug. Informants explained at the start of the process that a decision to deny or approve restricted subsidy for a pharmaceutical would only follow a deeper evaluation of individual drugs, since these decision justification documents would be subject to scrutiny and possible appeal.[66] However, undertaking a second phase of evaluation did not automatically mean that the Board would choose to deny a product subsidy, or decide on a restriction of subsidized use.

During both of the project groups' first few months of work, a shared focus was on organizing the forthcoming review. Informants spoke about their efforts to word requests for information from the pharmaceutical companies in the two groups, identify experts to second to both groups, and formally affiliate these experts to the project groups, to name a few.[67] Concurrently, questions were raised with respect to the impending evaluations. One issue centered on which pharmaceuticals should be compared with one another.

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[64] LFN 2003a, 1.

[65] LFN 2003b. The initial time plan, and the review process, was subsequently revised (LFN 2004a, 2005c).

[66] Interview project manager stomach-acid group, January 28 2004.

[67] Interview health economist stomach-acid group, November 20 2003; Interview project manager migraine group, January 28 2004.

Although the definition of comparable drugs had ostensibly been provided through the very creation of the two pilot groups, the basis for this classification of pharmaceuticals was brought into question. This is an early example of how multiple sources of knowledge were ambiguous about pharmaceuticals' characteristics, in this case their comparability.

Which 'comparable' drugs?

Both the migraine and stomach-acid groups were defined using ATC, Anatomical Therapeutic Chemical Classification System.[68] ATC is a system for classifying drugs which is maintained by the WHO Collaborating Centre for Drug Statistics Methodology.[69] The system classifies pharmaceuticals according to the organ or system on which they act, their therapeutic characteristics, and chemical composition. In all, ATC has five tiers, stretching from a first tier of anatomical groups down to the fifth level that identifies specific chemical substances.[70] The second tier – therapeutic subgroup – served as the primary point of departure when creating the migraine and stomach-acid groups since "this level corresponds in most cases to the pharmaceuticals which are treatment alternatives for an illness"[71]. This was in line with instructions in the legislative bill submitted to Parliament prior to the passage of the law creating LFN, which stated that the Agency's "review [for the previously subsidized

[68] LFN 2003b, 6.

[69] A precursor to the current classification system was first developed by Norwegian researchers in the late 1960s and early 1970s. In 1981, the WHO Regional Office for Europe recommended the ATC system for international drug utilization studies. In connection with this, the WHO Collaborating Centre for Drug Statistics Methodology was established in 1982. In 1996, the Centre was linked directly to WHO Headquarters in Geneva and efforts made to develop use of the ATC/DDD system as an international standard for drug utilization studies (WHO Collaborating Centre for Drug Statistics Methodology).

[70] The first level of the ATC code is based on a letter for the anatomical group, e.g. 'B' for *Blood and blood forming organs*. The second level is therapeutic subgroup, e.g. 'B03' for *Anti-anemic preparations*. Level three is pharmacological subgroup, e.g. 'B03A' for *Iron Preparations*. The fourth level is chemical subgroup e.g. 'B03AA' for *Iron, bivalent, oral preparations*. Finally the fifth level is the subgroup for chemical substance e.g. 'B03AA07' *Ferrous sulphate*. Since pharmaceuticals may have several therapeutic uses, the basic principle is that products are classified according to the main therapeutic use of the main active ingredient.

product assortment] should be performed based on therapeutic groups" (The New Pharmaceutical Benefits Bill 2001, 36).

When defining a 'comparable' group of pharmaceuticals using the ATC-code, the drugs' similar physical therapeutic impact was taken to mean that they were used for treating 'the same' medical condition. In the case of the migraine group, it was "straight-forward"[72] to use the ATC-defined group of comparable pharmaceuticals. The chosen ATC-code defined a group of drugs that were primarily used to treat a single medical condition: migraine.[73] In other words, ATC made a similar classification of pharmaceuticals as did medical practitioners. This was not immediately the case in the stomach-acid group.

Here, the chosen ATC-code defined drugs as 'similar' in a way that differed from how they were used to treat patients in medical practice. A specific problem, according to my informants in the stomach-acid group, was that the ATC-code did not differentiate sufficiently between the drugs. The ATC-code defined a group of 'Drugs for Acid-related Disorders'[74] that forged a link between *all* pharmaceuticals in this group and *all* acid-related disorders. This was not a sufficiently precise characterization of the drugs' properties. Notably, the ATC-based grouping of drugs was not coherent with the differences in treatment regimes for various acid-related disorders that were accounted for by the stomach-acid groups' seconded medical experts, and in clinical studies submitted to LFN by the pharmaceutical companies. Both of these sources differentiated between pharmaceuticals on the basis of how they were used to treat various medical conditions. Depending on which medical condition was treated, 'the same' pharmaceutical was used for different lengths of time and in different doses.[75] These differences in treatment regimes could mean variations

[71] LFN 2003b, 6.

[72] Interview project manager migraine group, February 13 2004; Interview health economist February 29 2004.

[73] The pharmaceuticals could also be used to treat a second, but significantly less common diagnosis: Horton's headache, also known as 'Cluster headaches' (LFN 2005a).

[74] LFN 2003c, 1.

[75] Treating a patient for a bacterial infection causing ulcers meant prescribing a fixed dose of a pharmaceuticals for a few weeks, whereas treating a patient for gastro-intestinal reflux disorder

in individual pharmaceuticals' cost-effectiveness as compared with other drugs depending on which medical condition was treated.[76]

A particular complication was that the ATC-based definition of similarity and difference was not coherent with that of another source: the treatment areas approved by the Medical Products Agency and set out in each drug's Summary of Product Characteristics (SPC).[77] The example of so-called proton pump inhibitors[78] illustrates this incoherence between multiple sources of classification:

The ATC-code used to create the stomach-acid group (A02) made all proton pump inhibitors 'the same' as other drugs. At lower levels in the classification scheme, proton pump inhibitors were 'different' from other kinds of drugs (A02BC) and different from each other (A02BC) (see Table 4).

***Table 4**: Drugs for 'stomach-acid related disorders' as defined by ATC*[79]

A02 DRUGS FOR ACID RELATED DISORDERS
1. A02A ANTACIDS a. A02AA Magnesium compounds b. A02AB Aluminium compounds c. A02AC Calcium compounds d. ...
2. A02B DRUGS FOR PEPTIC ULCER AND GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD) a. A02BA H2-receptor antagonists b. A02BB Prostaglandins **c. A02BC Proton pump inhibitors** i. A02BC01 Omeprazole ii. A02BC02 Pantoprazole iii. A02BC03 Lansoprazole

(GERD) could involve continuous medication or medication 'on demand' for years at a time, Interview project manager stomach-acid group, March 14 2004.

[76] Interview health economist stomach-acid group, March 23 2004.

[77] A pharmaceutical's Summary of Product Characteristics (SPC) is an official documentation of the product's properties which is issued in conjunction with approval of marketing authorization and then updated over time.

[78] The proton pump inhibitors are a group of drugs with a similar chemical structure. According to the final report issued by LFN, the proton pumpinhibitors constituted more than 90% of the sales of stomach-acid related drugs within the pharmaceutical benefit scheme during 2005 (LFN 2006A8).

[79] ATC/DDD Index 2006 (WHO Collaborating Centre for Drug Statistics Methodology 2006).

iv. A02BC04 Rabeprazole
v. A02BC05 Esomeprazole
d. A02BD Combinations for eradication of Helicobacter pylori
e. A02BX Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GERD)

In contrast, the approved treatment area in the SPC for each proton pump inhibitor was slightly different (see Appendix D, pp. 231-2 of this volume). The project manager in the stomach-acid group noted that: "to take the approval documents seriously would mean that all the proton pump inhibitors were different from one another"[80]. But differentiating between the proton pump inhibitors in this way was not coherent with the aforementioned ATC-based classification (where all the pharmaceuticals were classified in the same category). Nor was it coherent with drugs' use as treatment alternatives by medical practitioners – albeit in different ways depending on which medical condition was treated.

In short, there were two problems. First, an ambiguity about the degree of specificity between how the two classifications of pharmaceuticals (ATC and the SPC) defined which drugs were 'the same', and which were 'different' from one another. Second, an incoherence between these two sources and how the pharmaceuticals' were classified as treatment alternatives in medical practice. The latter meant that neither ATC nor SPC could be used outright by LFN as a basis for the Agency's own classification and comparison of drugs. The Agency needed the "real cost of real pharmaceutical usage"[81] if it was to judge whether a pharmaceutical had a 'reasonable' cost of use. LFN's classification of comparable drugs needed to reflect those differences in the use that affected the relative cost-effectiveness of products.[82]

[80] Interview project manager stomach-acid group, March 14 2004.
[81] Interview health economist stomach-acid group, June 9 2004.
[82] Interview project manager stomach-acid group, June 9 2004.

The recourse in the stomach-acid group was to combine elements of the ATC- and SPC-based classifications of similarity and difference.[83] The project manager described how a 'working classification' of five acid-related disorders was developed in consultations with the group's seconded medical experts (see Diagram 5). This classification would be used by the stomach-acid group in its subsequent evaluation of the products.

***Diagram 5**: Working classification of medical conditions in the stomach-acid project group*

Ulcer in upper part of intestine	Ulcer in stomach	Erosive reflux disorder	Symptomatic reflux disorder	Ulcer caused by NSAID/aspirin medication
With or without HP[84]		Urgent and/or maintenance treatment		
Indigestion/Functional dyspepsia				

The working classification included elements of various sources' of classification that provided a register of both similarity and difference; the drugs were neither 'the same' (ATC) nor 'different' (SPC) from one another.

The definition of a comparable group of pharmaceutical in the stomach-acid group was difficult not for a lack of classifications of pharmaceuticals' similarity and difference. On the contrary, there were several classifications of 'comparable' drugs. None of these were individually sufficient to define relevant comparisons for LFN's evaluation work. Yet, when taken together, there was ambiguity about which pharmaceuticals were 'comparable'. To resolve this incoherence, various classifications of pharmaceuticals from different sources were used to define a 'working classification' for the continuing review. The 'actual' use of drugs, as defined by medical practice, was ascribed particular importance in the creation of LFN's own definition of comparable pharmaceuticals. Taking medical practice into consideration in this way was

[83] Interview project manager stomach-acid group, June 9 and September 28 2004; Interview health economist stomach-acid group, September 28 2004; Interview Board member (health economist B), July 2 2004.

[84] HP – *Helicobacter pylori* – is the name of the bacteria that is known to cause stomach ulcers.

necessary for the credibility of LFN's decisions among medical practitioners, according to interviewed Board members. A failure to secure such credibility could threaten the Agency's ability to influence medical practitioners' use of pharmaceuticals, since it had no powerful means of ensuring compliance with other decisions than denial of subsidy.[85]

But pharmaceuticals' characteristics *as defined by use in medical practice* was not consistently the relevant, or readily available and coherent (re)source, for the migraine and stomach-acid project groups to draw upon. In the aforementioned case, it supplied a means of modifying and stabilizing a classification of 'comparable' pharmaceuticals. However, as the following examples will suggest, the 'actual' use of drugs could also disrupt the Agency's work to compare and evaluate drugs.

What pharmaceutical 'usage'?

Having defined two comparable groups of pharmaceuticals, the project groups turned to the matter of comparing these drugs' use. But what pharmaceutical usage was the Agency to evaluate?

This question arose in the migraine group with respect to those pharmaceuticals that had a different route of administration than tablets, such as nasal sprays or injection.[86] These drugs obviously constituted a form of pharmaceutical use. What more, it was a form of use where the price per dose was higher than for the tablet-based treatments.[87] Notwithstanding these circumstances, the project group requested the Board to agree to the proposal to exclude these drugs from a more detailed evaluation. The grounds for this

[85] Interview Board member (health economist A), June 23 2004; Interview Board member (medical practitioner B), June 17 2004; Interview Board member (medical practitioner A), July 1 2004.

[86] Three of the six active substances marketed in Sweden at the time of LFN's review had products with different route of administration than standard tablets: Imigran and Zomig were available as nose sprays or as rapid dissolving tablets, Imigran could also be administered by suppository or injection (LFN 2005a, 8).

[87] cf. LFN 2005a, 49. The total sales volume of migraine products amounted to 343 million SEK in 2004 (approximately 37 million Euro), and tablet-based treatment constituted 240 million SEK (approximately 70%) of this cost (LFN 2005a, 27-28).

proposal, which the Board approved, was that the need for treatment alternatives for patients unable to swallow tablets was such that the products were "obviously cost-effective"[88] – even if the precise value of having alternative routes of administration was difficult to specify.[89] The difference in how 'the same' product was administered was grounds for *not* comparing the pharmaceuticals with the tablet-based treatments, since they treated patients for whom tablets were not a treatment alternative. Although the pharmaceuticals were used in medical practice, it was not for 'the same' use as tablet-based treatments.[90]

In the stomach-acid group, the question of which pharmaceutical usage to evaluate arose in relation to the aforementioned 'working classification'. When formulating this classification, it had been important to reflect drugs' *actual use* and the *real* costs and effects associated with this usage. The classification differentiated between pharmaceutical use on the basis of five medical conditions. But to consider 'actual use' for different medical conditions was problematic:

A first, overarching problem was that the seconded medical experts in the stomach-acid group, and clinical practitioners on the LFN Board, agreed that there was "significant off-label prescription taking place for certain products".[91] In other words: the working classification was not coherent with *all* usage, as defined through medical practice. What more, 'pharmaceutical use' in medical practice was not coherent with usage as defined by the Medical Products Agency. This posed a problem for LFN when defining which product usage to compare when evaluating the drugs since "off-label usage creates costs the same as approved uses"[92].

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[88] Interview project manager migraine group, June 10 and September 9 2004.
[89] cf. LFN 2005a, 49.
[90] Interview health economist migraine group, June 7 2004.
[91] Interview project manager stomach-acid group, March 14 2004.
[92] Interview health economist stomach-acid group, March 23 2004.

A second problem, related to the broader concern of off-label prescription, was the specific suspicion that medical practitioners were prescribing proton pumpinhibitors to patients that had some form of functional dyspepsia (stomach-ache) rather than gastro-oesophageal reflux disease (GERD). These two medical conditions could have similar symptoms. But various sources – including multiple clinical studies of pharmaceuticals' treatment effect, the drugs' SPCs and a recent knowledge overview issued by the Swedish Council on Technology Assessment in Health Care[93] – agreed that the response to treatment varied. Whereas GERD could be successfully treated with drugs in the stomach-acid group, functional dyspepsia could not. The problem was that there was ambiguity about which patients had GERD and functional dyspepsia, respectively. How was LFN to define use for those patients who were 'treatable'?

As regards the first matter of off-label prescription, the project group concluded that while off-label use was a pharmaceutical usage in medical practice, it was not coherent with the Agency formal mandate to evaluate or even explicitly deny subsidy for such use:

> [W]e can't do anything about [off-licence use] because our rule is that a product can only be subsidized for treatment of an approved diagnosis. Since [unspecific stomach-acid ache] is not an approved diagnosis we can't raise the issue and place that restriction in our decision because [that restriction] already exists.[94]

In other words, it was pharmaceutical usage *as defined by drugs' approved treatment area* which defined 'usage' in LFN's work. Off-label[95] use was therefore excluded from consideration in the product assortment review – as it had been in the Agency's first two decisions concerning 'new' pharmaceuticals.[96] The example of off-label use illustrates how part of 'real' pharmaceutical usage

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[93] Östman et al. 2000.

[94] Interview project manager stomach-acid group, March 14 2004.

[95] The term "off-label use" refers to prescriptions of registered medicines for a use that is not included in the prescribing information or that is disclaimed in the approved information. This includes use outside approved indication [medical condition], dosage, age and route.

[96] In its first two decisions, LFN denied subsidy for off-label prescription of two drugs (see p. 106, 111 of this volume).

in medical practice was set aside when it interfered with the inferred classification of use in LFN's formal instructions.

The issue of off-label prescription was resolved within the first year of the stomach-acid group's work. The matter of identifying 'treatable' patients remained an on-going concern until the time of the project group's completion. An overarching problem was that the working classification of five medical conditions that had been developed in the stomach-acid group opened for the possibility of diagnosis-based restrictions on subsidy. Whether the same drug was cost-effective in relation to other drugs could differ depending on which condition was treated.[97] Thus, it could be 'reasonable' to restrict subsidy for certain pharmaceuticals to specific uses. But for LFN to set such restrictions was problematic:

For one, diagnosis-based restrictions did not align with the principle of a product-based system of pharmaceutical subsidy, which LFN's governing legislation instructed the Agency to strive to uphold.[98] A product-based system infers that a pharmaceutical has *one* effect and cost, which can be 'reasonable' to subsidize. In medical practice, however, a pharmaceutical could always be expected to be 'reasonable' to subsidize for some use since "nearly every product is cost-effective for *some* treatment".[99] Using the working classification in the stomach-acid group, a given pharmaceutical could have *multiple* effects (and costs) related to the treatment of several different medical conditions. To compare products in a way that reflected the treatment regimes for different medical conditions, or actual variations between the cost and effect of treating various patient groups with a given drug, could consistently lead to conclusions counter to the legislators' wishes of a product-based system. To compare pharmaceuticals on the basis of a differentiation between several medical

[97] Interview project manager stomach-acid group, June 9 2005; Interview Board member (health economist A), March 30 2005.

[98] The New Pharmaceutical Benefits Bill 2001, 37-38, see also p. 78 of this volume.

[99] Interview health economist stomach-acid group, September 28 2004.

conditions could mean that certain treatment regimes with a particular pharmaceutical were 'reasonable' – and others not.

A further concern with diagnosis-based restrictions was that they placed requirements on how medical practitioners were to behave. Hence, it was essential that diagnosis-based restrictions avoid being "too fussy", since this could potentially decrease medical practitioners' compliance.[100] Restrictions that were incoherent with medical practice would not be followed, even if they were "theoretically correct".[101]

The issue of coherent restrictions was brought to the fore in relation to the differentiation between 'reasonable' patients (with GERD) and 'unreasonable' patients (with stomach-ache) in the stomach-acid group. In the migraine group, there had been no such concern surrounding the diagnosis of patients. The project group had concluded that multiple sources agreed that the treatment of migraine was cost-effective *as such*, and that 'migraine patient' was characterized in a similar manner by different sources. *When* it was appropriate to prescribe a migraine pharmaceutical (and thereby reasonable subsidize the use of this drug) was therefore a less pressing problem than *which* migraine drug to prescribe (I will return to this matter later in the chapter). In contrast, the question of when to prescribe a pharmaceutical was more clearly problematic in the stomach group, at least as regards to the treatment of GERD:

> Everything else is clear-cut ... you have a bacterial infection, you have an ulcerous sore, and so on. With GERD, there is so much variation ... You have symptoms with sores, sores but no symptoms, symptoms with no sores.[102]

The variation in GERD was a problem since there were medical conditions which had *similar symptoms* to GERD, but which various sources agreed had had *different* effects of treatment. Of critical importance from the perspective of the stomach-acid group, there was no recognized documentation that there was

[100] Interview LFN Chairman of the Board, March 24 and June 28 2004.
[101] Interview project member stomach-acid group, June 1 2005.
[102] Interview project manager stomach-acid group, May 17 2005.

any meaningful effect of treating functional dyspepsia with drugs in the stomach-acid group. Yet it was suspected that patients with functional dyspepsia were prescribed pharmaceuticals with subsidy because GERD – in particular symptomatic GERD – was difficult for medical practitioners to unambiguously identify. Patients' symptoms, clinical measurements using gastroscopy[103], governmental agencies' reports and the approved treatment areas for the products in the stomach-acid group did not give a coherent account of *when* a patient had symptomatic GERD and was appropriate to treat.[104] This ambiguity about symptomatic GERD made it difficult for LFN to define 'reasonable' usage.

As a suggested means of addressing the suspected problem of inappropriate prescription to 'untreatable' patients, the project group proposed restricting subsidy to patients with a 'confirmed diagnosis' to the Board. One suggested means of delineating treatable patients was to make subsidy of treatment of GERD contingent on a gastroscopic examination. This suggestion (and others) was discussed several times by the Board. Ultimately, however, it was rejected. Informants noted that a key argument for this was that LFN could not standardize diagnostic practice. There was variation in medical practice that the Agency could not hope to control:

> The Board took a pragmatic view and said that we can't tell the doctors how they should make a diagnosis ... we don't know enough about what it would mean, what kind of equipment they have access to today.[105]

To explicitly restrict subsidy contingent on certain diagnostic practices was not deemed feasible in the stomach-acid case. So while the difficulty of diagnosing 'treatable patients' remained, it was left to medical practitioners to resolve.

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[103] Gastroscopy is an examination of the inside of the esophagus (gullet) and stomach. It is performed using a thin, flexible fibre-optic instrument that is passed through the mouth.

[104] Interview project manager stomach-acid group, September 2 2005; Interview health economist, November 16 2005.

There was broad agreement among informants that LFN dare not risk making decisions that became "a hard strike in the air".[106]

So far, I have illustrated efforts – most notably in the stomach-acid group – to define comparable pharmaceuticals, and pharmaceutical usage. In the migraine group these issues did not give rise to much work. In contrast, the stomach-acid group had to deal with several instances where there were multiple sources of knowledge about 'comparability' and 'use'. The problem, then, was not primarily a lack of existing classifications of pharmaceuticals' characteristics, or definitions of drugs' use. On the contrary, pharmaceuticals were classified by numerous sources: by ATC, the Medical Products Agency, in clinical studies, in accounts of medical practice and by the law. But these sources were not always coherent.

This became further evident in subsequent work to determine how to measure the pharmaceuticals' medical and economic effects, and relate them to one another.

How to measure effect(s)?

Issues related to the delineation of comparable product groups and pharmaceutical use pre-dated efforts to establish how to make comparisons *within* the migraine and stomach-acid groups. In this section I will give examples of efforts to determine pharmaceuticals' treatment effect(s). This was a concern in both project groups, as it constituted an important part of calculating and comparing pharmaceuticals' cost-effectiveness. But what was an 'effect of treatment'? As before, there were many sources of knowledge about this characteristic:

LFN itself was one such source. Informants in both project groups referred at an early stage to guidelines issued by LFN (LFNAR 2003:2), in which the Agency articulated a preference for cost and effect measurements using quality-

[105] Interview project manager stomach-acid group, November 23 2005.

adjusted life years, QALY.[107] As described earlier in greater detail (see pp. 84-5 of this volume), this health economic concept is designed to measure both the life *quantity* and life *quality* effects of medical treatment on a common scale, thereby allowing a comparison of cost-per-effect using a standardized metric.

According to informants in both groups, the use of QALY for comparing costs and effects was not strictly necessary for a comparison *within* either group. But using this metric would facilitate later comparisons between therapy areas. Since LFN had to evaluate the entire product assortment, the use of QALY would enable the Agency to be more consistent in its decision-making.[108] Effect metrics that were more closely linked to units of measurement specific to particular medical conditions or therapy areas would be difficult to compare between groups:

> We want to be able to compare different types of medicines with the same measurement in order to make consistent decisions. Otherwise we have to compare 'a day without stomach-acid symptoms' with 'a day without migraine' or 'one mmHg decrease in blood pressure'. Those are impossible comparisons. Or rather, they are possible but ... to make a decision you still need a valuation of those states, otherwise it is random.[109]

Starting out, then, it was uncontroversial *in theory* to use QALY as the chosen basis for measuring and comparing pharmaceuticals' effect. But determining 'good' QALY-measurements – or, as it turned out, any comparable effect metric – *in practice* required effort.

One shared complication was that a majority of clinical studies of pharmaceuticals' treatment effect were made in countries other than Sweden.

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[106] Interview project manager stomach-acid group, February 6 2006; Interview LFN Chairman of the Board, April 5 2004.

[107] Interview health economist stomach-acid group, November 20 2003; Interview project manger migraine group, January 28 2004.

[108] Interview Board member (health economist B), July 2 2004.

[109] Interview health economist migraine group, February 13 2004.

This was a problem, since the cost structure of healthcare services could differ between countries and between studies.[110] It was important that comparisons were relevant in a Swedish context.[111] The lack of Swedish studies and differences in cost levels could both, to an extent, be compensated for by using foreign studies as a template and modifying the actual numbers used in order to re-calculate measurements. There were ways which my informants described using to modify foreign studies:

One way was to replace the values used with domestic prices for pharmaceuticals and other cost components such as doctors' salaries, the cost of hospital treatment and so on.[112] Another way was to add costs, in order to broaden the perspective of a study. Different health economic studies had different definitions of relevant costs, depending on whether they referred to public healthcare providers, for-profit hospitals, Health Management Organizations (HMO) and so on. It was necessary to include the same costs in different studies to make them comparable with one another, and align them to LFN's instruction to take a "broad, societal view" of pharmaceutical costs.[113]

A further complication in the migraine group, however, was that there were few clinical studies that measured the effect of migraine pharmaceuticals using QALY. And the results of the studies that *did* calculate QALY were not coherent with other sources of knowledge about these pharmaceuticals' characteristics.

From one comparison to none

The problems of measuring migraine treatment effects, particularly using QALY, surfaced when two studies which *did* compute QALYs were identified. Previously, the project manager and health economist had speculated that there

[110] Interview health economic migraine group, March 29 2004; Interview Board member (health economist A) June 23 2004.

[111] Interview project manager stomach-acid group, March 14 2004; Interview Board member (patient organization), July 19 2004.

[112] Interview health economist stomach-acid group, June 9 2004.

[113] Interview health economist migraine group, June 7 2004.

were few studies with QALY because the condition was not amenable to quantification in terms of QALY. The specific problem was that QALY measured the life quality of different states of health (and illness), but migraine did not exhibit a "continuous state of illness".[114]

The problem with the identified studies was that the computed QALY value for migraine sufferers was a negative number. This, according to the health economist in the migraine group was a "theoretically thorny issue. QALY is *by definition* a value between 1 and 0".[115] The study's negative QALY value also posed a practical problem for the migraine project group:

> A negative QALY suggests that suffering from migraine is worse than being dead. That may be the case for certain sufferers of Hortons, it's actually called "suicide headaches" .... [But] how does that value generally reconcile with migraine as we know in medical practice .... How does it reconcile with LFN deciding anything about pharmaceutical subsidy?[116]

Incoherence between different sources of knowledge about migraine made the use of the negative QALY values to evaluate the pharmaceuticals in the migraine group not an option. Although these results were eventually reconciled with results from other studies (that had used other effect measurements) which showed that the treatment of migraine was "not just cost-effective but cost-saving"[117], the migraine group sought a more robust effect metric.

There were several alternative ways of measuring treatment effect. Many of the clinical studies cited by pharmaceutical companies in their responses to the migraine group's questions used different measurements of treatment effect. Which comparisons were made of treatment effect also varied: many studies compared one pharmaceutical with placebo, or with the first patented drug

[114] Interview project manager migraine group, February 27 2004. Interview health economist migraine group, March 29 2004.

[115] Interview health economist migraine group, March 29 2004.

[116] Interview project manager migraine group, April 19 2004.

within the dominant class of drugs (the triptanes). Fewer studies had direct, so-called head-to-head, comparisons of pharmaceuticals. The studies also differed as regard the selection of patients, and length of time during which the study was carried out.

All in all, the multitude of effect metrics complicated a direct comparison between pharmaceuticals. Each clinical study provided a *partial* account of *certain* treatment effects for *a few* drugs. Individual studies tended to highlight *differentiating* characteristics of individual pharmaceuticals, such as a high speed of effect or a long-standing effect, rather than *similarities* between larger groups of drugs. Thus, the various studies' measurements were not formulated in accordance with the project group's instruction to make a *general* comparison of *all* products using a *common* metric.[118]

After discussions with the group's seconded medical experts and the Board, the migraine group decided to use the effect metric: pain relief within two hours. This definition of a 'successful treatment' was in accordance with a standard of the International Headache Society (IHS). Since most pharmaceutical companies had used this IHS definition in their clinical studies of pharmaceuticals, the use of this metric made it possible to compare some – if not all – results from various clinical studies. The chosen effect metric was nevertheless the "most inclusive".[119]

But the decision to use the aforementioned IHS metric did not put an end to the problem of determining migraine drugs' treatment effect. New complications surfaced. One problem was that the International Headache Society's standard had changed over time. While there was a 'golden standard' at any given time, there was not a *common* golden standard over time.[120] The aforementioned metric – pain relief within two hours – was an older standard. Ultimately, it was substituted for the more recent IHS standard (pain *free*

[117] Interview project manager migraine group, September 9 2004.

[118] Interview project manager migraine group, June 10 2004. See also discussion about the lack of "ideal effect metric" (LFN 2006a, 41-2).

[119] Interview health economist migraine group, September 8 2004.

[120] Interview project manager migraine group, June 10 2004.

within two hours) a few months before the formal completion of the migraine group review. This second metric measured "more of the right things", according to the project group manager, elaborating that it was coherent with what determined if patients went home from work or not, thereby incurring a costly productivity loss.[121] (However both the migraine group's health economist and project manager also noted that "[the two measurements] pretty much say the same thing".[122])

Even as the discussion about the choice of IHS-metric continued, the problem of measuring treatment effect for migraine pharmaceuticals changed focus. The issue *had* centered on which common effect metric to use when comparing migraine pharmaceuticals. But this was now no longer the key problem. Rather, it was that it was not possible to foresee which patient would have an effect of treatment with a particular drug, combined with a variation in which drug could provide a particular patient with effective treatment. As the migraine group's final report put it:

> Triptanes effect and tolerance for the individual patient varies and is difficult, even impossible, to foresee .... In practice, doctor and patient must test until a triptane with good effect and acceptable tolerance is identified. (LFN 2005a, 23)

So, although there was a common metric for measuring treatment effect there was no common treatment effect to measure since the drugs were not interchangeable treatment alternatives for individual patients. As the health economist in the migraine group succinctly summarized: "basically, you could say we ended up with no comparison".[123]

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[121] Interview project manager migraine group, January 25 2005.

[122] Interview project manager migraine group, February 22 2005; Interview health economist migraine group, February 22 2005.

[123] Interview health economist migraine group, February 22 2005.

I will return to what followed the conclusion that the migraine drugs were not *generally* comparable later in the chapter. For now, I will focus on the matter of how pharmaceuticals' effects were sought in the stomach-acid group.

Same, same or different effect?

In the previous example, the migraine group grappled with trying to define a common effect measurement – only to conclude that the chosen effect metric did not capture a critically important factor: *who* received an effect of using *which* pharmaceutical. The stomach-acid group faced a somewhat different set of concerns related to the question of how to measure treatment effect.

A matter which came to dominate much of the stomach-acid group's work from the Spring of 2004 until the group's completion in February 2006, was the identification of a study[124] where the authors claimed that all of the proton pump inhibitors (with one exception) had an equal effect of treatment *per milligram*. A number of activities were undertaken by the project group members in order to determine whether the study was true and relevant for LFN's evaluation.[125] These will not be considered in any detail here, given the study's interest in ambiguous knowledge rather than the construction of facts. It is enough to note that the various efforts did not disprove the study. (This would arguably have excluded it from further consideration by the stomach-acid group's work). But the equipotence of proton pump inhibitors (except one) per milligram raised a set of difficult question. One question was how the stomach-acid group was to compare the drugs. A particular concern was whether to compare the stomach-acid pharmaceuticals' effects by milligram or by dose.

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[124] Hellström, Per M and Sigurd Vitols. 2003. "Proton pump inhibitors equally efficacious in standard dosages". *Läkartidningen*. 100: 2212-6.

[125] These activities included inviting the researchers to the Agency for meetings and talking to the project group's seconded experts. The group also presented material to the Board and read other articles. The question was whether the study was relevant for LFN:s evaluation. One specific issue was whether the results were relevant *in clinical practice*. This was not certain, since the study was a pharmacological study, and had a different focus than the clinical studies which were 'normally' considered by LFN. Interview project manager stomach-acid group, September 28 2004.

That the proton pump inhibitors had been characterized as having 'the same' treatment effect per milligram was not coherent with how the drugs were marketed in tablets with different weights of active substance.[126] This discussion about whether to use weight or dosage as a basis for comparing treatment effect segued into a debate over how to define the relevant comparable 'dose.' There were many sources to draw on:

One source of 'dose' was each pharmaceutical's Summary of Product Characteristics (SPC), which included the dosage(s) that the Medical Products Agency (or its European equivalent, EMEA) had approved when granting marketing authorization. There could be many approved dosages, for treating different medical conditions (see Diagram 6)

***Diagram 6**: Approved dosages for stomach-acid drugs(mg) (LFN 2006a, 54)*

Tabell 6. Dagligt intag i milligram vid den för indikationen godkända doseringen

Indikation	Omeprazol	Lanzo	Pantoloc	Pariet	Nexium/ Nexium HP
Erosiv GERD	20	30	40	20	40
Långtidsbehandling erosiv GERD	20	15	20	20	20
Symtomatisk GERD	20	15	20	10	20
Magsår med HP-eradikering	40	60	80	40	40
Sår i tolvfingertarm	20	30	40	20	
Sår i magsäck	20	30	40	20	
NSAID-relaterade magsår	20	30	40		
Profylax NSAID-relaterade magsår	20	15	20		

A second source of 'dose' was the daily defined dose (DDD) issued by the World Health Organization. DDD is a standardized treatment dose definition linked to the ATC-classification system and used in drug utilization comparisons between countries and regions. The official definition of a DDD is: "the assumed average maintenance dose per day for a drug used for its main indication [according to

[126] In the stomach-acid group's final report, it is noted that: "In light of the findings of Hellström and Vitols, the variation in approved dosages between the pharmaceuticals appear to not be of a pharmacological or therapeutic nature" (LFN 2006a, 58).

the ATC classification system] in adults".[127] Clinical trials of pharmaceuticals in the stomach-acid group were a third (albeit it, multiple) source of 'dose'. As the product manager in the stomach-acid group noted, each of these sources of dose were more or less incoherent with one another – and with the dosage typically prescribed in Swedish by medical professionals.[128]

At the outset, the articulated goal was to use as close an approximation of "actually used" dose as possible, since this was what was paid for through the public pharmaceutical benefits scheme.[129] In comparison, several of the aforementioned sources were "more theoretical measurements".[130] But the discussion about how to approximate a 'real dose' were put on hold when questions were raised regarding the legal status of the Medical Product Agency's approved treatment doses. An evaluation by the Agency's lawyers concluded that LFN was required to use the Medical Product Agency's 'dose' when comparing the treatment effect of pharmaceuticals in the stomach-acid group.[131] (What happened after that is described further on in the chapter).

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The examples in this section have illustrated how the definition of a comparable effect metric was principally resolved through the choice of QALY, but reopened when QALY measurements were not readily available in the two pilot groups. To define an alternative effect metric it was necessary to confront alternative characterizations of pharmaceuticals' treatment effect (and dose) in SPCs, scientific articles and medical practice to name a few. In the stomach-acid case, the incoherence between different dose definitions was resolved when the Medical Product Agency's dosages was judged to be the legally required definition. In the earlier example taken from the migraine group's work, the difficulties with comparing pharmaceuticals' treatment effect was initially

[127] The DDD – definition and principles (WHO Collaborating Centre for Drug Statistics Methodology 2006).

[128] Interview project manager stomach-acid group, June 9 and September 28 2004.

[129] Interview project manager stomach-acid group, June 9 2004; Interview health economist stomach-acid group, June 1 2004.

[130] Interview health economist stomach-acid group, June 1 2004.

solved by using the standard effect metric defined by the International Headache Society. But the common metric did not make the drugs comparable, since the pharmaceuticals were not common treatments for all patients.

In the following section, I will give examples of efforts to determine the cost of pharmaceuticals' use, in particular their price.

Which price is right?

A common preoccupation in the stomach-acid and migraine groups was the characterization of pharmaceuticals' medical, but also financial, effects. In this section I will focus on efforts to determine pharmaceuticals' price. Informants agreed that price was a critical determinant of pharmaceuticals' relative cost-effectiveness. It was particularly important in the migraine and stomach-acid groups, the project members of both groups remarked at an early stage, because of *differences* in the price of drugs within each respective group.[132] But, as the following examples illustrate, determining the price of a pharmaceutical required effort to reconcile different sources of knowledge with one another. There were multiple prices for an individual drug depending on package size, the timing of LFN's evaluation relative patent expirations and whether prices changed due to the Agency's on-going review.

Which package size?

The same pharmaceutical could have a different price per tablet (or other pharmaceutical form), depending on the size of the package. Often, if not always, a larger package had a lower price per tablet than a smaller package. A question was therefore whether the project groups should evaluate the different package sizes (and their different prices). One reason for evaluating different packages was that paying a higher price for the same tablet was "by definition

[131] Interview health economist stomach-acid group, August 24 2004.

not cost-effective".[133] The strict use of a health economic perspective would only support an approval of subsidy for the package with the lowest price per tablet.[134] Yet such a decision was not coherent with pharmaceuticals' usage in medical practice:

Smaller, and often more costly, packages were used to test whether a pharmaceutical had an effect on a particular patient. Only approving subsidy for larger package sizes would increase the risk that pharmaceuticals were prescribed in large volumes to patients that did not receive an adequate effect of treatment. This was a particular concern in the migraine group, since these drugs needed to be tested on individual patients (as discussed above).[135] The project manager in the stomach-acid group similarly noted that it was not an effective use of resources to prescribe too large quantities. In the stomach-acid group, for example, there were differences in the expected length of time for which different medical conditions were treated using the same pharmaceutical.[136]

In a direct comparison of price per tablet, pharmaceuticals did not have a 'package size' characteristic. But this was not coherent with the characterization of pharmaceuticals in medical practice, where package size *was* an important property. An attempt to reconcile the characterization of package size as an irrelevant and relevant property was made in a joint presentation to the Board in May 2004. Here the two project groups proposed a 'decision rule' for deciding which pharmaceuticals to approve for further subsidized usage. Briefly, the proposal was for LFN to deny subsidy to *all packages of drugs* where the *cost per tablet* was *more than 50%* of the cheapest tablet in each group. (An underlying, and then unproven assumption, was that the products in each

[132] Interview project manager migraine group, February 27 2004; Interview health economist stomach-acid group, March 23 2004.

[133] Interview health economist migraine group, March 29 2004.

[134] Interview health economist stomach-acid group, March 23 2004.

[135] Interview project manager migraine group, April 19 2004.

[136] Interview project manager stomach-acid group, March 14 and June 9 2004.

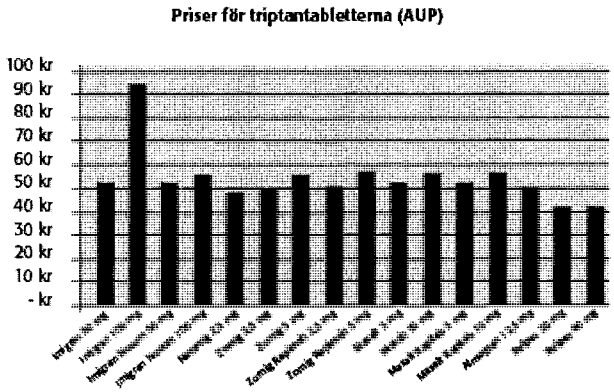
respective group were equipotent and/or interchangeable treatment alternatives). This proposal was "an experiment to gage the Board's reaction".[137]

The reaction was not positive. Two specific problems were highlighted by my informants in the Board, and recounted by informants in the project goup. The first was that using the proposed decision rule would lead to a denial of subsidy for approximately 80% of the package sizes in the stomach group. This was an "overly dramatic decision to make".[138] In the stomach acid group, in particular, the use of the decision rule would deny subsidy for most – if not all – other substances than that whose patent had expired and had lower priced generic competitors.[139] The second problem was that the Board did not want to make "fussy" decisions.[140] LFN needed to make decisions that were coherent with pharmaceuticals' use in medical practice; that were uncomplicated to follow. Making decisions which gave different package sizes of the same pharmaceutical different subsidization status would be overly complicated. The principle decision made by the Board was that the project groups should not make a separate evaluation by package size.

In the migraine group, this led to the decision to use the price per tablet of the largest package size for each product when making price comparisons. This was also the price comparison that was ultimately presented in the migraine group's final report (see Diagram 7).

[137] Interview project manager migraine group, June 10 2004.
[138] Interview Board member (medical practitioner A), July 7 2004.
[139] Interview project manager stomach-acid group, June 9 2004.
[140] Interview LFN Chairman of the Board, June 28 2004.

Diagram 7: *Price per triptane pill (LFN 2005a,29)*



Figur 2. Pris per tablett för de olika triptanerna i dess största tillgängliga förpackningar.

Using the chosen price was justified on the grounds that it was the most commonly sold package size: "so it is an adequate approximation of the pharmaceuticals' real costs".[141]

There was no similar choice of a single price for each pharmaceutical in the stomach-acid group's final document. Although explicit choices were made in those cases where the approved treatment dosage was defined as an interval rather than an individual dose[142], the comparison of pharmaceutical prices included both different package sizes *and* dosages:

[141] Interview health economist migraine group, October 5 2004.
[142] LFN 2006a, 54.

Diagram 8: *Price per milligram for proton pump inhibitors in marketed dosages and package sizes (LFN 2006a, 55)*

Tabell 7. Pris per milligram (kronor AIP) för protonpumpshämmare i förekommande styrkor och förpackningsstorlekar september 2005

		Förpackningsstorlek							
Produkt	Styrka	7	14	28	56	98	100	112	120
Omeprazol Merck NM	10 mg		0,31				0,36		
	20 mg		0,16	0,20	0,22		0,19		
Pantoloc	20 mg	0,29		0,24	0,25		0,23		
	40 mg		0,22	0,22	0,22		0,22		
Lanzo munsönderfallande	15 mg		0,32		0,32	0,32			
	30 mg		0,29		0,29	0,29			
Pariet	10 mg			0,53	0,53				
	20 mg		0,45	0,45	0,45				0,45
Nexium	20 mg		0,53	0,52	0,52	0,52	0,52		
	40 mg	0,32	0,32	0,32	0,32		0,32		

In the stomach-acid group, then, the final review document ultimately showed that there were multiple prices for pharmaceuticals. However, these were multiple prices at one particular point in time, namely September 2005. In the migraine and stomach-acid groups there were also issues centered around the possibility of multiple prices *over time*.

Changeable prices

Informants agreed that price was an important pharmaceutical characteristic in the Agency's work to evaluate whether drugs should be approved or denied further subsidy. But it was also acknowledged to be difficult to make decisions on the basis of a changeable characteristic. In the case of pharmaceutical prices, a change could make conclusions about relative cost-effectiveness obsolete:

> If you have a group of pharmaceuticals and one of them undergoes a radical change in price - then the basis for your conclusions [about the drugs' subsidization status] may no exist.[143]

[143] Interview health economist migraine group, June 7 2004.

Cost-effectiveness, as one Board member described it, "is fresh produce, it does not keep long".[144] But that the same pharmaceutical could have different prices over time was not immediately coherent with the Agency's mandate to make a decision about pharmaceuticals' subsidization status at a specific point in time.

The issue of changing pharmaceutical prices was brought to the fore in the migraine group's work in relation to a pending patent expiration. At the time of LFN's review, all of the drugs within the class of pharmaceuticals with the largest volume of sales[145], the so-called triptanes, had patent protection. However, the patent for one of the drugs' was set to expire in a few years time. This pharmaceutical (henceforth referred to by its Swedish market name, Imigran) was the current market leader, in volume of sales. It was also regarded as a "true innovation" in the treatment of migraine, having been the first of the triptanes introduced on the market.[146]

Imigran was sold in two tablet strengths: 50mg and 100mg. The tablet with the larger dosage had the highest price per tablet.[147] This higher price did not provide a significantly greater medical effect. Hence, the tablet was not cost-effective in a direct comparison of price-per-effect. However, the price of the tablet was expected to fall when the product's patent expired and generic producers started competing with the original pharmaceutical. The question was: should LFN take this anticipated drop in price into consideration? Calculating the cost of treatment with current practices supported a decision to deny further subsidy for the tablet, but a calculation with a hypothetical future price might not.

To deny subsidy for one dosage of Imigran, and approve subsidy for the other, could lead to difficulties in medical practice. But there were also problems with trying to calculate and compare cost-effectiveness with future prices. It was

[144] Interview Board member (health economist A), March 30 2005.

[145] According to the migraine group's final report, the total sales volume of migraine products amounted to 343 million SEK in 2004 (approximately 37 million Euro). Of these, 323 million SEK (approximately 94%) referred to use of triptanes (LFN 2005a, 27).

[146] Interview project manager migraine group, February 27 2004.

argued that using current prices was correct since it did not "anticipate the market".[148] "Trusting the market"[149] was considered both theoretically correct and necessary: "on what basis could we formulate some other price?"[150]

But even using current market prices was not without its problems. For one, as noted earlier, there were *multiple* current prices. Another problem was that the use of current prices made any calculations of cost-effectiveness, and decisions justified on the basis of these calculations less robust. The stomach group's health economist noted that pharmaceuticals financial characteristics such as price or cost-effectiveness were not a "cumulative science".[151] The results of earlier studies could often be irrelevant at a later stage. Both migraine group's members spoke of how changes in prices could change the placement of the "cost-effective frontier" and also the placement of a particular product in relation to this frontier.

As part of the discussion about current and future prices, questions surfaced about when and how LFN should re-evaluate individual pharmaceuticals; whether it was intended for the Agency to make continuous revisions of its review of therapy groups, for example. These principle matters were not resolved in detail, however the Board agreed to a principle stance that a lack of temporal robustness was a general problem facing the Agency's judgments. As such, it was not an adequate justification for not using current market prices.

But the efforts to determine pharmaceuticals' price did not end here. In the stomach-acid group, there emerged a debate over whether the current market price of patented and non-patented pharmaceuticals were directly comparable.

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[147] The cost of Imigran 100mg was almost 100% higher than that of the lower dosage (50mg) of the same drug *and* other competing products (see Diagram 7, p. 142 of this volume).

[148] Interview project manager migraine group, June 10 2004.

[149] Interview health economic migraine group, June 7 2004.

[150] Interview health economist stomach-acid group, September 28 2004.

[151] Interview health economist stomach-acid group, September 28 2004 and also Interview Board member (health economist B), March 30 2005.

Comparable prices?

The Board of LFN reached a principle decision for the migraine and stomach-acid groups to compare drugs' *current* price. But were current prices *comparable* prices? This question arose in relation to the stomach-acid group, which included both generic and brand-name pharmaceuticals.[152] Was 'patent protection' a characteristic that should define the comparison of drugs' price(s)?

The argument put forth by some of the pharmaceutical companies against a direct comparison was that it was not coherent with patent legislation, and specifically would limit their ability to recoup research costs through higher prices.[153] The effect of competition on price formation was a further argument for *not* comparing branded and generic pharmaceuticals too closely, since the branded drugs higher prices would mean they were denied subsidy. In addition to limiting *present* therapeutic choice, this could also be detrimental to *future* medical research if only the cheapest product(s) were left in a group.[154]

But differentiating pharmaceuticals on the basis of patent status was not coherent with the products use as treatment alternatives by medical practitioners, or with their similar (if not identical) approved treatment areas in their respective SPCs. What more, having patent protection – and the exclusive right to market a particular active substance – could not preclude the existence of different pharmaceutical treatment for the same disease:

> To have a patent does not mean a lack of competition. It only says no one else can produce and sell a specific substance .... [and] therapeutic competition between substances is both widespread and well known .... So on the one hand you want competition but also incentives for further research.[155]

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[152] A brand-name or *patented* pharmaceutical is 'the first' drug of its kind. The patent(s) of the patented drugs active substance gives it the exclusive right to produce and sell or license production for the active substance. When a patent has expired, this exclusive right is lost. So-called 'generic' pharmaceuticals, which contain the same active substances as the brand-name drug, can then be introduced.

[153] Recounted in interview with project manager stomach-acid group, April 22 2005.

[154] Interview health economist stomach-acid group, December 17 2004.

[155] Interview health economist stomach-acid group, June 1 2005.

For LFN to *avoid* comparing the price of generic and brand name drugs on the basis of differences in patent was not coherent with the Agency's mandate to evaluate the 'value-for-money' of different treatments:

> A patent does not imply a purchase imperative. It must still be possible to say no and if doctors and patients don't say no - for various reasons - then there is a need for [LFN] to say no for them with the argument that those resources can be used to save more lives - buy more benefits - elsewhere.[156]

An in-principle agreement was eventually reached within the Agency Board and Bureau that LFN's decisions would be based on a direct comparison of the price of all pharmaceuticals used to treat the same illnesses. However, resolving the ambiguity about which pharmaceutical characteristics were relevant to compare did not resolve all matters in the stomach-acid group. Characterizing patented and non-patented products as 'the same' were found to have potentially far-reaching implications for the decisions that the Agency could make regarding the various pharmaceuticals' subsidization status. A direct comparison suggested that several, and possibly all, of the brand-name pharmaceuticals should be denied continued subsidy. To deny subsidy for all but the most cost-effective product (or substance) might be considered a strict application of the health economic principle of cost-effectiveness, but it was undesirable for several reasons according to informants. I will return to the matter of how LFN sought to achieve reasonable *outcomes* on the basis of a direct comparison between patented and generic pharmaceuticals, later in the chapter.

A further concern with price was that it not only changed due to occurrences such as patent expiration. The migraine and stomach-acid groups also found that the Agency's work to evaluate the subsidization status of these pharmaceuticals could influence the drugs' price(s).

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[156] Interview project manager migraine group, September 9 2004.

Influenced prices (and product assortment)

The possibility that the Agency might approve subsidy for more or less all products in the existing assortment was raised in early interviews with informants. If companies lowered prices, then it was conceivable that drugs which were unreasonable to subsidize at a higher price became reasonable to use with subsidy. But having price as both an input and a possible output of LFN's evaluations was problematic:

> We're shooting a moving target .... And we're doing it while we're in motion. Health economics can help us with comparisons but you still need to know that what you've included is relevant and stable.[157]

Nevertheless, the discussions about LFN:s possible influence on prices were hypothetical – until the Fall of 2004. Prior to this, the principle decision had been made to compare pharmaceuticals' current price. As discussed above, this meant that one dosage of one pharmaceutical in the migraine group had a significantly higher price per tablet relative other products with a similar treatment effect. As informants had noted earlier, this suggested that the tablet (Imigran 100mg) should be denied subsidy. But in September and October, my questions concerning whether Imigran 100mg *would* be denied subsidy were met with comments that I should wait and see since the Board was evaluating the subsidization status of a 'new' pharmaceutical. Or was it?

On November 25 2004, LFN approved subsidy for a new drug: Imigran Novum 100mg. Two months earlier, the Medical Products Agency had judged this drug to be *exchangeable* with Imigran 100mg.[158] Because the two drugs were exchangeable, patients holding prescriptions for one of the drugs could now have their prescription filled with either this drug *or* the other. They were 'the same'. One difference – but from the perspective of LFN, a critical one – was that the 'new' drug was priced 42% lower than the 'old' one. So, under the

[157] Interview health economist stomach-acid group, June 9 2004.
[158] Medical Products Agency 2004.

rule of generic substitution[159], patients holding prescriptions for the more expensive Imigran would henceforth receive the cheaper Imigran Novum.

The introduction of Imigran Novum 100mg made the subsequent decision to deny Imigran 100mg subsidy much less dramatic than expected.[160] Whether it was reasonable and feasible to deny subsidy for one dosage of one drug had been extensively debated within the Agency prior to the completion of the migraine group. But when the outcome of the group review was announced it was met with little comment in the media.[161] Informants directly attributed this to the introduction of Imigran Novum. Had Imigran Novum not been introduced in Sweden, and had the two products *not* been judged exchangeable, then patients holding Imigran 100mg prescriptions would have been required to pay the cost of treatment or get a new prescription in order to get their migraine medication subsidized. This would have made the denial of subsidy for Imigran 100mg a more dramatic, and more difficult, choice to make.[162]

The example of Imigran/Imigran Novum illustrates that removing incoherence between different sources of pharmaceutical characteristics did not automatically resolve whether a particular decision about pharmaceutical subsidy was reasonable – and *feasible* – to make.

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[159] Generic substitution requires Apoteket to exchange a more expensive drugs for a cheaper alternative if and when an exchangeable drug exists (Act (SFS 2002:160) on Pharamceutical Benefits, section 21). Generic substitution is not required if a special note has been made by the prescribing medical practitioner that a patient is to receive the more expensive pharmaceutical with subsidy or if the patient pays the cost differential between the cheaper alternative and the prescribed drug (Ibid.).

[160] Interview project manager migraine group, February 22 2005.

[161] Informants recounted that individual patients had been in contact with the Agency, expressing concern that Imigran 100mg and Imigran Novum 100mg were not exchangeable *for them*. Interview project manager migraine group, February 22 2005; Interview health economist migraine group, February 22 2005.

[162] Interview project manager migraine group, February 22 2005; Interview LFN Chairman of the Board, April 5 2005.

What are reasonable outcomes?

That the Agency's decisions themselves needed to be reasonable and feasible was a common concern for both pilot group and Board member. Comparing the cost of pharmaceuticals using a common effect metric did not, for example, resolve the question of what constituted a 'reasonable' cost. The comparison provided an order of *relative*, not absolute, cost-effectiveness.[163] Another problem was that the project group's calculations and comparisons tended to create 'too precisely' defined categories of cost-efficient patients and treatments. This was not coherent with the 'sliding scale' of actual cost-effectiveness in medical practice:

> There is no measurement where at 100 you're ok and at 98 you're not. There are no clear limits .... When looking at cost-effectiveness you have a patient with a cost of 1 SEK and then a progressively increasing cost. You don't have one group with a common cost of 100 SEK for each QALY and another where the cost is 10,000 SEK and it is easy to define.[164]

The efforts to define representative, accurate and common measurements of cost and effect did not resolve crucial matters regarding the *absolute* and *precise* characteristics of a pharmaceutical. Notably, a recurring view was that LFN's calculations should not be used to remove of all but one 'cost-effective' product within a given therapy area.[165] There was a value of diversity which needed to be secured, and the calculative tools used by LFN to create comparable registers of effects and costs were not themselves a source of this particular characteristic:

> Theoretically, even the smallest difference in price for the same effect of treatment means an infinite cost per QALY. But that is not

[163] Interview health economist migraine group, October 26 2004.

[164] Interview project manager stomach-acid group, May 25 2005.

[165] Interview LFN Director-General, October 24 2003; Interview project manager stomach-acid group, October 9 2003.

> reasonable, to exclude everything else but one... So the question remains: what is an acceptable cost for diversity?[166]

How to ensure an adequate product diversity was a critical issue during the latter half of the stomach-acid group's work.

Ensuring product diversity

As described earlier, the stomach-acid group had worked to determine whether the various proton pumpinhibitors had 'the same' treatment effect. When it was concluded that there were no significant differences between these drugs (barring one pharmaceutical), it raised the question as to how to ensure that there was product diversity. Although the pharmaceuticals' effect was 'the same', the drugs' price per dose – and thus their cost of treatment – was not. In particular, the price per dose of patented substances was higher than the price per dose of products with the substance (omeprazole) whose patent had expired.

An early attempt to formulate a 'decision rule' in the Spring of 2004, had been rejected on the grounds that it would not secure an adequate diversity of treatment alternatives (see pp. 140-1 of this volume). One year later, in the Spring of 2005, a new proposal was put before the Board. In brief, this proposal suggested that products were to be removed on the basis of a maximum price differential. Specifically, the suggestion was that pharmaceuticals with 'the same' treatment effect could not be priced at more than 25% of the cheapest pharmaceutical.

Allowing for variation in the price of different products with 'the same' effect was intended to secure a diversity of products used to treat stomach-acid disorders. Denying subsidy for all but the single most cost-effective product would have been a strict application of the health economic principle of cost-effectiveness. However, approving subsidy for *one* drug was incoherent with

[166] Interview health economist stomach-acid group, June 1 2005.

how the drugs were use to treat a diverse patient population in medical practice. It was also incoherent with the characterization of pharmaceuticals' treatment effects in clinical studies, which did not use the chosen comparison metric. Denying subsidy for all but one drug would also undermine competitive pressure on pricing within the therapy group, and possibly have a negative impact on incentives for future research.[167]

The price tolerance gave pharmaceutical companies *some* compensation for differences in treatment effect that were not captured by the chosen comparison metric. This gave some incentives for incrementally better products. But the price tolerance also capped the tolerated price differential between products which were 'the same' according to the standardized effect measure. The price tolerance also upheld price competition between the generic pharmaceuticals. Since these products had an identical active substance, a strict application of health economic principles would also have removed subsidy for all but the single, cheapest product. Creating a monopoly in this manner was not desirable, since it was expected to lead to higher prices over time.[168]

However, which precise price a pharmaceutical with approved subsidy would have within the set price tolerance was not set out. This was "for the market to decide".[169]

Ordering pharmaceuticals with approved subsidy

In an earlier section I described some of the difficulties that the migraine project group encountered when determining which of multiple effect metrics to use when comparing pharmaceuticals' treatment effect. Ultimately, the recourse was to define a 'successful treatment' in accordance with the International Headache Society's standard. Since most clinical studies used this metric (albeit in combination with other measurements), it could be used to compare results from multiple studies. However, it was recognized that the chosen metric did

[167] Interview project manager stomach-acid group, September 2 2005.
[168] Interview project manager stomach-acid group, November 16 2005.
[169] Interview health economist stomach-acid group, November 23 2005.

not capture a number of potentially clinically relevant characteristics (as was also concluded in the stomach-acid group, see previous section). Yet settling on a "less ambitious"[170] effect measure did not end the list of thorny issues.

Following the efforts to define a common effect metric for comparing the migraine pharmaceuticals, the subsequent comparison was initially couched as a matter of deciding how many of drugs were needed to have adequate product diversity. The project member likened the matter to an analysis of "marginal rate of return", where the first product might treat a certain percentage of patients and subsequent pharmaceuticals successfully treating an increasingly smaller group of new patients.[171] However, these discussions ceased when the project group's seconded medical experts and various other parties highlighted a critical problem: it was not possible to foresee which patient would respond to which pharmaceutical. In other words, the drugs were not general treatment alternatives for individual patients. The chosen effect metric standardized the pharmaceuticals' effects, but was incoherent with the (potential) *incomparability* of drugs in medical practice.

The subsequent approval of all the triptanes was a direct consequence of the conclusion that the pharmaceuticals – for LFN – were not general substitutes, combined with the calculated cost of not treating migraine. These two reasons made it 'reasonable' to approve subsidy for all the drugs (except the aforementioned dosage of Imigran). Yet despite the lack of *general* treatment characteristics, the drugs had similarities and differences in their calculated cost-effectiveness. These were important to communicate, according to informants:

> [LFN] may have said yes to everything, but we still have a preference as to the order in which patients are prescribed drugs.[172]

[170] Interview Board member (health economist A), June 23 2004.
[171] Interview project manager migraine group, April 19 2004.
[172] Interview project manager migraine group, January 25 2004.

LFN's final report for the migraine group included a ranking of the products based on their calculated cost-effectiveness (Diagram 9):

***Diagram 9**: Ranking of migraine pharmaceuticals' cost-effectiveness (LFN 2005b, 3)*

- Maxalt (rizatriptan) 10 mg appears to be the most cost-effective choice.
- Relpax (eletriptan) 40 mg could be the most cost-effective alternative, but only under certain conditions. There are certain gaps in the documentation, as there is a lack of direct-comparative studies of good quality.
- It is difficult to see a cost-effective use of Imigran (sumatriptan) 100 mg if the price is higher than the price for the other products. However, the case for Imigran is superior clinical experience, extensive documentation and the widespread access to various forms of dosage.
- The recommended starting dose for Zomig (zolmitriptan) is 2.5 mg, but seen from the perspective of cost-effectiveness 5 mg seems like a more appropriate dose to begin with.
- Relpax (eletriptan) 80 mg is because of its high price not a cost-effective solution in the first case. But it can be valuable for patients not helped by any other triptan.
- Naramig (naratriptan) 2.5 mg is a secondary alternative and should only be used if the price is not higher than for Almogran (almotriptan) 12.5 mg.
- There is no reason to re-examine the treatment alternatives which are secondary choices amongst the triptans as they are not cost-effective as primary alternatives. This is valid for Relpax (eletriptan) 20 mg and 80 mg, Naramig (naratriptan) 2.5 mg and Maxalt (rizatriptan) 5 mg.

It was stressed that the ranking was not a *treatment recommendation*. Rather it: "shows how to make treatment decision based on cost-effectiveness considerations".[173] It was an order in which to test drugs' treatment effect "if one took cost-effectiveness into consideration. But there are other things that need to be taken into account as well, of course".[174] The responsibility for considering *other* relevant characteristics for the individual patient lay with the treating medical practitioners. Informants also repeatedly stressed that the ranking did not have a binding legal status. The Agency would not monitor whether medical practitioners actually followed the ranking, and LFN did not have the means of forcing compliance. This was considered appropriate by informants, who noted

[173] Interview health economist migraine group, January 25 2005.

that subsequent changes in matters such as the prices of pharmaceuticals could be expected to make the project group's conclusions obsolete in time. It was therefore not desirable for the ranking to have *too much* influence.[175]

The end is...

...near?

With increasing frequency as the prospect of a Board decision drew nearer, my informants talked about a "decision imperative" facing the Board. The project manager for the migraine group noted, echoing similar sentiments as other informants within the Bureau:

> Not making a decision is also a decision since this upholds the status quo of subsidizing the pharmaceutical in question .... To say that there isn't enough information to make *any* decision is still to de facto make a decision to approve subsidy.[176]

But there needed be justification to support a decision – whatever it was. It is perhaps not surprising that in the months leading up to the completion of the migraine and stomach-acid groups, significant and increasing effort went into drafting decision justification documents. The migraine group also began drafting a "group document" in the Fall of 2004, and the stomach-acid group soon followed suit. Subsequent to the release of the final documents, these various drafts were circulated and rewritten.

Even before then, both project groups had authored various 'test documents' and presented them to the Board throughout the evaluation process. An example of this was the joint proposal of a decision rule, presented

[174] Interview project manager migraine group, February 22 2005.

[175] Interview project manager migraine group, February 22 2005; Interview health economist migraine group, February 22 2005.

[176] Interview project manager migraine group, September 9 2004 and also verbatim in Interview project manager stomach-acid, April 22 2005.

in May 2004. Authoring test documents was described by project members as a way to account for the on-going evaluation work: "we're working on this all the time, the Board only sees it once a month or so".[177]

The migraine project manager described how the group raised issues over time, in order to secure incremental approval from the Board. For example, the Board was asked to sign off on matters such as the project group focusing primarily on the triptanes; not spending significant time considering the cost of side effects; only comparing drugs taken as tablets; and using specific meta-analysis[178] as its point of departure since it was "the best available material". Involving the Board in these detailed questions was important as a means of developing practice for coming reviews – but also as a means to prepare for a final decision:

> We're involving the Board in a lot of nitty-gritty, but that is useful at this stage. We need to know which direction to take. And they need to know what lies behind the material we send them.[179]

The drafting of mock decision justification documents was a particular means of "testing the weight of the arguments".[180] It was employed in the stomach-acid group also as a means of communicating with the Board:

> You have to write it to see if the arguments, when taken together, are tenable. It isn't always clear what the consequences of different principle decisions are until you start writing it all down.[181]

As part of the evaluation process, the drafted group reports were also circulated beforehand to other governmental agencies, to the effected pharmaceutical companies and (in the stomach-acid group) to patient organizations for comments. This led to certain changes, although it was acknowledged that the

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[177] Interview project manager stomach-acid group, May 25 2005.

[178] A meta-analysis is a statistical practice of combining the results of a number of studies. Meta-analysts translate results from different studies to a common metric and statistically explore relations between study characteristics and findings.

[179] Interview project manager migraine group, September 9 2005.

[180] Interview project manager stomach-acid group, November 16 2005.

documents became more and more fixed over time. A few weeks before the final announcement, in conjunction with a final presentation to the Board, the project manager commented that the outcome of the evaluation was now more or less decided:

> The Board can not change their minds now - there is not time to re-write the decision justification documents![182]

The end is - here?

The outcome of the migraine group was announced on February 18 2005. As regards the subsidization status of these drugs, the Board had decided to deny further subsidy to Imigran 100mg, but grant all of the remaining pharmaceuticals in the therapy group continued subsidy (without restrictions). In one case (Naramig 2,5mg), the decision to approve further subsidy was announced concurrently with a 14% decrease in the price of the drug.[183]

In addition to these decisions, LFN's final evaluation report for the migraine group also included the aforementioned ranking of products based on their calculated cost-effectiveness (cf. Diagram 9, above). LFN had never previously issued a ranking, but the project manager in the migraine group speculated that it might become a common part of the Agency's product group reviews since they made it possible for LFN to differentiate between pharmaceuticals that were granted continued subsidy.[184]

The outcome of LFN's review of the stomach-acid group was announced on January 19 2006. On the basis of the price tolerance principle described earlier in the chapter, the Agency approved continued subsidy to those pharmaceuticals that were priced within 25% of the lowest priced product. These drugs were: generic producers of omeprazole and Pantoloc (pantoprazole). Two drugs –

[181] Interview project manager stomach-acid group, November 23 2005.
[182] Interview project manager stomach-acid group, December 23 2005.
[183] LFN 2005a, 5.
[184] Interview project manager migraine group, February 22 2005.

Nexium and Cytotec – were approved subsidy with restrictions. In the case of Nexium, it is "only reimbursed for diagnosed ulcers in the oesophagus or where generic omeprazole or other proton pump inhibitor has not given satisfactory treatment results".[185] Cytotec, meanwhile, was approved subsidy for "prevention of ulcers caused by antiinflammatory (sic) medicines (NSAID)".[186]

The remaining drugs, including Losec and Losec MUPS (the brand name drug containing omeprazole) and two patented proton pump inhibitors (Pariet and Lanzo), were denied subsidy. In these cases, the denial of subsidy was justified on the grounds that "the price ... is too high to accommodate the pricing band of 25 percent".[187]

A few weeks following the announcement of the stomach-acid groups results, LFN issued a 'fact sheet' summarizing which stomach-acid pharmaceuticals had been included and excluded from the pharmaceutical benefits scheme. The document went on to explain that all of the Agency's decisions to deny a pharmaceutical subsidy had been appealed to the Stockholm County Administrative Court. As a result of these appeals: "these pharmaceuticals continue to be subsidized until a court rules differently".[188]

After more than two years, the final outcome regarding the stomach-acid pharmaceuticals' subsidization status still lay somewhere in the future.

What now?

In this chapter I have used examples from the migraine and stomach-acid groups work to illustrate how an ostensibly simple sentence – for example "if two drugs are equally good then one cannot cost twice as much as the other one" – was complicated to make. The chapter illustrates how making such a knowledge-based statement about pharmaceuticals' characteristics required the

[185] LFN 2006a, 6.
[186] Ibid.
[187] LFN 2006a, 13, 14.

project groups to deal with multiple sources of knowledge that, when taken together, were ambiguous about drugs' comparability, use, treatment effect, price, and – ultimately – 'reasonable-ness'. The chapter suggests that 'decision-able knowledge' is an achievement and an outcome of ordering work, rather than a readily available resource.

In the next chapter, I use examples from my study of LFN's pilot projects for the product assortment review to characterize methods for *how* coherent knowledge can be achieved by removing ambiguity between multiple sources of knowledge (Chapter 7). In the following chapter (Chapter 8), I will go on to characterize how decisions can be formulated when attempts at removing ambiguity between multiple sources fail to achieve coherent knowledge.

[188] LFN 2006b, 1. One month later, LFN announced that parallel importers of Nexium – who had appealed the Agency's decision to restrict subsidy for the drug – had withdrawn this appeal (LFN 2006c).

7. AGREED? ATTEMPTING TO REMOVE AMBIGUITY AND MAKE DECISIONS

In this chapter, I will discuss how the project groups in LFN dealt with ambiguous knowledge about pharmaceuticals' characteristics.[189] My analysis is based on material presented in Chapter 6. Using examples from the migraine and stomach-acid groups' work to define comparable groups of drugs, measure treatment effect, and compare prices, I characterize various methods of attempting to achieve coherence between multiple sources of knowledge.

The concepts of coincidence, privileging and calibration (Mol 2002) are the starting point for my discussion of the project groups' behavior. To briefly recapitulate, these three concepts characterize different ways in which "clashes" between multiple versions of an object can be resolved. Coinciding sources 'add up' to a coherent characterization of an object. Privileging removes ambiguity between sources by using one sources, and excluding others. Calibrating, finally, removes ambiguity by standardizing multiple sources using a common metric.[190] In this chapter, I will elaborate this typology using examples of how ambiguity about pharmaceuticals' characteristics was dealt with in the stomach-acid and migraine groups.

Of course, not all incoherence between multiple sources of knowledge led to attempts to remove this ambiguity. Multiple sources could also coincide.

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[189] This chapter is based on Sjögren and Helgesson (forthcoming [2007]).

However, my account of LFN's work with the stomach-acid and migraine groups includes few instances of such coinciding sources of knowledge. This follows, in part, from the study's methodological focus on controversy (see discussion on pp. 67-8). Coinciding sources were also difficult to identify due to the limited effort made to relate coherent sources to one another. When it was "straightforward" to use the ATC-based classification of comparable pharmaceuticals in the migraine group, since it agreed with how the pharmaceuticals were used in medical practice then no further effort was made to achieve coherence between these two sources. However, this and a few other examples of coinciding sources of knowledge can be identified through comparisons between the stomach-acid and migraine groups.

For instance, in the stomach-acid group there was ambiguity about the characteristics of 'treatable patients'. Of particular concern was the identification of patients with symptomatic GERD (gastro-intestinal reflux disorder). This medical condition had similar symptoms to another medical condition (functional dyspepsia). Multiple sources gave coinciding accounts of the limited effect of treating patients with this second condition using a category of stomach-acid pharmaceuticals (the so-called proton pump inhibitors). But there was ambiguity between multiple sources of knowledge about who was a 'patient with GERD'. Patients' descriptions of symptoms were not obviously coherent with clinical measurements using gastroscopy, or with governmental agencies' treatment recommendations or the treatment areas that had been approved by the Medical Products Agency. This ambiguity about the delineation of 'treatable patients' gave raise to various attempts to achieve a coherent characterization. I will return to these efforts later in the chapter.

In contrast, there was no controversy about the characteristics of treatable patients in the migraine group. The 'migraine patients' delineated by medical practitioners was coherent with the 'migraine patients' in clinical studies and in the drugs' SPCs. These *coinciding* sources of knowledge did not prompt further

[190] For a more detailed presentation, see pp. 47-50 of this volume.

efforts to resolve incoherence between them. It is to attempts at removing ambiguity to which I now turn.

Privileging one source over others

Several attempts were made to remove ambiguity by privileging one source of knowledge over other sources. One example of this from my study of the stomach-acid group was the work to define pharmaceuticals' 'treatment dose' (see pp. 136-8 of this volume). There were many sources of pharmaceuticals' treatment dose. The Medical Products Agency's marketing authorization documents was one source. Another source of 'dose' was the package sizes and tablet dosages sold by Apoteket. A third source was scientific articles about clinical trials measuring drugs' treatment effects.

The many versions of 'treatment dose' became problematic when a scientific article was identified describing a study that showed all but one of the proton pump inhibitors to have the same treatment effect *per milligram*. Which treatment dose was used to compare pharmaceutical's costs and effects was therefore of considerable importance. A pharmaceutical with a low relative price *per milligram* might be sold in larger tablet doses which gave it a high relative price *per tablet*. Which treatment dose was LFN to use to evaluate the drugs?

The incoherence between different sources in this case was removed by privileging the Medical Product Agency's definition of treatment dose, and excluding those of other sources. Informants noted that the marketing authorization documents had a legal status that required them to use this source of 'treatment dose'.

However, the Agency did not always privilege the Medical Product Agency over other sources of knowledge about pharmaceuticals' characteristics. For example, as I will discuss later in this chapter, the Medical Products Agency's definition of 'approved treatment' was not used to the exclusion of other sources when delineating comparable pharmaceuticals in the stomach-acid group. Thus, rather than privileging one source *in all aspects*, LFN's behavior in the stomach-

acid group suggests a form of partial privileging. A source was privileged in some cases, but not in others.

Another instance where ambiguity was removed by privileging one source of knowledge about a pharmaceutical's characteristics was the exclusion of so-called off-label prescription[191] from the Agency's evaluation of the stomach-acid group (see pp. 124-7 of this volume). Off-label prescription was known to occur in medical practice as regards pharmaceuticals in the stomach-acid groups. But, by definition, off-label use did not exist in the Medical Products Agency's marketing authorization documents. By privileging this version of 'pharmaceutical use', this incoherence was removed *for LFN*. However, it was noted that off-label prescription remained a concern for other parties. For example, county councils who had fiscal responsibility also for the cost of off-label prescription of subsidized drugs would have difficulty. LFN's removal of ambiguity postponed having to deal with this incoherence by suppressing certain sources of knowledge that were expected to resurface in other site.

The examples of privileging from my study of LFN's work in the migraine and stomach-acid groups outline a more incomplete and unstable privileging than that characterized by Mol. But removing ambiguity by privileging one source and excluding others was not the only method of attempting to achieve coherence between multiple sources. Another method was to calibrate different sources to one another using a common metric.

Calibrating sources

Privileging one source of knowledge over others attempts to remove incoherence between multiple sources by excluding all but one source. Another method for attempting to remove ambiguity about pharmaceuticals' characteristics was to calibrate different sources of knowledge to one another using a common metric.

[191] The reader is reminder that 'off-label prescription' refers to the prescription of a pharmaceutical for other uses than those for which the drug has been formally approved, see p. 126 of this volume.

The efforts to define a common measurement of 'treatment effect' for the triptanes in the migraine group are an example of calibration. As presented in Chapter 6 (pp. 132-5), there were many versions of 'treatment effect' in the clinical studies cited by the pharmaceutical companies marketing these drugs. 'Treatment effect' was measured using a variety of different metrics, time intervals and so on. Informants concluded that the differences in how and when 'treatment effect' was measured meant that the studies, when put together, were ambiguous about an individual drug's treatment effect as compared to the other triptanes in the migraine group. In an attempt to make the studies' results coherent and comparable, the migraine project group used an effect measurement as defined by the International Headache Society to standardize a common 'treatment effect' metric. While this measurement was acknowledged to not capture *all* characteristics of pharmaceutical treatment, it made 'treatment effect' a less ambiguous and more coherent characteristic.

Translating foreign studies and making them relevant in a Swedish setting using 'known techniques' was another example of calibration (see p. 130 of this volume). By changing specific values, the foreign studies became standardized to Swedish conditions. Thus, it was no longer necessary to undertake separate studies of pharmaceuticals' use *in Sweden*. The calibrated foreign studies were comparable to having undertaken the studies in Sweden in the first place.

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So far, I have discussed the stomach-acid and migraine groups' efforts to remove ambiguity about pharmaceuticals' characteristics using Mol's concepts of privileging one source of knowledge over others or calibrating sources using a common metric. In the next section, I introduce another pattern of behavior for removing ambiguity: mediating between multiple sources of knowledge.

Mediating between sources

Mediating between sources of knowledge differs from the aforementioned methods of privileging and calibrating in that it involves compromising between

different sources in an attempt to construct a *composite* of multiple sources of knowledge (cf. composite objects, Mol 2002, 71).

The effort to create a 'comparable' group of stomach-acid drugs is a first illustration of mediating. As I described earlier in this chapter, there was no efforts made to remove ambiguity between multiple sources of knowledge in defining a 'migraine group', since these various sources gave a coinciding characterization of comparable pharmaceuticals. The same was not the case in the stomach-acid group, where various sources made different classifications of 'comparable drugs'. One incoherence highlighted by informants was between the ATC-based classification of stomach-acid pharmaceuticals and the characterization of similarities and differences inferred by the approved treatment areas in the Medical Products Agency's marketing authorization documents. Whereas the ATC-code classified all the pharmaceuticals as 'the same', the marketing authorization documents characterized them as 'different' (see pp. 119-24 of this volume).

In an attempt to reconcile the two characterizations of pharmaceuticals' properties, the stomach-acid group drew on accounts of how medical practitioners used the drugs in question. This resulted in the articulation of a 'working classification' for stomach-acid pharmaceuticals. The classification included elements of both the ATC- and Medical Products Agency-based characterization of the pharmaceuticals, as well as representations of the drugs' use in medical practice. But, the classification neither *privileged* any one of these sources nor *calibrated* the multiple sources using a common metric.

The introduction of a price tolerance in the stomach-acid group is another example of mediation, this time between various sources of knowledge about 'reasonable' pharmaceuticals – and reasonable outcomes of LFN's decision-making (see pp. 150-2). The price tolerance principle mediated between 'reasonable' drugs as defined by health economic calculations, in medical practice and according to notions about competitive market efficiency in economic theory.

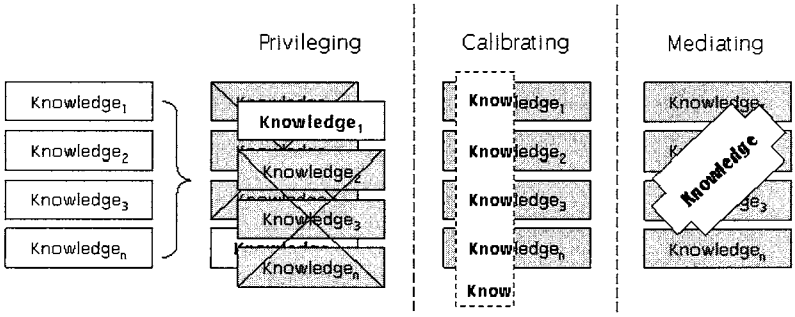
The price tolerance set a framework for defining whether drugs fulfilled the criteria for subsidy: that a pharmaceutical with 'the same' treatment effect had a maximum price differential of 25% compared with the lowest priced drug. However, a *precise* characterization of a 'reasonable' drug within this framework was not given. There was an allowed price variation between drugs which had 'the same' treatment effect, according to the standard metric. As in the case of the aforementioned 'working classification' in the stomach-acid group, then, none of the individual sources of knowledge about what was a 'reasonable drug' was privileged over the others, nor used as a standard to which others were calibrated.

Methods for removing ambiguity

In the chapter, I have used examples from my study of LFN to characterize three methods for removing ambiguity of knowledge when trying to make decisions: privileging, calibrating or mediating between sources. In each case, the attempts to remove ambiguity were precipitated by situations where there was incoherence between multiple sources of knowledge about pharmaceuticals' characteristics.

Based on examples from my study of the stomach-acid and migraine groups, I have proposed two modifications to Mol's notion of privileging. The first is the introduction of partial privileging, which refers to how one source of knowledge may be privileged regarding *certain aspects*, but not consistently and wholly privileged to the exclusion of all other sources. The notion of suppressing sources, in turn, is used to characterize privileging that is potentially unsustainable *for others*. Based on my study, I have also proposed that attempts can be made to remove ambiguity by mediating between multiple sources of knowledge. Mediation involves a compromise between multiple sources such that no single source is privileged to the exclusion of others, nor used as a common standard to which others are calibrated (as illustrated in Diagram 10, below).

Diagram 10: *Methods for removing ambiguity between multiple sources of knowledge*[192]



Existing theories of organizational choice commonly assume that decision-making requires coherent knowledge about reality. My findings show removal of ambiguity as an achievement, requiring effort. A first answer to the study's question of *how* organizations deal with ambiguous knowledge when making decisions is therefore: that efforts are made to remove ambiguity of knowledge using various methods, in order to achieve a 'decision-able' form and contents of knowledge. But in my study of LFN's two decision-making processes, there were efforts to remove ambiguity which failed in their attempts to achieve coherence. In the next chapter (Chapter 8), I will examine how *unsuccessful* attempts to remove ambiguity were dealt with.

[192] For presentational reasons, the diagram suggests that 'knowledge' is an object that takes a standardized, 'packaged' form. The formatting of knowledge has not been considered explicitly in this study. However, previous research on representation and metrology highlight precisely the standardizing and performative function of quantification (cf. MacKenzie 1981; Porter 1992, 2000; Mallard 1998; Hacking 1998) and classification (Bowker and Star 1999).

8. No choice: Delaying decisions or Delegating ambiguity

In the previous chapter, I characterized three methods of removing ambiguity between multiple sources of knowledge. Using examples from my study of the stomach-acid and migraine groups I proposed that coherent forms of 'decision-able' knowledge can be achieved by *privileging* one source over others, by *calibrating* sources to a common metric or by *mediating* between multiple sources. But attempts to remove ambiguity are not inherently successful achievements. In this chapter, I will use examples from my study of LFN's work in the stomach-acid and migraine groups to outline two organizational responses to unsuccessful attempts to remove ambiguity: *delaying decisions*, pending additional efforts to remove ambiguity, and making decisions that *delegate ambiguity* to others.

Delaying decisions when attempts to remove ambiguity fail

During most of the time that I followed LFN's work with the stomach-acid and migraine groups there were no decisions made about the subsidization status of these pharmaceuticals. LFN announced its decisions concerning the migraine group in February 2005, sixteen months after the group's evaluation was publicly initiated in October 2003. The Agency's decisions in the stomach-acid group were announced almost one year later, in January 2006. In several

instances, decisions were delayed pending further attempts to remove ambiguity about pharmaceuticals' characteristics.

In the stomach-acid group, for example, the scientific article which concluded that a certain group of pharmaceuticals were equipotent per mg was identified during the first year of the group's work. Much effort was then made to determine *how* this article related to other characterizations of pharmaceuticals in medical practice, in the drugs' marketing authorization documents and so on. This took time. There were various attempts made to relate multiple sources to one another. An early attempt at mediating between different characterizations of 'reasonable' drugs was a joint proposal from the stomach-acid and migraine groups to the Board of LFN in the Spring of 2004 was that the Board should deny subsidy for all *pharmaceutical packages* that had a *cost per tablet* greater than *50% of the lowest priced product.* At the time, this suggestion was turned down on the grounds that it was not feasible (see pp. 140-1 of this volume).

Specifically, this means of characterizing 'unreasonable' pharmaceuticals did not reconcile with how the pharmaceuticals were used in medical practice. Excluding individual packages on the basis of their cost-per-tablet would be "too fussy" (as described on p. 128). Denying subsidy for individual package sizes was also expected to lead to inefficient resource use, since small packages with a higher cost-per-tablet were used to test whether patients received any effect of treatment. In short, the Board did not make decisions based on the project groups' suggestion. Both groups were instructed to continue their evaluations.

One year later, the stomach-acid group attempted another version of mediation, this time suggesting that products with *the same treatment effect* and a *cost-per-tablet* for the most commonly used package size that was *more than 25% higher* than the lowest priced drug should be denied subsidy. This second version of what came to be called a "price tolerance principle" (LFN 2006a, 12) subsequently became the basis for LFN's decision to deny a number of pharmaceuticals subsidy.

This example illustrates how decisions about subsidy were delayed when attempts at removing ambiguity did not achieve a 'decision-able' coherence between multiple sources. An alterantive means of delay, exemplified in Chapter 5 (see p. 107 of this volume), could have been to set *time-based restrictions* on pharmaceutical subsidy. That LFN did not reach such an outcome in the product assortment review could, perhaps, be due to the lack of strict time line for the Agency's decision-making as regards these drugs. LFN is required to reach an outcome in 180 days when evaluating 'new' pharmaceuticals. In addition, the pharmaceuticals in the product assortment review are already in use. In the decision justification documents with time-based restrictions, references were made to the need for additional insight into the effects of the pharmaceuticals' use in medical practice. The examples in Chapter 6 suggest that difficulties in the stomach-acid and migraine groups arose in relation to reconciling multiple sources of knowledge, rather than a lack of knowledge.

That organizations respond to ambiguity by delaying decisions has also been observed in earlier studies of organizational decision-making. For example, studies have shown that demanding adherence to a rational choice model of decision-making and pointing out additional information needs or new decision alternatives is a way to delay decision-making (cf. Brunsson 1989 for examples).

Yet despite the aforementioned delays, the Agency *did* eventually reach conclusions about drugs' subsidization status in both the migraine and stomach-acid groups. To indefinitely delay decisions was not a sustainable response to ambiguity about pharmaceuticals' characteristics; "to not make a decision about a pharmaceutical is a de facto decision, since it upholds the status quo of subsidizing the drug in question" (Interview project manager migraine group, September 9 2004; see p. 155 of this volume). Delay was not the only way to handle unsuccessful attempts at removing ambiguity. In the next section, I will argue that LFN also dealt with ambiguous knowledge by making decisions that delegate unresolved ambiguity to others.

Making decisions that delegate ambiguity...

The outcome in the migraine group is my study's foremost example of decision-making involving delegation of ambiguity.

In the migraine group, the decision to approve subsidy for all but one dosage of one pharmaceutical followed attempts to calibrate incoherent measurements of treatment effect using an International Headache Society standard (see pp. 134-5). Initially, these attempts at calibrating different measurements of treatment effect to one standard were successful. After various discussions, a standard metric was agreed upon and the drugs' treatment effect could be compared using this common scale. The planned next step was to compare the cost-per-treatment effect of the various drugs, and determine whether any of the drugs failed to meet the criteria for subsidy. Although the treatment of migraine had been determined to be cost-effective, there was a question as to whether *all* of the pharmaceuticals should be subsidized in order to ensure that a high enough percentage of patients had access to a treatment alternative that worked. There were differences in price and treatment effect indicating that this might not be the case.

Determining which of the migraine pharmaceuticals to subsidize was described as a question of comparing pharmaceuticals' relative cost-effectiveness and 'adding up' the percentage of patients treated with different drugs. The *cumulative* treatment coverage needed to be sufficiently high. Hence, the dual challenge was to determine what constituted a 'reasonable' cost-effectiveness and a 'high enough' percentage of coverage.

But both the discussion about treatment coverage, and the use of the common treatment effect metric for comparing pharmaceuticals, was abandoned when it was concluded that the migraine pharmaceuticals were not interchangeable treatment alternatives for individual patients. Medical practitioners could not foresee which patients would successfully be treated with a drug. The project group members, after discussions with the Board, concluded that a general comparison of pharmaceuticals' treatment effect was *possible* – but not *relevant* in relation to making a decision about subsidy.

Neither the calibrated measurement of treatment effect, nor the discussion about cumulative treatment coverage, could be used as a basis for justifying the denial of subsidy for a drug since the measurements did not refer to populations of patients. (This can be compared to the situation in the stomach-acid group that was described above, where the creation of a price tolerance allowed for differences in cost between products with 'the same' treatment effect. In the migraine group, there was no such 'same' treatment effect).

Since the Agency could not draw general conclusions about whether a drug fulfilled the criteria for subsidy, all of the pharmaceuticals were approved continued subsidy. By approving subsidy, the matter of determining when to prescribe and subsidize a *particular* drug for a *specific* patient was left to others. Only in the case of the drug dosage that the Agency denied subsidy for did it make a general characterization that "it is difficult to see any cost-effective use of Imigran (sumatriptane) 100mg if its price is higher than the price of the other products" (LFN 2005, 6; emphasis added).

The stomach-acid group gives an additional example of how LFN made decisions that delegated ambiguity about pharmaceutical characteristics elsewhere. The price tolerance principle articulated in the stomach-acid group document stated that products with 'the same' treatment effect could not have a price per tablet that was more than 25% higher than the cheapest of the drugs. This led the Agency to deny subsidy for several pharmaceuticals, while approving the continued subsidy of others. As in the migraine group, the Agency made an unambiguous characterization of those pharmaceuticals which were denied subsidy. They were "more expensive" than other drugs, but had "the same", "similar" or "no different" treatment effect (LFN 2006a, 7, 85, 100).

But in those cases where continued subsidy was approved on the basis of the 25% price corridor, the Agency delegated ambiguity about *which* specific pharmaceutical treatment effects and costs fulfilled the criteria for subsidy. The exact pricing of individual drugs within the allowed 25% tolerance was left to 'the market'. Similarly, the precise specification of 'reasonable' treatment effects

was not set out. The approved drugs were "the same" according to the common measurement of treatment effect (LFN 2006a, 57). Yet the price corridor was also justified, in part, on the grounds that this metric did not measure all potentially relevant treatment characteristics (Ibid., 12, 82, 58).

The previous examples of the migraine and stomach-acid groups show LFN making decisions *despite* ambiguity about specific pharmaceuticals' characteristics (such as price), and ambiguity about *when* a given drug fulfilled the criteria for subsidy. In other words, a failure to remove ambiguity between different sources of knowledge did not prevent LFN from making decisions. By approving subsidy, the Agency delegated the precise characterization of a pharmaceutical as 'reasonable' to other parties, notably medical practitioners. Approving subsidy combined decision-making with a delegation of the resolution of ambiguity concerning particular characteristics (cf. Rappert 2001). In the next section, I will argue that the delegation of ambiguity also delegated the choice of a pharmaceutical's subsidization status to others.

...and choice...

By approving subsidy pharmaceuticals, LFN delegated the matter of determining *when* a pharmaceutical had 'reasonable' characteristics to others. It is my argument that making such decisions also delegates *choice* to others.

The decision to approve subsidy for a drug is not a choice, in the theoretical sense, since it leaves open for the pharmaceutical to be prescribed both with and without subsidy. Approving subsidy does not involve the choice of one future course of action to the exclusion of other actions. The choice of subsidization status for a pharmaceutical is left to others, such as individual medical practitioners.[193] There is no similar possibility (at least in theory) to choose between these alternatives courses of action when the Agency denies a

[193] As an aside, it is interesting to note that – using my proposed definition of decision versus choice – medical practitioners may not make choices about pharmaceutical subsidy either. When a patient is prescribed a drug (with subsidy) that has a cheaper generic substitute, then the choice of subsidization (or, at least the level of subsidy) is delegated to the patient. (S)he

product subsidy. In these cases, the drug is not sold by Apoteket with subsidy and compliance is enforced by the organization's monopoly on the sale of prescription drugs in Sweden.[194] Thus, the denial of subsidy can be characterized as *a choice* of one future course of action (no subsidy) to the exclusion of others (subsidy).

Differentiating between decisions and choices runs counter to the assumption in the rational choice model that the outcome of decision-making is choice (as discussed on pp. 28-30 of this volume). It is also a different point than that made by researchers who have studied why a chosen course of action is difficult to fully implement in practice.[195] My argument here is that organizations that are required to justify decisions as knowledge-based will tend to avoid making choices *in the first place* when there is unresolved ambiguity between multiple sources of knowledge. The justification of *a choice* that excludes future courses of action presumes precisely that which is lacking: a coherent account of reality. A rationalized account of the world is needed for (rational) actors to make (rational) choices about future actions (cf. Brunsson 1989; cf. Meyer 1994). Making decisions that delegate ambiguity can fulfill the requirement to reach a (justifiable) outcome at the end of decision-making processes, thereby signaling a commitment to procedural – if not substantive – rationality (cf. the discussion in Feldman and March 1981 about information collection signaling commitment to rationality).

But does coherent knowledge always lead to a choice? Speculatively, I would argue that coherence is a necessary but not sufficient requirement for a

must choose whether to pay the cost differential for the prescribed pharmaceutical *or* be given the generic substitute with full subsidy.

[194] I have not looked into whether it might be possible to circumvent a denial of subsidy in practice. However, whether an outcome is a decision and or a choice *in practice* clearly hinges on the actions taken once outcomes have been reached.

[195] There are various explanations for implementation difficulties including: differences in expectations and commitments about what actions should be taken between those who make choices, and those who are supposed to act in accordance with these choices (Brunsson 1985; Brunsson and Olsen 1998); the inherent need for interpretation (cf. Wittgenstein 1953; Garfinkel 1967); the translation which occurs when general ideas are materialized in the local practice (see examples in Czarniawska and Sevón 1996).

choice to be made. Examples from my study of LFN illustrate how the Agency justified decisions to deny pharmaceuticals subsidy using generalized statements above the pharmaceuticals' 'unreasonable' characteristics. For instance, it was "difficult to see any cost-effective use" of Imigran 100mg (cf. LFN 2005, 6). In contrast, it was not possible to make generalized statements about the other drugs in the migraine – which were all approved continued subsidy. Attempts to make a generalized comparison of these pharmaceuticals' treatment effect using a common metric failed. The drugs' treatment effects, as measured by the common metric, were not comparable since the pharmaceuticals were not interchangeable for individual patients in medical practice. Thus, none of the pharmaceuticals were denied subsidy.

Another example of the need for general, coherent knowledge is the case of GERD in the stomach-acid group (see pp. 128-30 of this volume). Here, there was a lack of *generally valid* means of identifying patients with symptomatic GERD. The difficulty with identifying patients was not due to a lack of knowledge. On the contrary, there were numerous ways to define a 'GERD patient', including gastroscopy, patients' description of symptoms and prescription of a drug to see whether there was a treatment effect. Each of these characterizations could be used to determine whether a patient had GERD and should receive subsidized treatment. But *together* these sources did not give a coherent and generally valid classification of 'reasonable' patients. This made it difficult to make subsidy contingent on a diagnosis of GERD. Equally, it was not possible to deny any pharmaceutical subsidy on the grounds that its use was categorically 'unreasonable' – despite suspicions about off-label prescription of drugs (LFN 2006a, 10).

The need for *generally valid,* coherent knowledge when making a choice can be understood in light of the exclusion of all but one future action. When the Agency denies subsidy for a pharmaceutical, this excludes the possibility of subsidized treatment for *all* out-patient prescription of this drug. This arguably increases the need for coherent knowledge about pharmaceuticals' characteristics that is generally valid. The previous chapter illustrated how coherence is an achievement, requiring effort. Earlier research similarly points

to the efforts needed to resolve controversies. That the coherent knowledge also needs to be generally valid is a further reason for why *any choice* is a 'tough choice' for LFN to make (and justify).

By not denying subsidy and instead approving subsidy, LFN can fulfill the requirement to make a decision. But having decided to approve subsidy and left the choice of subsidized treatment to others, my study shows that the Agency sought to influence how such choices about subsidy were made using 'other means' than decision outcomes.

...while attempting to influence 'by other means'

When it decides to approve subsidy for a drug, the Agency does not determine *when* the pharmaceutical is subsidized in practice. This is left to others to choose. But the Agency's approval of subsidy for drugs in the migraine and stomach-acid groups were combined with attempts to influence how subsequent choices about pharmaceutical treatment and subsidization were made. In this section, I will look closer at these attempts to influence 'by other means', both *prior* to making decisions and *after* having decided to approve subsidy.

LFN is supposed to influence how pharmaceuticals are subsidized. However, this influence was not solely related to the outcome of the Agency's work to determine pharmaceuticals' characteristics and compare them with other drugs based on knowledge from multiple sources. LFN also influenced drugs' comparisons and characteristics. An example of this was the denial of subsidy for 100mg tablets of Imigran. As described earlier, this dosage was denied subsidy after an exchangeable drug had been approved for use in Sweden by the Medical Products Agency. The cost per tablet of this 'new' pharmaceutical was 42% lower than the 'old' drug, and approximately the same as the other pharmaceuticals in the migraine group. Under the rules of generic substitution, patients holding a prescription for the 'old' (now unsubsidized) pharmaceutical would be offered the new, subsidized drug. The new product's introduction, and its price, was attributed to be a direct consequence of LFN's evaluation of the

migraine group, and specifically the conclusion that the cost of using Imigran 100mg was unacceptably high in comparison to other products in the group (cf. LFN 2005, 5, 29).

Two other examples of when LFN's work influenced the characteristics of pharmaceuticals were the price changes for Naramig (in the migraine group) and Pantoloc (in the stomach-acid group) that led to the approval of continued subsidy for both products (LFN 2005, 5; LFN 2006a, 13). In contrast, the Agency noted as regards two pharmaceuticals in the stomach-acid group that "Losec and Losec Mups [do not fall within] the price tolerance that we use and will therefore not have continued subsidy. The company has not made use of the possibility of lowering its prices to meet the price tolerance and receive continued subsidy" (Ibid.).

The previous examples illustrate how LFN influenced pharmaceuticals' characteristics *prior* to reaching outcomes. Attempts at influencing the choice of pharmaceutical and subsidization status also came *after* decisions had been made to approve subsidy for drugs.

The most prominent example of this came in the migraine group report which included a cost-effectiveness ranking of pharmaceuticals that had all been approved further subsidy (see pp. 152-5 of this volume). Although the specific choice of *when* to subsidize a specific drug had been delegated, the Agency sought to influence this choice by suggesting *an order* in which to test approved pharmaceuticals. The ranking of pharmaceuticals in order of decreasing cost-effectiveness was described as a tool for encouraging a more economically efficient use of resources. However, an explicit caveat was that the drugs had been ordered on the basis of only one characteristic: their calculative cost-effectiveness (LFN 2005, 6). The responsibility for considering *other* relevant characteristics for the individual patient lay with the treating medical practitioners.

Informants repeatedly stressed that the ranking was *not* a treatment recommendation. Nor did it have a binding legal status. The Agency would not monitor whether medical practitioners actually followed the ranking, and LFN

did not have the means of enforcing compliance. This was considered appropriate by informants, who noted that subsequent changes in matters such as the prices of one or more of the evaluated pharmaceuticals drugs were expected to make conclusions obsolete in time. It was therefore not desirable for the ranking to have *too much* influence.

The price tolerance principle in the stomach-acid group similarly sought to influence future price movements among pharmaceuticals with 'the same' treatment effect – without exerting too much influence on the precise pricing choices made as regards individual drugs.

In this section, I have illustrated how LFN's decisions to approve subsidy, and delegate ambiguity and choice to other parties, were preceded by influence on the characteristics of pharmaceuticals. Decisions to approve subsidy were also combined with attempts at influencing how subsequent choices were made. The cost-effectiveness ranking, for example, has characteristics of a written rule that is voluntary to follow. Yet this standard (Scott 1998; Brunsson and Jacobsson 2000) did not make definitive statements about how the subsidized pharmaceuticals were to be used *in specific cases*.

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Thus far in the chapter, I have argued that LFN's tendency to make decisions rather than choices can be understood in light of the difficulties with achieving coherence between multiple sources of knowledge. This difficulty might be further exacerbated by 'counter-strategies': activities that can serve to increase ambiguity of knowledge, or avoid action based on choices that have been made.

'Counter-strategies': Making it (even more) tough to choose?

Preventing choice

I have characterized *delay* as an organizational response to unsuccessful attempts at removing ambiguity between multiple sources of knowledge. Based on the discussion in this chapter, more ambiguous and less general knowledge will tend to lead to a decision being made, rather than a choice. Introducing new knowledge could therefore be one means of preventing choices, by highlighting the failure to consider all possible alternatives and all available information in accordance to the rational ideal of organizational choice (cf. Brunsson 1985). Greater demands on rationality should increase the visibility of incoherence between multiple sources of knowledge – to the detriment of efforts to justify outcomes on the basis of these sources.

In my study of the migraine and stomach-acid groups, there were several examples of how the characteristics of pharmaceuticals were changed during the course of LFN's evaluation. Two previously mentioned examples are the changes in price for Naramig and Pantoloc. Before the prices of these two drugs were changed, they had risked being denied continued subsidy. Their changed characteristics (as regard price) prevented this choice to deny them subsidy (LFN 2005, 5; LFN 2006a, 13).[197]

An alternative means of preventing choices from being made might be to make knowledge less generally applicable, since this can complicate the

[197] Chapter 5 also includes examples of how new knowledge led LFN to reverse earlier choices to deny subsidy. The denials of subsidy for Concerta and Cerazette were reversed on the grounds that new knowledge made the earlier decisions obsolete. In one case, the Medical Products Agency had judged that the pharmaceutical was not comparable to another product – a comparison on which LFN had based its choice to deny subsidy. In the other case, the Medical Products Agency had changed the product's SPC such that it had a better treatment effect than certain types of comparable products. LFN had denied the drug subsidy on the grounds that its treatment effect was not adequate compensation for a higher cost.

specification and comparison of choice alternatives – and the possibility of choosing one course of action to the exclusion of others.[198]

That clinical studies of pharmaceuticals used for the treatment of similar medical conditions tended to differ as regards measurements of treatment effect and so on could be taken to suggest that pharmaceutical companies see advantages in *not* having generally comparable products – of being differentiated.[199]

Avoiding action

The findings in this study suggest that knowledge-based choices are difficult to make if multiple sources of knowledge are ambiguous, and there is a need for coherent justification of outcomes. To avoid having to act on knowledge-based choices, those targeted could seek to encourage further public justification. An alternative, which is in line with the aforementioned 'strategy' to make knowledge less generally applicable, could be to point to exceptions that undermine general knowledge claims.

My study highlights several examples where additional justifications for choices were sought. The most prominent example of this was the consistent appeal of the Agency's denial of subsidy. Lodging an appeal serves to delay having to act on the Agency's decisions, since a drug continues to be subsidized pending the completion of a judicial review. In its annual report, LFN noted that the Agency's work in the migraine group had led to savings of 34 million SEK (approximately 3.7 million Euro) following the denial of subsidy for Imigran 100mg subsidy and the concurrent approval of subsidy for an exchangeable

[198] See parallels to Alexius's (forthcoming) discussion of how business consultants avoid attempts at regulation by 'disorganizing' and emphasizing they to be vague, unique and changeable characteristics.

[199] Studies in economics have, along these lines, posited that firms will differentiate their quality in order to avoid price competition (Shaked and Sutton 1982). In a recent treatment, Grönqvist and Lundin (2006) argue that additional clinical evidence establishing the relative effectiveness of pharmaceuticals within a class of drugs increases expected product differentiation, thereby raising prices for both high-quality and low-quality drugs.

drug with a 42% lower price (LFN 2005b, 10). Yet the same document also notes that despite the denial of subsidy for numerous drugs in the stomach-acid group "only 55 of the close to 180 million SEK that could have been released through our decisions can be used for other urgent pharmaceutical treatments next year" (Ibid.) due to appeals of these outcomes.

In addition to delaying action, an appeal can also result in choices being overturned. By the end of 2005, this had already occurred in three cases.[200]

During 2004, LFN argued four cases of denied pharmaceutical subsidy before *Länsrätten* (the Stockholm County Administrative Court, henceforth also 'the lower court'). In three of four cases, concerning drugs for the treatment of male impotence, the Agency's denial of subsidy was overturned through court rulings that approved restricted subsidy for the drugs in question (Länsrätten 2004a, b, c). Subsequent to the Agency's appeal of these rulings, *Kammarrätten* (the Stockholm Administrative Court of Appeals, henceforth also 'the appellant court') ruled in 2005 to uphold the lower court's decision to approve restricted subsidy for the three pharmaceuticals – albeit on different grounds and with different restrictions (Kammarrätten 2005a, 18-19; 2005b, 20-21; 2005c, 17). As of November 1 2006, the cases are still pending in *Regeringsrätten* (the Supreme Administrative Court).

In its four decision justification documents[201] LFN gave three overarching reasons for why the products were neither approved subsidy outright, nor approved subsidy for certain restricted areas of use:

- First, that the drugs were not generally reasonable to treat all forms of male impotence, since the medical condition was not a sufficiently urgent societal concern.
- Second, that there was no dependable way in which to identify the specific groups of patients that were 'reasonable' to treat. This was the reason for why the Agency had not approved subsidy of the pharmaceuticals for

[200] The following discussion is based on (Sjögren forthcoming [2006]).
[201] Viagra 2003-03-27; Cialis 2003-05-15; Levitra 2004-04-06, 2004-09-01.

restricted uses. Specifically, LFN argued that a proposed diagnostic tool was not an adequate means of classifying patients.

- Third, that the three pharmaceuticals were not comparable with two drugs that have been approved subsidy for treatment of male impotence[202] since the drugs were not treatment alternatives *for the same patients.*

The lower court ruled to reverse LFN's denial of subsidy, and approve subsidy *with restrictions* to patients with certain medical conditions such as diabetes or cardiovascular diseases, *or* who were prescribed the drugs by an urologist[203] (Länrätten 2004a, 27; 2004b, 24; 2004c, 15). Unlike LFN, the lower court concluded that the scientific studies submitted by the pharmaceutical companies showed the pharmaceuticals to be *generally* cost-effective. In contrast to LFN, the lower court also judged that two other pharmaceutical-based treatments of male impotence *were* relevant comparisons. The three pharmaceuticals that had been denied subsidy by LFN were therefore cost-effective in comparison to drugs that had been approved subsidy (Länsrätten 2004c, 13).

The lower court also disagreed with LFN's conclusion that patients with severe medical conditions could not be reliably identified in clinical practice. However, it was not sufficient to apply the diagnostic tool suggested by the pharmaceutical companies. Therefore, subsidization was restricted to initial prescription by an urologist (Länsrätten 2004a, 26-7). That the lower court approved subsidy for particular patient groups was argued on the grounds that these categories of patients were more likely to have severe forms of male impotence. While it might lead to the unnecessary subsidization of treatment for certain patients with less serious forms, " [this] is not ... reason to deny subsidy

[202] Bondil and Caverject, both 2003-05-15.

[203] An urologist is a physician who has specialized knowledge and skill regarding problems of the male and female urinary tract and the male reproductive organs.

to patient groups that can be definitively determined on the basis of the aforementioned criteria" (Länsrätten 2004c, 26).

LFN's subsequent appeals of the lower court's three rulings were not upheld by the appellant court. However, the appellant court did change the definition of the restrictions for approved subsidy. In the appellant court's rulings, the three pharmaceuticals were granted restricted subsidy for:

> ...patients with the [medical condition] severe erectile dysfunction, regardless of underlying illness. Initial prescription to be made by a physician with specialist competence in urology (Kammarrätten 2005a, 18-19; 2005c, 17)

In contrast to the lower court's conclusion, the appellant court agreed with LFN's initial conclusion that the cited clinical studies showed that only patients with severe male impotence were reasonable to treat. However, the appellant court agreed with the lower court's argument that medical practitioners could dependably identify patients that were 'reasonable' to subsidize. Yet the diagnosis-based restriction set by the lower court were not deemed to correctly identify those patients who should received subsidized treatment. Restricting subsidy to initial prescription by a medical specialist on male reproductive organs was a (more) dependable way of delineating 'reasonable' patients.

The lower and appellant court rulings to overturn LFN's choices to deny subsidy for three drugs serves as an illustration of how 'successful' attempts to achieve coherent knowledge that led to a choice can be brought into question. In particular, the courts' rulings provide an interesting contrast to LFN's decision justification documents. First, because the former are not justified in the same way as the decision justification documents: neither as regards scientific knowledge claims, nor as regards principles such as that of a product-based subsidy system. Second, because other sources, such as clinical studies and especially medical practice, are privileged over LFN as the source of knowledge about pharmaceuticals characteristics. Even if LFN has 'succeeded' in removing ambiguity, there is not a guarantee that its version of coherent knowledge about

pharmaceuticals' characteristics is stable over time and space, if it is subject to both procedural and substantive review.

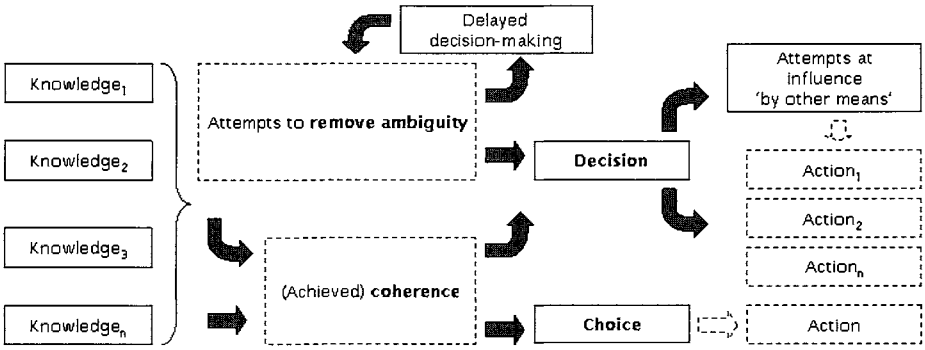
The example of LFN's appealed and overturned choices illustrate how extensive public justification could contribute to avoiding action based on choices. On the other hand, it is open question as to what would be the influence on decision-making practices if there were limited public scrutiny. Had there been no means of appealing its decisions, would it be even harder for LFN to make the choice to deny subsidy for a pharmaceutical?

Conclusions

In this chapter, I have elaborated on the model proposed in the previous chapter of ways to remove ambiguity. Specifically, I outlined two responses to failed attempts at removing ambiguity: delaying decision-making and making decisions that delegate ambiguity. I also proposed a differentiation between making decisions and making choices, arguing that organizations will tend to make decisions rather than choices if efforts to remove ambiguity between multiple sources fail to achieve generally valid, coherent knowledge.

As illustration of this point, I considered LFN's decisions to approve subsidy for pharmaceuticals in the stomach-acid and migraine groups. As discussed at the beginning of this chapter, the decision to approve subsidy for a pharmaceutical excludes neither the possibility of subsidizing this drug, nor prescribing the drug without subsidy. Hence, I have suggested the relevance of differentiation between two outcomes of decision-making with ambiguous knowledge: *decisions* that delegate unresolved ambiguity and choice to others, and *choices* that exclude all but one future course of action. I have illustrated how making a knowledge-based *decision* does not require coherent knowledge, in contrast to making a knowledge-based *choice* (see Diagram 11, below).

Diagram 11: *Organizational responses to failed attempts at removing ambiguity*



Following my argumentation in this chapter, it is only when LFN decides to deny a pharmaceutical subsidy that the Agency makes a choice. It is only then that one future action (no subsidy) is chosen to the exclusion of other possible actions. What more, it is only then that the Agency changes the status quo of leaving the choice of subsidization status to others. When the Agency approves subsidy for a pharmaceutical, the choice of subsidization status for this drug is – as before the creation of LFN – left to other parties to determine.

I have also speculated that the tendency to make decisions rather than choices can be enforced by activities which serve to increase ambiguity in the decision-making process – for example by changing pharmacueticals' properties – or delaying action if and when a choice has been made, by making it subject to further scrutiny and demands for justification.

By making approving subsidy for pharmaceuticals, LFN does not directly control whether or not these drugs are subsidized. But making decisions does not leave the Agency without influence. In the migraine and stomach-acid groups, LFN combined decisions to approve subsidy with influencing pharmaceuticals' characteristics, and setting standards for how subsequent choices are to be made. However, it is important to note that these *decisions* and attempts to exercise influence 'by other means' did not require justification on the basis of generally valid coherence between multiple sources of knowledge.

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In the next chapter, I will summarize my study's conclusions about how organizations deal with ambiguous knowledge in decision-making processes. I will also discuss my findings in relation to earlier studies of decision-making with ambiguity and comment on implications of my study for knowledge-based decision-making in practice.

9. MAKING DECISIONS WITH AMBIGUOUS KNOWLEDGE

The question raised in the introductory chapter about how organizations make decisions with ambiguous knowledge was posed in relation to the rationalistic assumption that knowledge – particularly scientific knowledge – is coherent, and an objective representation of a (coherent) reality. In other words, that multiple sources of knowledge 'add-up' to a cumulative and qualitatively better whole on which to base optimal choices. The question was also posed in relation to behavioral studies of organizational decision-making which argue that organizations deal with ambuiguity (of preferences) through separation in time and space, and interpret knowledge flexibily and strategically to legitimate or influence decision-making processes. My contention has been that both approaches avoid taking the content of knowledge seriously, leaving a gap in understanding of how organizations deal with knowledge – in particular scientific knowledge – that is ambiguous *and* expected to provide justification of decision outcomes.

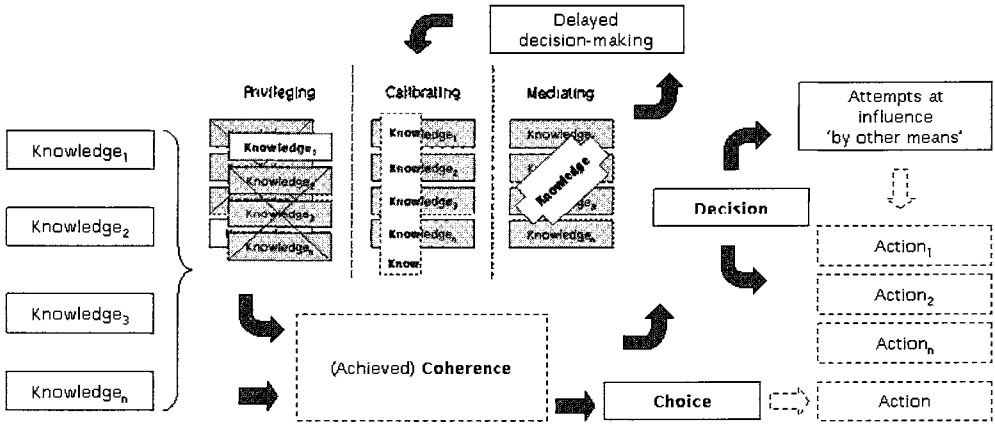
To answer this question, I have inquired into how a Swedish governmental agency works to determine whether prescription drugs' have medical, humanitarian and socio-economic characteristics that made their cost of use 'reasonable' to subsidize. It is my argument that this organization employed other means than more well-known methods for dealing with ambiguity.

In Chapter 7, I characterized three methods for attempting to remove ambiguity between multiple sources of knowledge. Following earlier work by Mol (2002), I first elaborated on how coherence between multiple sources of knowledge can be sought by *privileging* one source over other sources, or by *calibrating* multiple sources to a common metric. I went on to propose that ambiguity can also be removed by *mediating* between sources. By employing one or more of these methods, it is possible to remove incoherence between multiple sources of knowledge. However, attempts to remove ambiguity using these methods may not succeed.

In Chapter 8, I discussed two organizational responses to unsuccessful attempts to remove ambiguity. The first: to *delay decisions*, pending additional attempts to remove ambiguity. The second: *to make decisions that delegate unresolved ambiguity* to others. Delegation of ambiguity was exemplified with LFN's approval of subsidy. I argued that when the Agency approves subsidy for a drug, it does not determine *when* the pharmaceutical fulfills the criteria for subsidy. The approval of subsidy is therefore not a choice, in a theoretical sense, since it does not exclude the possibility of alternative future actions (subsidy and no subsidy for a drug). While reaching a decision, LFN's approval of subsidy delegates the choice of whether to subsidize an approved pharmaceutical is delegated to others.

In conjuction to this discussion of organizational responses to unsuccessful attempts to remove ambiguity, I also highlighted how other actors could increase the propensity to make decisions rather than choices. I noted that actors could prevent choices from being made by changing the characteristics of pharmaceuticals during the decision-making process. Alternatively, I suggested that actors could delay taking action based on choices that had been made by bringing these choices and their justification under further scrutiny. These further requirements on choices could lead to more decisions, and attempts to seek influence over future actions by other means, for example by setting voluntary rules about how subsequent choices should be made (see Diagram 12, below).

***Diagram 12**: An extended model of knowledge-based decision-making*



This model characterizes knowledge differently from both rational and behavioral theories of organizational decision-making. In opposition to the rational choice model, knowledge – and particularly coherent knowledge – is an outcome, rather than an exogenous given. In contrast to behavioral decision theory, knowledge is not only a resource to legitimate or structure decision-making. *How* multiple knowledge claims are related to one another – and whether ambiguity is successfully removed – has implications for the outcome of the decision-making process.

Specifically, my findings elaborate on the basic assumption that *decisions* require coherent knowledge, by proposing a differentiation between choices of one future course of action, and decisions that defer choices to others and do not exclude many alternatives future actions. Unless ambiguity is removed and coherence achieved between multiple sources of knowledge, it is my contention that organizations will tend to make decisions, rather than choices.[204] Instead of choices, there can be other attempts at influence that are less susceptible to

[204] Note that this model does not explicitly consider issues related to implementation (see footnote 195, p. 175 of this volume).

'counter-strategies' that can prevent choices or delay actions following a choice having been made.

In the next section, I discuss how the conclusions of my study relate to existing theories about organizational decision-making with ambiguity. Specifically, I highlight circumstances which may contribute to why the studied organization did not handle ambiguity using more well-known methods employed by other organizations. These circumstances are characteristics of other organizations where the findings of this study could be relevant for understanding organizational behavior.

Why not deal with ambiguity in 'the usual ways'?

In this book I have argued for the relevance of making ambiguity of knowledge – particularly scientific knowledge – a topic of inquiry within behavioral studies of organizational decision-making. It has been my contention that researchers have largely avoided doing do (although see Fernler and Helgesson 2006; Fernler 2003, Helgesson 2004 for recent examples to the contrary). Previous studies have primarily focused on other sources of ambiguity such as future preferences or past events. In particular, researchers have characterized various methods in which organizations deal with ambiguity *of preferences*. These methods include the separation of multiple preferences in time and/or space, and the use of vague outcomes as a means of avoiding conflict. However, several circumstances make it difficult for LFN to deal with ambiguity using these more well-known methods. These circumstances are characteristics which could also apply to other organizations than the studied Agency.

The requirement to make decisions is one circumstance which can complicate for an organization to use more well-known methods to deal with ambiguity. The requirement to make decisions places a variety of expectations on what the organization should do, related to the ideal of rational choice (Brunsson 2000). Without a particular demand for decision-making, an organization might employ other methods to inform action.

If there are time requirements on *when* an organization must reach an outcome in its decision-making, this should also make it difficult to delay decisions indefinitely or be vague about whether an outcome has been reached at all. If there are further limitations placed on the outcomes the organization can reach, this arguably also makes it more difficult to be vague about the contents of the decision outcome (cf. Baier, James and Saetren 1986; Sahlin-Andersson 1989).

LFN is explicitly tasked "to make decisions" about pharmaceutical subsidy (Act (SFS 2002:160) on Pharmaceutical Benefits, section 7). The Agency is also required to reach one of three possible outcomes regarding pharmaceutical subsidy – and to do so within a certain time period.[205] These circumstances together limit the Agency's ability to avoid decision-making altogether – or to indefinitely delay reaching an outcome. LFN is also limited in its ability to be vague about what subsidization status it has decided on for a given pharmaceutical.

An additional circumstance which can complicate for an organization to use more well-known methods to deal with ambiguity is the need to justify outcomes on the basis of knowledge. Many organizations are not required to primarily justify decision-making outcomes on the basis of knowledge – in particular scientific knowledge. For organizations that have authority vested in particular positions, such as that of manager or policy-maker/politician, an outcome can be justified based on *who* has made a decision and *how* decision-making has been organized, rather than *what* has been decided on. A political organization can justify an outcome as being the will of the majority. Similarly, a firm can justify decisions made by managers on the basis of their hierarchical authority.

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[205] As described in Chapter 4, LFN can only decide to approve subsidy (with or without restrictions), or choose to deny subsidy for a given drugs. What more, the Agency must reach a decision within 180 days of having received an application for subsidy for a newly approved pharmaceuticals. As regards the existing product assortment, LFN was expected to complete its

Although LFN arguably has positional authority, as a governmental agency with the legal mandate to decide status pharmaceuticals' subsidization, the Agency must justify outcomes as being in accordance with the legal decision criteria for subsidy: that a pharmaceutical has "a reasonable cost of use ... from humanitarian, medical and socio-economic perspectives" (Act (SFS 2002:160) on Pharmaceutical Benefits, section 15). That LFN has the authority to make decisions and has made decisions in an appropriate way does not preclude an appeal of a decision based on the (knowledge-based) justifications provided in the relevant decision justification document. Hence, a reference to expertise as such is not an adequate basis for justification, since the organization is required to provide both producedural and substantive justification.[206]

Having to substantively justify decisions on the basis of multiple sources of knowledge – at the same time – is a further circumstance which should complicate the separation of these sources (and their consideration) in time or space. Previous studies have highlighted how ambiguity of preferences can be dealt with by paying sequential attention to goals, or dividing larger issues into smaller decisions that are dealt with in separate organizational sub-units (Cyert and March 1963) or in parallel processes (Jacobsson 1987). Alternatively, different sub-units can be made responsible for talk, decisions and action – thereby making it possible to avoid potential conflicts between multiple preferences or environmental demands (Brunsson 1989; Lawrence and Lorsch 1967; Oliver 1991; Meyer and Rowan 1977). To separate the consideration of multiple sources of knowledge in time or space should be difficult if the justification of decisions presumes concurrent – and coherent – consideration of these various sources.

review of the existing product assortment within five years (SOU 2000:86, 312). The Agency has subsequently revised this time plan to six years (LFN 2006d, 25).

[206] Other organizations that have similar needs to justify activities 'by other means' than hierarchy include standard-setters, which are characterized as constructing authority by reference to other organizations (with authority) or to scientific expertise (cf. Tamm-Hallström 2000; Jacobsson 2000). These organizations, like LFN, lack various organizational elements – notably the capacity to enforce compliance with outcomes.

LFN is an example of an organization with such difficulties. The Agency must provide knowledge-based justification of decision outcomes – and handle multiple sources of knowledge. It is difficult in principle to justify why the Medical Products Agency's marketing authorization documents, or medical practitioners' use of drugs, or the results of clinical studies undertaken by pharmaceutical companies should *not* be considered. What more, several sources of knowledge about drugs are also intended targets for the Agency's decision-making. There is no simple division between senders and receivers of knowledge (Brunsson and Jönsson 1979; cf. Lagrelius 2004 for an example taken from the healthcare sector).

Thus, to remove ambiguity by one or more of the three aforementioned methods (privileging, calibrating or mediating) may be difficult since each involves simplification – and in certain cases the direct exclusion – of sources. It is my speculation that LFN's and similar organizations' ability to remove ambiguity of knowledge between multiple sources is limited for the same reason that ambiguity may be a concern in the first place: there are many *legitimate* sources of knowledge.

This problem should be exacerbated if the organization is primarily made accountable for decision-making, rather than actions. Many organizations face an explicit 'decision imperative' *in combination with* having to act on these decisions. Certain organizations, such as political organizations or courts, are expected to make decisions, but not necessarily act on these outcomes. Yet the separation of decision-making and action does not typically preclude decision-makers, such as policy-makers, from being made responsible for actions that others are to take.

That decision-makers are responsible for actions is in accordance with the rational idea that actions follow from decisions. Separating decisions from actions in space and time are methods for avoiding conflict related to differences in what is decided and taken actions (Cyert and March 1963; Meyer and Rowan 1977; Brunsson 1989). This makes it possible to hide difficulties of

fulfilling rational ideal that actions be determined by the outcome of decision-making processes. Especially when an organization lacks the means to enforce compliance with decision outcomes, it could be advantageous to be made accountable for decisions rather than actions (cf. Brunsson 1989). But if the organization must justify decisions based on multiple sources of (ambiguous) knowledge – then the inability to rationalize outcomes on the basis of (positive) consequences of actions could be a disadvantage. Highlighting loose couplings between decision-making and action might also be a basis for questioning the decision-makers' activities.

LFN is tasked with deciding pharmaceuticals' subsidization status. But it is other organizations and their individual members – such as Apoteket, the county council pharmaceutical committees, medical practitioners and pharmaceutical companies – that are supposed to act in certain ways, depending on what outcome LFN reaches. The Agency is primarily made accountable for its decision-making. It must publicly justify the reasons for conclusions about pharmaceutical subsidy. LFN can also be required to provide further justification for why it has reached a particular conclusion by having its outcome appealed to court.

In contrast, the Agency is not made accountable in the same way for how a pharmaceutical is used after LFN has reached conclusions about the drug's subsidization status has been reached. LFN is not responsible for if its outcomes can be realized within the budget(s) for pharmaceutical spending. Nor does the Agency give accounts of whether actions follow from outcomes. LFN does not (at least at the time of this study) monitor whether restrictions on pharmaceutical subsidy are adhered to in practice. The Agency also lacks means of enforcing compliance with its decisions to approve subsidy.[207]

[207] It is interesting to note that LFN's annual report for 2005 includes a discussion about why the Agency has not succeeded in its task of ensuring an appropriate and cost-effective use of resources since: "there are several other parties that play a decisive role in whether the goals are fulfilled, for example the pharmaceutical industry, Apoteket, other governmental agencies, the county council pharmaceutical committees and not the least the physicians who prescribe pharmaceuticals" (LFN 2005d, 10).

LFN's limited accountability for actions, in combination with the greater requirements placed on coherent justification of denials of subsidy, arguably contribute to the Agency's tendency to approve subsidy for drugs. Had the Agency been responsible for managing the budget for pharmaceutical spending, it would probably have had greater difficulty also in approving subsidy for drugs. If LFN were to have fiscal responsibility for its decisions, I would further speculate that Agency would justify choices on other grounds than knowledge about the drugs' 'unreasonable' characteristics. Having to consider budget restrictions would arguably place a greater emphasis on the *feasibility of acting on decision outcomes*. In the present study, feasibility was primarily discussed in relation to whether possible restrictions on subsidy would be followed by medical practitioners (see pp. 129, 131, 107-8). Financial responsibility would also give the Agency other means of enforcing compliance both to its decisions *and* choices.

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It is my argument that the aforementioned circumstances contribute to LFN's use of other methods for dealing with ambiguity *of knowledge*, than those previously outlined in relation to how organizations deal with ambiguity *of preferences*. The study's findings could therefore by relevant for understanding organizations that, like LFN, must make decisions that are subject to substantive review based on multiple sources of (legitimate) knowledge. There are probably few organizations that exactly mimic all of the aforementioned characteristics. As discussed in Chapter 4, there are a multitude of different organizational structures, mandates and so on – even within the narrow field of pharmaceutical subsidy (see pp. 86-9 of this volume). However, there could be *parts of organizations* that face these circumstances.

LFN is itself part of a larger organization: the Swedish state (cf. Ahrne 1998). Several circumstances that the Agency must deal with – the requirement to make decisions, to reach one of a limited possible outcomes, to justify this outcome on the basis of multiple sources of knowledge, and so on – follow from

the organization being tasked to do so. (By applying the proposed model about how organization make decisions with ambiguous knowledge, the creation of LFN could be explained as a consequence of delegation of the resolution of ambiguity about when pharmaceuticals are 'reasonable' to subsidize by legislators seeking to avoid having to make choices).

I would speculate that organizations or organizational units that are similar to LFN could be found in the boundaries between 'valuation practices', where different metrics of value and different modes of calculation are brought together.[208] In particular, the findings of this study should be relevant for understanding areas where there is a lack of consensus around how to make these calculative practices coherent.[209] Previous studies, particularly within STS, suggest that this lack of consensus is widespread in issues that are framed as matters pertaining to health and environmental safety. But there are many areas where 'the facts of the matter' are expected to resolve value conflicts as regards what are appropriate choices of future actions. The findings of this study therefore have possible implications for the use of knowledge-based decision-making in practice.

Implications

This study suggests that an organization (or part of an organization) which is required to make and justify decisions based on multiple sources of knowledge, will have a tendency to make decisions rather than choices. A reason why organizations will do so is that decisions do not preclude a variety of future actions. This means that decisions do not require coherent justification in the same way as *general* choices. By making decisions, the *specific* choices of a particular action are left to others.

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[208] Espeland and Stevens (1998, 326-8) discuss this in relation to incommensurability as an outcome of efforts to achieve commensuration (cf. also discussion of rational contradictions in relation to valuation in Espeland 1998, 245-52). For a discussion of the realization of calculative agency through specification of objects' qualities, see Callon 1998; Callon, Cécile and Rabeharisoa (2002) and Callon and Muniesa (2005).

[209] This is a parallel argument to the discussion of scientific advisors inability to reconcile different knowledge claims without a shared view of 'the evidence' (pp. 44-6 of this volume)

The tendency for knowledge-based decision-making to result in decisions can be accentuated by ways in which other actors can prevent choices from being made. For instance, actors can provide additional information. Actors can also prevent actions that are supposed to follow from a choice that has already been made. For example, actors can make the choice – and its justification – subject to additional public scrutiny.[210] However, making decisions and delegating choice may be combined with attempts to exercise influence by other means that place lesser requirements on coherent justification. When taken together, these conclusions have potential implications for the use of knowledge-based decision-making in practice.

Specifically, the study's illustration of the minutiae involved in removing ambiguity between multiple sources of knowledge brings into question the sustained – some even characterize it as a resurgent (Dorey 2005) – interest in implementing "evidence-based policy-making" (Nutley and Webb 2000, 14; Barker 1996). It raises serious questions about the capacity for knowledge-based decision-making to resolve value conflicts, in general, and value conflicts related to priority-setting in healthcare, in particular. In this, the present study expands on Tenbensel's (2004) conclusions based on his study of the New Zealand experience with explicit priority-setting during the 1990s: that a pressing problem in healthcare is not to get *more evidence* but rather a greater understanding of "how policy processes deal with divergent implications of different types of knowledge and evidence" (Ibid., 205). These are issues that cannot be resolved by recourse to evidence.

What this study argues, then, is that rationalistic demands for both 'knowledgeable' *and* 'justifiable' decision outcomes when taken seriously – as they arguably are in the case of LFN – make it difficult to make choices. In the absence of other organizational elements such as fiscal responsibility or monitoring of compliance, the institution of transparent, inclusive and

[210] It could also be that a tendency for choices *not* to be implemented makes it less problematic to reach such an outcome. The present study leaves this matter an open question.

deliberative knowledge-based decision-making processes[211] could tend to be conservative vis-à-vis the practices that they seek to control. In other words, the difficulties in achieving coherence between multiple knowledge claims will tend to lead to a delegation of the actual choices to practice.

[211] This is in line with the widely acknowledged accountability-for-reasonableness proposed by (Daniels and Sabin 2002).

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Concerta 2003-03-24
Concerta 2003-06-10
Crestor 2003-06-26
Caverject 2003-05-15
Duodopa 2004-01-23
Elidel 2004-05-28
Ezetrol 2003-06-26
Elidel 2005-06-29
Flutide 2003-02-17
Forsteo 2003-12-22
Glivec 2004-04-23
Glucosine2003-06-30
Keppra 2004-09-01
Levemir 2004-10-12
Levitra 2004-09-01
Levitra 2004-04-06
Menopur 2004-12-21
Niferex 2003-12-19
Onsenal 2004-07-01
Ovitrelle 2003-12-18
Procren Depot 2004-02-19
Raptiva 2004-12-21
Reductil 2003-06-30
Risperdal Consta 2004-04-20
Robinul 2003-01-30
Xenical 2003-06-04
Xyzal 2004-09-02
Xyzal 2004-11-09
Teveten Comp 2004-10-25
Totelle 2003-11-06
Valoid 2004-02-17
Viagra 2003-03-27
Vesicare 2004-12-20
Yentreve 2004-11-10
Zyban 2004-09-28
Zyrlex 2004-03-16

APPENDIX A

A1: Project description

Extended excerpt of document sent to LFN's Director-General, members of the LFN Board members and prospective to informants (in Swedish).

Projektbeskrivning: Kunskap i regleringsprocesser

1. Bakgrund

Projektet *Kunskap i regleringsprocesser* ingår i ett större forskningsprogram – *Regelsättande och regelföljande* – finansierat av Riksbankens Jubileumsfond. Programmet leds av prof. Nils Brunsson (företagsekonomi, Handelshögskolan i Stockholm) och prof. Göran Ahrne (sociologi, Stockholms Universitet). Det är inriktat på att bättre förstå användningen av annan reglering än inomstatlig lagstiftning, exempelvis standardisering (t ex med certifieringar som ISO, Krav o s v), transnationella överenskommelser (t ex Global Compact, Kyoto-överenskommelsen) och formellt frivilliga rekommendationer (t ex kliniska riktlinjer för behandlingspraktik). Fokus ligger särskilt på tre empiriska områden: miljö, arbetsmarknad och hälso- och sjukvård.

Denna undersökning kommer att mynna ut i en doktorsavhandling i företagsekonomi vid Handelshögskolan i Stockholm.

2. Frågeställning

Syftet med studien är att undersöka hur olika kunskapsområden vägs samman inom ramen för en regleringsprocess och vilken påverkan detta har på den regleringspraxis som utvecklas. Vilken kunskap – och i vilken form – bedöms vara relevant?

3. Teoretiskt ramverk

Avhandlingens teoretiska utgångspunkt är en problematisering av antagandet som görs i flertalet modeller kring beslutsfattande, regelsättande och organisationsstyrning: att kunskap är exogent given, entydig och stabil. Kunskap, inte minst sådan kunskap som anses vetenskaplig, har i många sammanhang en betydande roll i formulering av regler och kan också ge en grund till varför och hur regler skall följas. Men det är inte sällan som det råder osäkerhet om vad man faktiskt vet och/eller i vilken grad en viss kunskap är tillämpbar för det område som en viss regel avser att reglera. Det kan också finnas olika kunskapsanspråk som är mer eller mindre motstridiga. Dessa olika kunskapsanspråk kan samexistera genom att de utvecklas och diskuteras inom ramen för olika discipliner och forskningstraditioner. Dock riskerar dylika inkonsekvenser att bli problematiska när en regel ska formuleras. Det är mot denna bakgrund som jag ställer frågan om hur motstridiga kunskapsanspråk vägs samman och jämkas i en regelsättande situation.

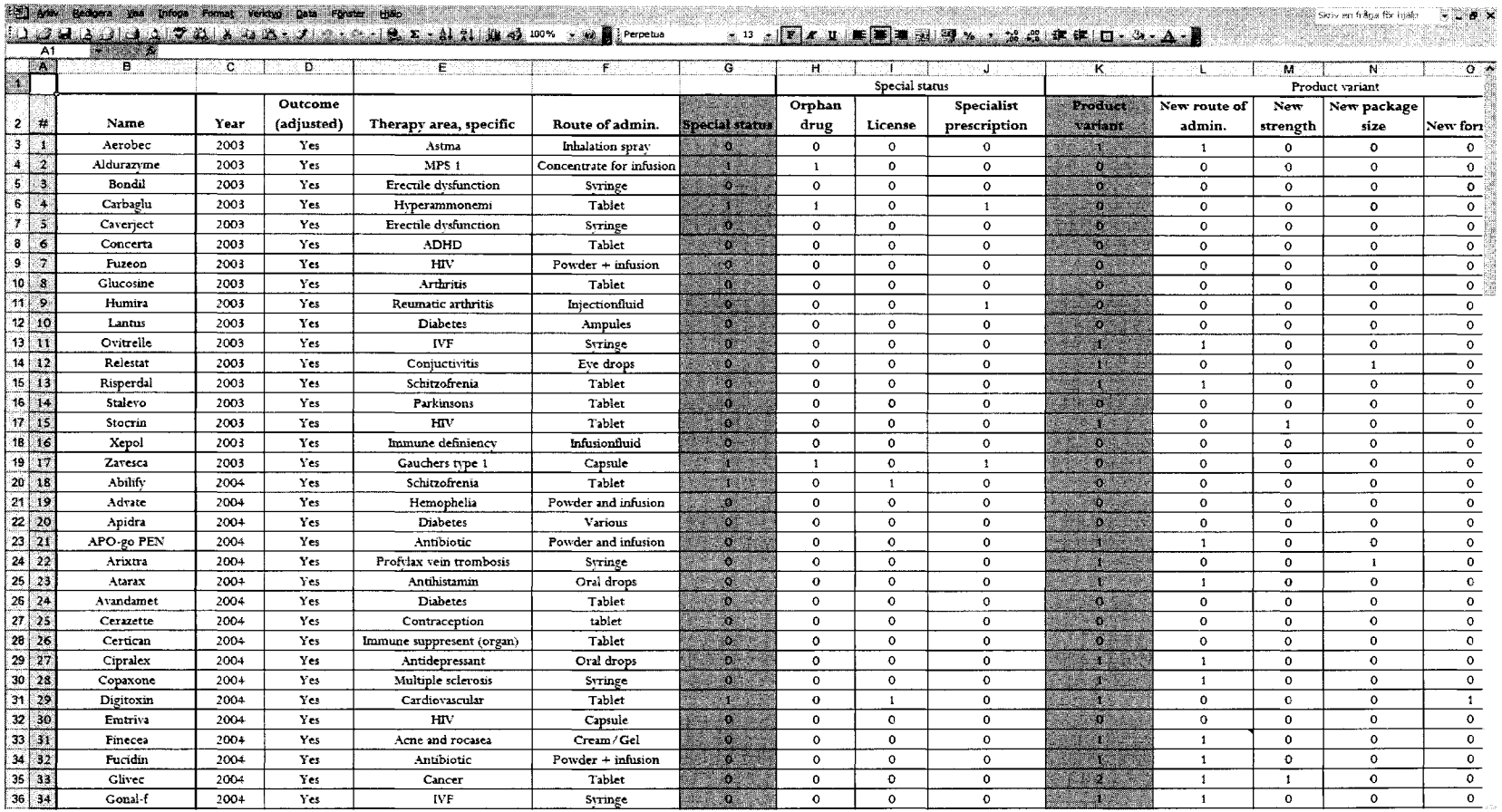
4. Tillvägagångssätt

Valet att studera LFN bygger på organisationens position som 'gatekeeper' till den svenska marknaden för receptbelagda läkemedel. I LFN:s uppdrag ingår att väga samman ekonomiska, medicinska och sociala faktorer när beslut fattas om ett läkemedels subventioneringsstatus. Denna ställning torde göra organisationen till en plats för olika intressenter att argumentera för riktigheten i sina kunskapsanspråk om en produkts ekonomiska, medicinska och sociala fördelar (eller nackdelar).

Studiens empiriska material kommer i första hand att utgöras av intervjuer med nämndledamöterna samt dokumentstudier. Det intressanta är att följa framväxten av regleringspraxis, d v s att se hur tänkandet kring kunskap ser ut och hur den eventuellt förändras över tiden. Min avsikt är att följa nämndens arbete under minst ett års tid och under den tiden genomföra mellan fem och tio intervjuer med utvalda ledamöter i LFN:s beslutsnämnd samt med personal på LFN:s kansli. Det är önskvärt att intervjuerna genomförs i nära anslutning till nämndens sammanträden. Jag uppskattar att dessa intervjuer kommer ta ca 1 timme.

A2: Outcome study

Coding of decision justification documents



								Special status					Product variant		
#	Name	Year	Outcome (adjusted)	Therapy area, specific	Route of admin.	Special status	Orphan drug	License	Specialist prescription	Product variant	New route of admin.	New strength	New package size	New form
1	Aerobec	2003	Yes	Astma	Inhalation spray	0	0	0	0	1	1	0	0	0
2	Aldurazyme	2003	Yes	MPS 1	Concentrate for infusion	1	1	0	0	0	0	0	0	0
3	Bondil	2003	Yes	Erectile dysfunction	Syringe	0	0	0	0	0	0	0	0	0
4	Carbaglu	2003	Yes	Hyperammonemi	Tablet	1	1	0	1	0	0	0	0	0
5	Caverject	2003	Yes	Erectile dysfunction	Syringe	0	0	0	0	0	0	0	0	0
6	Concerta	2003	Yes	ADHD	Tablet	0	0	0	0	0	0	0	0	0
7	Fuzeon	2003	Yes	HIV	Powder + infusion	0	0	0	0	0	0	0	0	0
8	Glucosine	2003	Yes	Arthritis	Tablet	0	0	0	0	0	0	0	0	0
9	Humira	2003	Yes	Reumatic arthritis	Injectionfluid	0	0	0	1	0	0	0	0	0
10	Lantus	2003	Yes	Diabetes	Ampules	0	0	0	0	0	0	0	0	0
11	Ovitrelle	2003	Yes	IVF	Syringe	0	0	0	0	1	1	0	0	0
12	Relestat	2003	Yes	Conjuctivitis	Eye drops	0	0	0	0	1	0	0	1	0
13	Risperdal	2003	Yes	Schitzofrenia	Tablet	0	0	0	0	1	1	0	0	0
14	Stalevo	2003	Yes	Parkinsons	Tablet	0	0	0	0	0	0	0	0	0
15	Stocrin	2003	Yes	HIV	Tablet	0	0	0	0	1	0	1	0	0
16	Xepol	2003	Yes	Immune definiency	Infusionfluid	0	0	0	0	0	0	0	0	0
17	Zavesca	2003	Yes	Gauchers type 1	Capsule	1	1	0	1	0	0	0	0	0
18	Abilify	2004	Yes	Schitzofrenia	Tablet	1	0	1	0	0	0	0	0	0
19	Advate	2004	Yes	Hemophelia	Powder and infusion	0	0	0	0	0	0	0	0	0
20	Apidra	2004	Yes	Diabetes	Various	0	0	0	0	0	0	0	0	0
21	APO-go PEN	2004	Yes	Antibiotic	Powder and infusion	0	0	0	0	1	1	0	0	0
22	Arixtra	2004	Yes	Proftlax vein trombosis	Syringe	0	0	0	0	1	0	0	1	0
23	Atarax	2004	Yes	Antihistamin	Oral drops	0	0	0	0	1	1	0	0	0
24	Avandamet	2004	Yes	Diabetes	Tablet	0	0	0	0	0	0	0	0	0
25	Cerazette	2004	Yes	Contraception	tablet	0	0	0	0	0	0	0	0	0
26	Certican	2004	Yes	Immune suppresent (organ)	Tablet	0	0	0	0	0	0	0	0	0
27	Cipralex	2004	Yes	Antidepressant	Oral drops	0	0	0	0	1	1	0	0	0
28	Copaxone	2004	Yes	Multiple sclerosis	Syringe	0	0	0	0	1	1	0	0	0
29	Digitoxin	2004	Yes	Cardiovascular	Tablet	1	0	1	0	1	0	0	0	1
30	Emtriva	2004	Yes	HIV	Capsule	0	0	0	0	0	0	0	0	0
31	Finecea	2004	Yes	Acne and rocasea	Cream / Gel	0	0	0	0	1	1	0	0	0
32	Fucidin	2004	Yes	Antibiotic	Powder + infusion	0	0	0	0	1	1	0	0	0
33	Glivec	2004	Yes	Cancer	Tablet	0	0	0	0	2	1	1	0	0
34	Gonal-f	2004	Yes	IVF	Syringe	0	0	0	0	1	1	0	0	0

Pharmaceuticals denied or restricted subsidy 2002 - 2004

#	Outcome	Name of product	Date of decision 1	Date of decision 2
1	Restricted	Yentreve	2004-11-10	
2	Restricted	Levemir	2004-10-12	
3	Restricted	Forsteo	2003-12-22	
4	Restricted	Reductil	2003-06-30	
5	Restricted	Crestor	2003-06-26	
6	Restricted	Ezetrol	2003-06-26	
7	Restricted	Xenical	2003-06-04	
8	Restricted*	Duodopa	2004-01-23	
9	Restricted*	Raptiva	2004-12-21	
10	Restricted*	Reyataz	2004-05-26	
11	Restricted*	Risperdal Consta	2004-04-20	
12	Restricted*	Velcade	2004-10-12	
13	Restricted*	Zyban	2004-09-28	
14	Denied	Xyzal**	2004-09-02	2004-11-09
15	Denied	Levitra**	2004-04-13	2004-09-01
16	Denied	Elidel	2004-06-01	
17	Denied	Niferex	2003-12-19	
18	Denied	Totelle	2003-11-18	
19	Denied	Cialis	2003-05-15	
20	Denied	Cerazette***	2003-04-10	2004-08-30
21	Denied	Concerta***	2003-06-11	2003-04-02
22	Denied	Viagra	2003-03-27	
23	Denied	Flutide	2003-02-17	
24	Denied	Robinul	2003-01-31	
25	Denied	Aunativ	2003-01-31	

** Time restriction, classified as 'approval of subsidy' by LFN.*

*** Two decisions to deny subsidization*

**** Initial decision to deny subsidization reversed*

A3: Process study

Informants and interview dates

Position	Name	Interviews	
		#	*Dates*
Project manager (migraine group)	Niklas Hedberg	9	2004-01-28 2004-02-27 2004-04-19 2004-06-10 2004-09-09 2004-10-05 2004-10-26 2005-01-25 2005-02-22
Health economist (stomach-acid group)	Douglas Lundin	11	2003-11-20 2004-03-23 2004-06-09 2004-09-28 2004-12-17 2005-06-01 2005-08-24 2005-09-29 2005-11-16 2005-11-23 2006-02-06
Project manager (stomach-acid group)	Anders Wessling	13	2004-01-28 2004-03-14 2004-06-08 2004-06-09 2004-11-30 2005-02-21 2005-05-17 2005-05-25 2005-09-02 2005-11-16 2005-11-23 2005-12-23 2006-02-06

Position (continued...)	Name	Interviews	
		#	*Dates*
Health economist (migraine group)	Joachim Ramsberg	9	2004-02-13 2004-03-29 2004-09-08 2004-09-08 2004-10-05 2004-11-24 2004-11-30 2005-01-25 2005-02-22
LFN Director-General	Ann-Christin Tauberman	1	2003-10-24
LFN Chairman of the Board	Axel Edling	5	2003-10-09 2004-03-24 2004-06-28 2004-12-21 2005-04-05
LFN Board member (health economist A)	Lars-Åke Levin	2	2004-06-23 2005-03-30
LFN Board member (health economist B)	Ulf Persson	2	2004-07-02 2005-03-30
LFN Board member (medical practitioner A)	Anna-Karin Furhoff	1	2004-07-01
LFN Board member (medical practitioner B)	Ingmarie Skoglund	1	2004-06-17
LFN Board member (patient organization A)	Christina Wahrolin	1	2004-07-19
LFN coordinator	Thord Redman	2	2003-11-20 2004-10-20
	Total	**57**	

Interview questions

Example 1: From interviews with project manager, stomach-acid and migraine, both January 28 2004 (translated from Swedish)

1. Themes

Contents of companies responses

LFNs process

Question marks so far as regards process and contents

2. Questions

2.1 Contents

Have all the contacted companies answered? If not, who has not?

What do the answers look like? Are they what you expected? (What did you expect?)

Are the contents the same? Different? (Elaborate). Are the same studies cited?

2.2 Process

What has happened so far? Important events?

Have the experts been chosen? What were the alternatives? What are you planning to do with the experts?

2.3 Going forward

What do you know about the pharmaceuticals in the two groups? (Different, the same?)

How would you characterize the state of knowledge?

Is anything difficult today?

What do you see as 'key issues' going forward? What might become difficult? What happens next?

Example 2: From interview with Joakim Ramsberg, 2004-03-23 (translated from Swedish)

Who are your experts?

What studies have the companies cited? What have you found?

What economic measurements seem important?

Are there differences between the drugs? What kind of differences?

How did the first Board meeting go?

What are you comparing? How are drugs classified? (Are there sub-groups of drugs? Different medical conditions? Substances? Patient groups? Geography?)

To think about...

Recurrent theme is that they want many drugs in one category to ensure competition. What is 'the category'? What is competition? What is 'the market' for migraine drugs?

Example 3: From interview with LFN Board member (patient organization A), 2004-07-19 (translated from Swedish)

Tell me about the decision to go on to phase 2 in both groups?

Which key issues need to be resolved before a decision can be made in either group? What is difficult to know about the drugs in each group?

What are your views about the issues raised at the last Board meeting (suggestion to deny subsidy for drugs with 50% higher price per tablet; how to deal with price changes following patent expiration or new introduction; comparison between patented and generic products)

How has medical practice been considered in the two group's evaluations? Health economics?

Competition – between what?

How does LFN relate to other agencies, pharmaceutical committees and medical practitioners?

APPENDIX B

B1: Pharmaceuticals stomach-acid group

Company	Pharmaceutical
Alpharma AB	Link
Antula Healthcare	Inside Brus
AstraZeneca Sverige AB	Losec Losec Mups Nexium Nexium HP Novaluzid
Biochemie, Novartis Sverige AB	Omeprazol Biochemie Ranitidine Biochemie
Eli Lilly Sweden AB	Nizax
GEA Farmaceutisk Fabrik AB	Acinil Artonil
GlaxoSmithKline AB	Tagamet Zantac Zantac Brus
Janssen-Cilag AB	Pariet
Merck Sharp and Dohme AB	Pepcidin
NM Pharma AB	Ranitidin NM Pharma
Nordic Drugs AB	Gaviscon
Nycomed AB	Pantoloc
Orion Pharma AB	Andapsin
Pfizer AB	Cytotec
PLIVA Pharma A/S	Ranitidin PLIVA
Ratiopharm AB	Omeprazol ratiopharm
Recip AB	Ranitidin Recip
Scand Pharm Generics AB	Omeprazol Scand Pharm
Wyeth Lederle Nordiska	Lanzo

B2: Pharmaceuticals migraine group

Company	Pharmaceutical
AstraZeneca Sverige AB	Zomig Zomig Nasal Zomig Rapimelt
GlaxoSmithKline AB	Imigran Naramig
Merck Sharp and Dohme AB	Maxalt Maxalt Rapitab
Novartis Sverige AB	Cafergot Migranal Orstanorm Sandomigrin
Nycomed AB	Almogran
Pfizer AB	Relpax
Recip AB	Anervan

APPENDIX C

Approval of subsidy (extended excerpt)

LFN
Läkemedelsförmånsnämnden

BESLUT 1 (3)

Datum	Vår beteckning
2004-09-01	867/2004

SÖKANDE

UCB PHARMA AB (SWEDEN)
Murmansgatan 126A
212 25 Malmö

Företrädare: Charlotta Wängberg

SAKEN
Ansökan inom läkemedelsförmånerna

LÄKEMEDELSFÖRMÅNSNÄMNDENS BESLUT
Läkemedelsförmånsnämnden beslutar att nedanstående läkemedel skall ingå i läkemedelsförmånerna från och med den 1 september 2004 till i tabellen angivet pris.

Namn	Form	Styrka	Förp.	Varunr.	AIP (SEK)	AUP (SEK)
Keppra	Oral lösning	100 mg/ml	300 ml	014081	1 401,60	1 494,50

ANSÖKAN
UCB PHARMA AB (SWEDEN) har ansökt om att nedanstående läkemedel skall ingå i läkemedelsförmånerna och att pris fastställs

Namn	Form	Styrka	Förp.	Varunr.	AIP (SEK)
Keppra	Oral lösning	100 mg/ml	300 ml	014081	1 401,60

UTREDNING I ÄRENDET
Keppra är ett epilepsiläkemedel med levetiracetam som aktiv beståndsdel. Det fick sitt godkännande för försäljning av EMEA i september 2000 och har funnits på den svenska marknaden sedan slutet av det året.

Läkemedelsverket har i sin produktmonografi gjort följande värdering av Keppra: ".. ett nytt alternativ vid tilläggsbehandling av partiella epileptiska anfall. I förhållande till flera andra antiepileptika är farmakokinetiken okomplicerad och biverkningsprofilen förefaller vara gynnsam. Effekt i förhållande till andra antiepileptika med add-on indikation kan ej värderas då jämförande studier saknas."

Ansökan avser en ny beredningsform av ett läkemedel som redan omfattas av läkemedelsförmånerna. Priset för den orala lösningen ger ett pris per mg substans som ligger 60 procent högre än priset för tabletter i lägsta styrkan, 250 mg. Skillnaden i behandlingskostnad i förhållande till tablettbehandling är väsentlig – i det lägre dosintervallet i storleksordningen 60 procent, i det övre en fördubbling av kostnaden.

Postadress: Box 55, 171 11 SOLNA | Besöksadress: Sundbybergsvägen 1 | Telefonnummer: 08-5684 20 50 | Telefaxnummer: 08-5684 20 99

Den orala lösningen av Keppra har tagits fram bland annat för att vara ett alternativ för patienter som inte klarar av att ta läkemedlet i form av tabletter. Andra epilepsiläkemedel utgör inte generellt alternativ till Kepra, som har egenskaper som särskiljer det från övriga epilepsiläkemedel.

SKÄLEN FÖR BESLUTET

Enligt 15 § lagen (2002:160) om läkemedelsförmåner m.m. skall ett receptbelagt läkemedel omfattas av läkemedelsförmånerna och försäljningspris fastställas för läkemedlet under förutsättning

1. att kostnaderna för användning av läkemedlet, med beaktande av bestämmelserna i 2 § hälso- och sjukvårdslagen (1982:763), framstår som rimliga från medicinska, humanitära och samhällsekonomiska synpunkter, och
2. att det inte finns andra tillgängliga läkemedel eller behandlingsmetoder som enligt en sådan avvägning mellan avsedd effekt och skadeverkningar som avses i 4 § läkemedelslagen (1992:859) är att bedöma som väsentligt mer ändamålsenliga.

Från och med den 1 oktober 2002 har lagen om läkemedelsförmåner ersatt den tidigare gällande lagstiftningen om högkostnadsskydd vid köp av läkemedel. Enligt övergångsbestämmelser till lagen skulle de läkemedel som sedan tidigare hade ett av Riksförsäkringsverket fastställt pris ingå i läkemedelsförmånerna. Dessa läkemedel har inte värderats enligt den nya lagen med avseende på kostnadseffektivitet m.m. I Läkemedelsförmånsnämndens uppdrag ingår det att göra en genomgång av hela det befintliga läkemedelssortimentet. Detta kommer att ske för varje terapiområde. I avvaktan på en genomgång av aktuellt terapiområdet utgår nämnden vid sin prövning av en ansökan om subvention för ett nytt läkemedel normalt från kostnaden och nyttan av redan befintliga och subventionerade läkemedel inom det terapiområdet.

Keppra tabletter ingår sedan tidigare i läkemedelsförmånerna. Med det pris företaget angett för Keppra oral lösning blir skillnaden i behandlingskostnad i förhållande till tablettbehandling väsentlig. Andra epilepsiläkemedel utgör inte generellt alternativ till Kepra, som har egenskaper som skiljer det från övriga epilepsiläkemedel. Keppra i form av oral lösning är därmed för vissa patienter en förutsättning för en adekvat behandling och behandlingskostnaden måste värderas med hänsyn till detta. Den ökade kostnaden som ett byte från tabletter till oral lösning medför kan inte förväntas nämnvärt förändra kostnadseffektiviteten för preparatet i sin helhet.

Vid en samlad bedömning finner nämnden att förutsättningarna enligt 15 § lagen om läkemedelsförmåner m.m. är uppfyllda för att Keppra oral lösning skall få ingå i läkemedelsförmånen till det begärda priset. Ansökan skall därför bifallas.

Denial of subsidy (extended excerpt)

BESLUT

Läkemedelsförmånsnämnden

Datum
2003-12-19

Vår beteckning
1162/2003

SÖKANDE

Erol AB
Kontaktperson: David Ehrlich
Box 95
274 22 SKURUP

SAKEN

Ansökan inom läkemedelsförmånerna

BESLUT

Läkemedelsförmånsnämnden avslår ansökan.

ANSÖKAN

Erol AB (företaget) har ansökt om att Niferex skall ingå i läkemedelsförmånerna och att pris fastställs. Företaget begär ett pris på 73,70 kronor (AIP) för en förpackning om 50 kapslar.

BAKGRUND

Järn är nödvändigt för energiöverföring och transport av syre i kroppen. Enligt WHO:s definition har 30 procent av jordens befolkning anemi (blodbrist), varav hälften har järnbrist. Undernäring är idag ovanligt som enda orsak till bristtillstånd och man bör alltid misstänka en bakomliggande sjukdom vid brist på järn. Vid järnbrist hos vuxna och icke-gravida kvinnor bör man utgå från att orsaken är ökade blodförluster. Hos fertila kvinnor leder blödningsrubbningar inte sällan till järnbrist och järnbristanemi. Cirka 10 procent av kvinnorna har rapporterats ha blödningsmängder som innebär stor risk för utvecklande av järnbristanemier.

Järnbrist bör behandlas medicinskt så snart diagnosen ställts. Behandling kan ske parallellt med utredning av orsaken. I första hand sker behandlingen peroralt (tabletter, kapslar eller lösning), i vissa fall med järninjektioner och i enstaka, framför allt akuta fall, med blodtransfusioner. Peroralt järn ges i doser 100 mg Fe^{2+} två till tre gånger per dag, lämpligen till måltid för att minska eventuella gastrointestinala biverkningar, (magtarmbiverkningar). Vid järnbrist ökar absorptionen av peroralt järn och man kan initialt ge en högre dos om patienten tolererar detta. Man kan utgå från att behandlingsperioden i optimala fall kan begränsas till 3-4 månader.

Postadress
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Besöksadress
Sundbybergsvägen 1

Telefonnummer
08-5684 20 50

Telefaxnummer
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SKÄLEN FÖR BESLUTET

Enligt 15 § lagen (2002:160) om läkemedelsförmåner m.m. skall ett receptbelagt läkemedel omfattas av läkemedelsförmånerna och försäljningspris fastställas för läkemedlet under förutsättning

1. att kostnaderna för användning av läkemedlet, med beaktande av bestämmelserna i 2 § hälso- och sjukvårdslagen (1982:763), framstår som rimliga från medicinska, humanitära och samhällsekonomiska synpunkter, och

2. att det inte finns andra tillgängliga läkemedel eller behandlingsmetoder som enligt en sådan avvägning mellan avsedd effekt och skadeverkningar som avses i 4 § läkemedelslagen (1992:859) är att bedöma som väsentligt mer ändamålsenliga.

Av 4 § Läkemedelsförmånsnämndens föreskrifter (LFNFS 2003:2, ändrad 2003:4) om receptfria läkemedel enligt lagen (2002:160) om läkemedelsförmåner m.m. framgår att vad som sägs i 15 § nämnda lag även skall tillämpas vid bedömningen av om receptfria läkemedel skall ingå i läkemedelsförmånerna (jfr 17 § samma lag och 5 § förordningen [2002:687] om läkemedelsförmåner m.m.)

Ett antal perorala preparat innehållande Fe^{2+} för järnbrist och järnbristanemier ingår redan i läkemedelsförmånerna. Samtliga är receptfria. Företaget har ansökt om att Niferex skall ingå i förmånerna till ett pris som ligger över priset på dessa. Avgörande för bedömningen av företagets ansökan är inte om behandling av järnbrist eller järnbristanemier som sådan är kostnadseffektiv utan om Niferex framstår som kostnadseffektivt i förhållande till jämförbara preparat inom gruppen. För att ett högre pris skall kunna motiveras vid en sådan jämförelse måste kostnaden framstå som rimlig i förhållande till effekt och de övriga kriterier som framgår av läkemedelsförmånslagen. Enligt 8 § lagen om läkemedelsförmåner m.m. åligger det sökanden att visa att kriterierna i 15 § är uppfyllda.

Läkemedelsförmånsnämnden gör följande bedömning.

Företaget har inte inkommit med några jämförande studier som visar att Niferex har bättre effekt och tolerans än de övriga preparaten i gruppen som t.ex. Duroferon, ett preparat av slow- releasetyp. Företaget har inte heller inkommit med någon hälsoekonomisk utredning.

Tabellen nedan visar kostnaden per dag vid järnbrist respektive järnbristanemi.

Namn	Styrka(Fe)	Pris/100mg Fe	AIP/st	Järnbrist	Järnbristanemi
Erco-Fer	60 mg	0,42	0,25	0,50 (2 tabl)	0,75(2-3 tabl)
Duroferon	100 mg	0,37	0,37	0,74 (2 tabl)	1,48(3-4 tabl)
Niferex	**100 mg**	**1,47**	**1,47**	**1,47 (1 kaps)**	**4,41(2-3 kaps)**

Av de prisjämförelser som kan göras framgår att det begärda priset innebär en ökad behandlingskostnad i förhållande till jämförliga läkemedel. Företaget har inte visat att den ökade behandlingskostnaden är förenad med några motsvarande hälsoekonomiska vinster. Inte heller i övrigt framstår kostnaden som rimlig. Slutsatsen blir därför att Niferex inte uppfyller förutsättningarna i 15 § lagen om läkemedelsförmåner m.m. Ansökan skall därför avslås.

APPENDIX D

Approved treatment areas for proton pump inhibitors

Examples taken from 'Terapeutiska indikationer' [Theraupeutic indications] in Medical Products Agency (1997, 1998b, 1999).

Product name (active substance)	**Approved treatment areas**
Losec MUPS (omeprazole)	*Vuxna:* Duodenalsår, ventrikelsår och refluxesofagit. I kombination med antibiotika vid behandling av duodenalsår orsakade av *Helicobacter pylori.* Behandling av NSAID-relaterade peptiska sår eller gastroduodenala erosioner. Profylaktisk behandling hos patienter med ökad benägenhet för NSAID-relaterade besvär, såsom peptiska sår, gastroduodenala erosioner eller dyspeptiska besvär. Långtidsbehandling av kroniskt recidiverande peptiska sår och refluxesofagit. Symtomatisk behandling av halsbränna och sura uppstötningar vid gastroesofageal refluxsjukdom. Symtomatisk behandling av ulcusliknande symtom. Zollinger-Ellisons syndrom. *Barn:* *Barn över 2 år* Refluxesofagit. Symptomatisk behandling av halsbränna och sura uppstötningar vid gastroesofageal refluxsjukdom. *Barn över 4 år* I kombination med antibiotika vid behandling av duodenalsår orsakade av *Helicobacter pylori.*
Lanzo (lansoprazole)	Duodenalsår, ventrikelsår och refluxesofagit. I kombination med antibiotika vid behandling av duodenalsår orsakade av *Helicobacter pylori.* Långtidsbehandling av kroniskt recidiverande refluxesofagit. Zollinger-Ellisons syndrome. Behandling av NSAID-relaterade peptiska sår. Profylaktisk behandling hos patienter med ökad benägenhet för NSAID-relaterade peptiska sår eller dyspeptiska besvär.

Product name (active substance)	Approved treatment areas
Pariet	Pariet tabletter är indicerade för:
(rabeprazol)	behandling av aktivit duodenalulcus.
	behandling av aktivit denignt verntrikelulcus.
	behandling av symtomatisk erosiv eller ulcerativ gastro-esofageal reflexsjukdom (GERD).
	långtidsbehandling av gastro-esofageal reflexsjukdom (GERD underhållsbehandling).
	Symtomatisk behandling av måttlig till mycket svår gastro-esofageal reflexsjukdom (symptomatisk GERD).
	Zollinger-Ellisons syndrome.
	I kombination med lämpliga antibiotika vid eradikering av *Helicobacter pylori* hos patienter med peptiska sår. Se 4.2.

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