What should an Optimal and Fair Introduction Process for Orphan Drugs look like?

Experiences and Views of County Officials and Politicians in Northern Sweden

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Abstract

Background: Increasing costs and quantities of orphan drugs within the European market has led to much debate in Sweden on how they should be handled within the existing reimbursement system. Previously, there has been little research looking at local and regional handling of and implications of these issues when it comes to decision-making, financing, and access. This study aims to provide insight into these issues through perspectives and experiences obtained in interviews with representatives working for County Councils in Northern Sweden.

Methods: A case study comprised of semi-structured interviews following a qualitative methodology with an inductive approach was used for this study. Five informants from three different work groups engaged with the orphan drug introduction process in Northern Sweden were interviewed. A thematic analysis was performed on the data where common themes were identified through several rounds of coding to allow cross-sectional analysis between data obtained from informants.

Results: The thematic analysis identified five major themes surrounding the introduction process for orphan drugs; centralization of processes, methods & standardization, ethical considerations, economics & price setting, and challenges & difficulties. Informants provided insights, opinions, and a deeper understanding of these themes within the introduction process for orphan drugs.

Conclusion: This study confirms many of the complexities in establishing a clear and fair process for introducing orphan drugs. In line with existing literature, informants highlighted how centralization and the pooling of resources and expertise is vital in ensuring equal quality and access to care for patients suffering from rare diseases. There is broad agreement how orphan drug legislation and processes should develop, but substantial hurdles concerning the specifics as well as issues with external actors on pricing of orphan drugs. Addressing these issues could potentially have important benefits, not only for healthcare budgets and patients suffering from rare diseases, but also in setting precedents for future processes where costs and ethics will again come to a head.
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Abbreviations

ARIL - Committee for Regional Introduction of New Pharmaceuticals

CHMP – Committee on Human Medical Products

COMP – Committee on Orphan Medical Products

EMEA – European Medical Evaluation Agency

EU – European Union

MPA – Medical Products Agency

NTC – New Therapies Council

NRF – Norrland Regional Federation

OOP – Out of Pocket Payments

QALY – Quality Adjusted Life Year

SALAR – Swedish Association of Local Authorities and Regions

SEK – Swedish Kronor

TLV – Dental and Pharmaceuticals Benefits Agency

VCC – Västerbotten County Council
Introduction

Orphan Drugs & Rare Diseases

The European Commission defines rare diseases as “Life-threatening or chronically debilitating diseases – mostly inherited – that affect so few people that combined efforts are needed to:

- reduce the number of people contracting the diseases
- prevent newborns and young children dying from them
- preserve sufferers’ quality of life and socio-economic potential” (1).

Under normal market conditions, pharmaceutical companies are hesitant to invest in the research and development for these types of diseases. The drugs for these rare diseases carry high development costs and the diseases are characterized by small patient groups leading to unusually small target markets for companies to sell the drug to (2). As a result, the European Parliament and the Council of the European Union adopted Regulation (EC) No 141/2000 on orphan medical products in 2000 to provide incentives encouraging the development of drugs targeting these diseases, so called orphan drugs (2). The regulation established the Committee for Orphan Medical Products (COMP) to evaluate applications for orphan designation and set out the criteria required to achieve orphan designation. This meant that an orphan designated product should be intended for the diagnosis, prevention, or treatment of a life-threatening or chronic debilitating condition that has a prevalence of not more than 5 in 10,000 persons in the EU while also demonstrating that there are no already existing satisfactory alternatives and that the proposed product has a ‘significant benefit’ to individuals (3). The incentives pharmaceutical companies receive for an orphan designation are:

- Market Exclusivity for 10 years (2, 3)
- Protocol Assistance where the European Medical Evaluation Agency (EMEA) can provide scientific advice and guidance on how to meet regulatory requirements (2, 3)
- Direct access to EMEA’s centralized procedure and fee reductions for reviews, inspections, and submissions (2, 3)
- EU funded research through research grants, tax incentives, and subsidies (2, 3)

Statistics indicate that the legislation has provided the desired results. Since 2000, the number of orphan designation applications has increased from 548 in the period 2000-2005 to 1,151 in the period 2010-2015 (4). In 2015, in analysis of several acts of orphan drug legislation in Europe and elsewhere, Tiwari states, “Without giving a second thought it can be said that the impact of the orphan drug rules and regulations has been tremendous and as a result of these there are many medicines available in market for rare diseases” (5).
According to the ethical principles outlined in the Health and Medical Services Act, People suffering from diseases or ailments should have equal access to the necessary treatment and medicine regardless of their status, sex, or place of residency (6). Every medical need cannot be met and healthcare services must work within budget parameters and with the finite resources at their disposal while weighing the very real ethical dilemmas of displacement effects and opportunity costs. However, when it comes to people suffering from rare diseases, is the current and rapidly evolving introduction process for orphan drugs excessively obstructing access to necessary medicines? Are the ethical guidelines being followed and interpreted as designated by parliament (7)? A model is needed to ensure equal access, transparent decision-making, and satisfactory accessibility to healthcare are being met according to the principles established by Swedish Parliament (8). The issue at hand is; what should this model look like and are the national, regional, and local actors pursuing the best course of action to ensure patients suffering from rare diseases have fair access to available treatments?

In 2015, 19 out of 21 counties indicated that costs for orphan drugs had increased, totaling a combined 1.2 billion Swedish kronor (SEK) for all counties (9, 10). This represents almost 5% of the entire pharmaceuticals expenditure in Sweden, having grown from just .6% in 2006 (11). The amount spent per resident in Sweden increased from 52 SEK to 111 SEK between 2006-2011, with large variations ranging from 84 SEK in Jämtland County to 173 SEK in Västerbotten County (12). During 2011, Jämtland and Västerbotten counties spent roughly 565 SEK and 850 SEK per resident respectively on pharmaceuticals provided through inpatient care not including orphan drugs (13).

There are also large variations in costs for orphan drugs and the size of patient groups being treated. Revlimid®, an orphan drug that treats a type of cancer called multiple myeloma, costs 290,000 SEK per patient per year with just over 200 patients in Sweden (14). Often cited as one of the most expensive orphan drugs on the market, Soliris® costs 4.5 million SEK per patient per year for around 40 patients with the rare, life-threatening, genetic disease atypical Hemolytic Uremic Syndrome (15). In stark contrast to these examples, Lipitor®, the third most sold drug in Sweden, costs 3,000-6,000 SEK per patient per year and is used by around 100,000 patients (16). Estimates show the Swedish orphan drug market growing steadily over the coming years while worldwide orphan drugs sales are expected to increase 12% per year between 2017-2020 (17).

An increase in the number of orphan drugs available within the European Market has led to much debate in Sweden on how to manage orphan drugs within the parameters of the existing drug reimbursement system. The rising costs related to orphan drugs has led to other areas of health care services being negatively impacted, pitting patient groups against one another in accessing the care and medicine required for their conditions (9). For many years, regulations and the process for introducing orphan drugs lacked consistency and clear, defined processes, leading to patients being offered different levels of care options as well as experiencing different price levels for different counties (18).
Managed Introduction of New Medicines

In Sweden, rare diagnoses are defined as sicknesses or conditions that are severely debilitating or life-threatening and prevalent in a maximum of 1 in every 10,000 citizens (19). However, in the classification of orphan drugs, Sweden follows the centralized process within the EU. In 2012, central government, the Swedish Association of Local Authorities and Regions (SALAR), and several other actors within pharmaceuticals developed the national pharmaceutical strategy, focused on several strategic areas including the managed introduction of pharmaceuticals and therapies (20). Managed introduction provides the various government and industry actors with a common process for the introduction of new medicines to ensure an equal, cost-effective, and appropriate use of new medicines for all patients (20).

The managed introduction process as seen in figure 1 works as follows;

- **Horizon Scanning**: The first step in the process, where new medicines or new uses for existing medicines are identified (22). The aim of the work is to gather, document, and validate information on new medicines before they are granted market authorization (22). This helps prepare the health care sector for the introduction of new medicines as well as providing county councils and New Therapies Council (NTC) with a basis for their decision making (22). The NTC is a group of experts supporting county councils on questions regarding new drug therapies (23). These experts are comprised of one representative with medical or pharmaceutical expertise per healthcare region, as well as members with expertise in ethics, health economy, oncology, and horizon scanning (23).
• **Decision on inclusion in the managed introduction process:** On the official website of Stockholm Läns Landsting, the decision on if a therapy should be included in the national managed introduction process is described as follows,

> “After scanning, the county councils and NTC decide on whether the medicine should be subject to national managed introduction, and at which of three potential levels:

1. High degree collaboration: National managed introduction with introduction/follow-up protocol, health economic evaluation and recommendation on use

2. National managed introduction including health economic evaluation, recommendation on use and sometimes follow-up

3. Introduction at local level: Medicines that according to the criteria are not selected to be included in the national process are introduced according to routines in each county council” (24).

• **Introduction & follow-up protocol:** For medicines included in the national process of managed introduction at the high degree collaboration level, an introduction- and follow-up protocol is developed (25). The protocol serves as a practical guide to the county councils in the introduction and follow-up of a medicine and helps ensure the medicine is introduced in an equal way throughout Sweden (25).

• **Market Authorization:** For the market authorization, the company responsible for the proposed medicine will apply for approval through the central procedure in the EU from the Committee of Human Medical Products (CHMP) (26). A positive opinion from the CHMP is the signal for the beginning of the process of health economic evaluation and, when applicable, the introduction- and follow-up protocol (26).

• **Health Economic Evaluation:** Before a medicine is subject to the national managed introduction, the cost effectiveness of the treatment needs to be determined by the Dental and Pharmaceuticals Benefits Agency (TLV) (27). For prescribed medicines, the TLV decides if they should be subsidized (27). For medicines used in hospital care that are selected for national managed introduction, the TLV, at the request of the NTC, performs a health economic evaluation and presents a report to the NTC, which the latter then uses as a basis for a decision on recommendation for use (27).

• **Negotiation & procurement:** In the negotiation and procurement step, the county councils work jointly to develop terms, including pricing, for drugs subject to the national managed introduction (28).

• **Recommendations:** Based on ethical considerations and the health economic evaluation the NTC provides a recommendation on use to the county councils (29).
• **Introduction:** After the NTC gives its recommendation, the medicine is introduced according to each county council’s routines, guided by the recommendation and introduction protocol (30).

• **Follow-up & feedback:** Finally, the Medical Products Agency (MPA), the TLV, the National Board of Health and Welfare, and the company responsible for the medicine collaborate to perform follow-up and provide feedback (31). The purpose being to understand whether the medicine has been used according to the recommendation (31). For the right patient, in the right way, and looking at the safety and efficacy of the medicine (31). The NTC then determines whether the drug should continue following the agreed upon protocol, whether the recommendation or protocol needs updating or if the introduction can be considered complete (31).

**The Swedish Healthcare System**

The goal of the Swedish healthcare system is to ensure the health of all citizens while adhering to the principles of human dignity, need and solidarity, and cost-effectiveness. The ethical platform the Swedish parliament adopted in 1997 were defined and ranked as follows:

“

1. The principle of human dignity means all human beings have an equal entitlement to dignity, and should have the same rights, regardless of their status in the community.

2. The principle of need and solidarity means that those in greatest need take precedence in medical care.

3. The principle of cost–effectiveness means that when a choice has to be made between different health care options, there should be a reasonable relationship between the costs and the effects, measured in terms of improved health and improved quality of life.

”(32, 33)

The central government is responsible for overall health policy, while funding and the provision of services is mainly the responsibility of municipalities and county councils. In 2015, 95% of healthcare was publicly funded by central government (1.8%), municipalities (27.5%), and County Councils (65.6%) (34). Swedish citizens pay a small out-of-pocket (OOP) fee for healthcare visits or when purchasing prescribed drugs. The national ceiling for OOP payments means an individual will not pay more than SEK 1100 for health care visits within a 12 month period (33). For prescribed drugs, an individual pays full cost for prescribed drugs up to SEK 1100, after which the subsidy level gradually increases to 100% with a maximum co-payment of SEK 2200 within a 12-month period (35). In order to provide municipalities and county councils with equal economic conditions for their activities there is a national system of tax equalization where their revenues are redistributed on the basis of differences in tax base and differences in local cost conditions and needs (33). Most orphan drugs are distributed directly to patients as part of in-patient care, meaning the health services
purchases the drug and provides them directly to the patient, mainly at the hospital where
they are being treated (36, 37).

**Financing of Pharmaceuticals**

There are currently three ways pharmaceuticals are paid for in Sweden. For inpatient care,
meaning care at hospitals or clinics, the drug costs are covered by the respective institution
(38). In outpatient care, some drugs, those approved by the TLV, are covered by the high cost
ceiling mentioned earlier and the county councils receive aid from the state (38). However, if
the TLV excludes a drug from the benefit system, the county council or treating clinic have to
cover all of the costs (38). The third method is that of joint financing where the state steps in
to prevent extreme budget strains on a single county council (38).

The concept of jointly financed pharmaceuticals currently only refers to pharmaceuticals in
the pharmaceutical benefits system. Joint financing means that all county councils pay the
average cost per capita for a medicine, regardless of the cost for the county council (39).
Since 2001, the model that allocates state subsidies to county councils takes into account the
composition of the population in terms of sex, age and certain socio-economic variables (40).
For a medicinal product to be eligible for joint funding, the following conditions must all be
fulfilled:

- Very expensive drug (39)
- Very uneven distribution of patients between county councils (39)
- A significant burden on a county budget (39)
- Documented efficiency of the drug (39)

Since 2002, Hemophilia, HIV drugs and the Cerezyme® (Gaucher’s disease) drug have been
covered by joint funding (39). There has been debate both for and against joint financing for
orphan drugs with detractors seeing it as a “golden ticket” for pharmaceutical companies and
supporters seeing it as the only way to ensure equal access for patients suffering from rare
diseases (41, 42).

**Aims**

This paper will explore the current discourse and issues that are facing the Västerbotten
County Council (VCC) and the Norrland Regional Federation (NRF) in relation to ethical,
organizational, and economic questions surrounding orphan drugs through the experiences
and perspectives of employees at both organizations.
Methods

Study Design
A qualitative methodology with an inductive approach was used for this case study (43). The qualitative methodology was used to explore the experiences and perceptions with orphan drugs of various work groups within the VCC and the NRF. This methodological approach provided a better understanding of the national, regional, and EU-level processes involved in the introduction process for orphan drugs and the discourse and issues surrounding it. The qualitative methodology allowed insight into the informants’ own experiences, perceptions, and opinions on the process currently, how it was, how it is evolving, and what they believe it should look like in the future. As described by Hancock, by using a qualitative case study approach, the aim was to capture as many variables as possible in order to identify how a complex set of circumstances come together to produce a particular manifestation, in this case, the orphan drug introduction process (44).

Rapid Literature Review
In preparation for the creation of the interview guide, a rapid review as described by Grant and Booth was performed (45). The aim of the review was to establish what was already known about the orphan drug introduction process and any effects on care or access resulting from it. The search for relevant literature focused on search terms related to organization, policy, implementation, and economics themes. A rapid review was utilized due to time constraints for this study. Limiting certain aspects of the systematic review process allowed for a shorter timescale.

The search process began with a broader, simpler search approach but was focused as key variables were identified and grey literature discarded. Multiple databases such as PubMed, Pharmaceutical Specialties in Sweden (FASS), and BMJ Journal were used as the primary source of academic papers. Additionally, radio, television, private and publicly funded reports, interest and advocacy groups, government institutions and authorities, and industry and profession journals were also sourced for guidelines, opinion pieces, debate articles, and reports.

An initial list of 168 relevant sources was developed. After further, more in-depth review the final list was reduced to 35 research papers and an additional 49 sources from other reference types. A core list of 28 search terms was used in a myriad of strings in the search for relevant sources. For a full list of terms please see Appendix A.

Participants
For this study, three work groups within the VCC and NRF were chosen to provide a more whole picture of the discussion and issues surrounding orphan drugs in Västerbotten. These three representative groups were local politicians working with health-related questions, county council officials with technical expertise, and county council officials working more broadly with strategy and planning.

Potential informants were provided by an official at the VCC with a comprehensive understanding of the structure and staff members working at the VCC and associated with the orphan drug introduction process. An initial list of six potential informants evenly split
between the three work groups was provided by this official. After the first contact with the initial six potential informants, four of these were interviewed while one new informant was interviewed at the recommendation of one of the initial informants. The final list of 5 informants were;

1. Local Politician 1 (LP1): Local politician primarily involved with the healthcare committee at the VCC

2. Local Politician 2 (LP2): Local politician primarily involved with public health and primary care committee at the VCC

3. Technical County Council Official (CCO1): County council official primarily involved in the Västerbotten pharmaceutical center

4. Technical County Council Official (CCO2): County council official primarily involved in Norrbotten pharmaceutical center

5. Strategy County Council Official (SCCO): County council official primarily involved with strategy and prioritization questions at the VCC

All five informants additionally had varying duties and cooperation in the NRF as well as close cooperation with, or seats on national committees.

Prior to interviews, verbal agreements were given by all five informants after an initial contact by e-mail where they received a brief explanation of the aim of the study and the structure of the interviews. In addition, prior to recording at the time of the interview informants were assured of anonymity as well as being able to review the paper to give final approval of their representation and how data from their interviews would be presented. All interviews were done in Swedish and subsequent quotes and data from interviews were translated into English by the interviewer.

**Interviews**

The interviews were semi-structured one-on-one interviews done either in person or by phone. The choice of setting, time, and whether by phone or in person was made by the informant. Interviews were recorded with an Olympus VN-7800 Digital Voice recorder with the audio files deleted after transcribing to assure anonymity of informants.

The interviews ranged in length from the shortest being 15 minutes and 51 seconds and the longest being 41 minutes and 17 seconds. During the interviews, the interviewer used an interview guide that contained 4 main questions along with prepared probing questions that were used when needed. Some questions during interviews were slightly altered based on the interviewer’s judgment depending on the informant and their knowledge in order to maximize the amount of data attained from each interview (46). In preparation for the interviews practice runs were performed to ensure questions were comprehensible and logical (47). At the end of each interview informants were also given a chance to provide
additional commentary. See Appendix B and C for interview guides in both Swedish and English respectively.

All data was transcribed by the interviewer 1-2 days after each interview, resulting in 21 pages worth of data from the five interviews.

**Data Analysis**

For the analysis of the data, a thematic analysis attempting to establish a relationship between the research question and the data, as described by Braun & Clarke, was used (48). A substantive orientation was decided on since the main concern was capturing and interpreting the meanings in the data from the interviews (43). Categories were developed to divide the data according to the type of information being referenced and then grouping them according to similarities and differences (49). To help locate themes and examples to aid in the development of conceptual, analytic categories a cross-sectional analysis was performed to devise an overall and common system of labels (43, 50).

Initially, a round of coding and the translation of the transcribed interviews was done for each interview separately. This was followed by a first attempt to identify common themes from each interview, resulting in the following five preliminary themes “Regional Cooperation / Organization”, “Process”, “Difficulties / Process”, “Nationalization / Process”, and “Pricing”. Once all the coded data had been grouped into the five initial themes, an additional round of coding was performed, resulting in five new themes “Centralization of Processes”, “Methods / Standardization”, “Ethical Considerations”, “Economics & Price Setting”, and “Challenges & Difficulties”. The data resulting from the second round of coding was then organized according to the new themes before a final round of coding.
Results

The five informants were asked questions focused on attaining their understandings of what the introduction process for orphan drugs looks like. How are decision made? Who is involved in the process? How is it implemented? The interviews also sought to highlight what the informants viewed as the biggest challenges and sources of debate in introducing new orphan drugs. What does the situation look like today? How should the process evolve? What are the biggest hurdles or challenges?

From these questions, five themes were identified. As seen in figure two, these themes centered both around the process itself as well as issues and challenges in improving and implementing the process. Informants provided insights into how the process needs to evolve if it is to improve through their insights on centralization, standardization, and financing. Simultaneously, detailing the issues making this process more difficult with the issues of ethics, financing hurdles, and overall challenges from a myriad of sources.

![Figure 2]

Results from the five interviews with local politicians and county council officials. The figure shows the five main themes as well as sub-themes identified in the data from the transcribed interviews.

Centralization of Processes

During the interviews, all the informants expressed overwhelmingly positive opinions regarding the centralization of the decision-making and introduction process of orphan drugs seen from a local, regional, national, and EU perspective. The common view was that the centralization of the processes has resulted in more equality between county councils and regions.

“With the regional federation we have up North and with ARIL the idea is that circumstances should be equal. . . Here in the Northern region there are no differences [between counties]” – CCO1

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“. . . regional cooperation here in the North feels good, the patient, no matter where they are from should get the same treatment.” – LP1

“We have a lot of collective discussion within the NRF since we’re trying to do things the same way” – LP2

Informants also explained the positive impact centralization had in creating more efficient processes characterized by more consistency in implementation and execution nationally as well as workflows optimized by new regional and national frameworks while still allowing for some flexibility regionally and locally when needed.

“. . . that a lot is done centrally has huge advantages . . . every county council doesn’t have to repeat the same work.” – CCO1

“. . . a clear guide of how to act when it comes to this particular drug and that they should act similarly in all county councils.” – CCO2

The centralization has also provided a stronger negotiating position when working on new agreements with external actors. The pooling of resources, knowledge, skills, experience, and the more unified front being represented by the health sector allows for better prices on drugs to be negotiated and better availability of necessary care.

“One can better agreements, better prices if Sweden negotiates as a whole as opposed to just Västerbotten or just the Northern Region.” – CCO1

“Nationally we manage to lower prices and get good deals, and all patients that need medicine get it” – CCO2

However, while the informants viewed centralization positively with CCO1 saying, “I actually don’t think there are many other alternatives if our highest goal is equal treatment in all of Sweden.” there was still a clear opinion that there also needs to be a combination of cooperation between local, regional, and national levels. Even a more centralized process needs to be a multi-way cooperation between the various levels utilizing the strengths of each one.

“Some questions are too difficult or too specific to one county council to be taken nationally.” – CCO2

“I think we need a mix of both . . . we shouldn’t have only a national structure, we need the regional and local dialogues where you connect budgets and steer things” – CCO2

**Methods and Standardization**

During the interviews, informants also discussed new methods and standards being developed. These being rooted in both evidence-based decision-making and ensuring that existing international and national evidence and expertise is utilized.
“In writing a recommendation . . . we look at how other countries have done and what documentation EMEA has.” – CCO1

“We look to the TLV for help on the economic evaluation, which they perform to see if a drug fits in the high cost ceiling protection and drug benefit system.” – CCO2

“. . . worked on a system that logically modulates willing to pay limits . . . it should be justifiable even with orphan drugs, so there is about the same decision-making base as with regular disease.” – CCO1

Informants also discussed how they were working to make the processes much clearer, not only establishing a better, more comprehensible structure between work groups, but also clearly defining criteria and terminology used.

“We have a special group that oversees and comes out with guidelines on what we should focus on . . . we more oversee information we receive and supervise the process allowing them to do their work.” – LP1

“. . . we have developed a procedure that includes horizontal prioritization and discussed the intervals on the national model; what do we mean by a 4? What is a severe disease compared to a moderate disease? . . . we are developing methods on the health side to attain as equal prioritization as possible.” - SCCO

The need for a comprehensive system, able to handle a wide range of situations and both the introduction and phasing out of treatments was also expressed.

“We need to create a decent evaluation process for the entire managed introduction and phasing out . . .” – SCCO

“But it’s two sides of a one thing, a small expensive patient group or a large relatively cheap group but where the volume causes budget strains. These systems need to be able to handle both of these situations.” - SCCO

**Ethical Considerations**
Among the informants, there was consensus that the principle of human dignity and equal care were the top priorities. The patient is the number one priority, and regardless of their status or where in Sweden they are, the same type of care should be available.

“All of us want healthcare that’s as equal as possible . . . very clear in the whole country that is what we’re striving for . . . I think it is very clear and very good that we are all in agreement that we want care to be as equal as possible and that we are trying to reach that in the best way possible.” – LP2

“We can’t have a society where we can attain new medicines with research and development that moves forward but then people don’t get the benefits.” – LP1
"I think there is a degree of agreement in regard to the human dignity principal and that everyone has equal worth regardless of where they live or what sex they are..." – CCO1

"Patients should have the same access to medicine that exists if they need them" – LP1

There was also agreement that there needs to be flexibility in evaluating the cost-efficiency of orphan drugs differently as well as making exceptions in certain cases. However, at the same time, the difficulty to define the limits of this flexibility and how to fairly make an evidence-based decision for these rare diseases was also discussed.

"It’s acceptable with higher cost per QALY because development costs are higher and can’t be spread out due to small patient groups... thinking about need & solidarity principle one could agree to worse cost-efficiency. It would be an acceptable reason based on the ethical platform.” – SCCO

"There is always a possibility to make exceptions in certain cases... it is up to the treating clinic to contact county council leadership and explain the situation to try and get acceptance to spend more than actually allocated in their budget.” – CCO1

"We have a simplified process for approving orphan drugs, but it still requires clinical studies and efforts by the pharmaceutical company. We also want to enable those with rare diseases to get the treatment they need. The human dignity principle is extremely important, number one.” – CCO2

There are several ethical dilemmas that arise in the process, particularly with opportunity cost, displacement effects, and patient groups being pitted against each other. It’s difficult to make evaluations and decisions between very different patient groups and to keep all actors on the same page regarding the basis of decisions for certain orphan drugs.

“. . . One wants to give treatment to the patient, but on the other hand one has to accept entirely different limits with willingness to pay that you otherwise wouldn’t. Sometimes there are opportunity costs where you could have much greater effect I another area.” – CCO1

“. . . there will be a bunch of other people that get worse healthcare and a broken health system if we allow much higher prices for orphan drugs. If we combine all the rare diagnoses, then we’re up to several hundred or several thousands of patients and every one of them needs expensive drugs then we will have displacement effects.” – CCO2

**Economics & Price Setting**
The economic questions and issues surrounding price setting was described as an evolving, very challenging area to deal with. Several of the informants touched on the issue of solidarity financing and evenly distributing costs to prevent smaller counties or institutions from being excessively disadvantaged.
“We have to work together on this and we have been clear that this is not something an individual county council can handle. . . solidarity financing is extremely important for those in need, since they usually belong to such small patient groups.” – LP2

“Does each county council have its fair share of the expenses? Or is it unequally distributed? If that is the case there can be reason to think if we shouldn't organize it nationally and have some type of national budget for these small, very expensive drugs.” – SCCO

Another big issue informants discussed was the negotiations with and price setting of the pharmaceutical companies for orphan drugs. The price setting was viewed as one of the biggest hurdles in introducing new orphan drugs, both due to companies’ inexperience in the process as well as suspect pricing methods and introduction strategies.

“Costing is a bit of a Wild West scenario. There are many small actors that are very inexperienced in negotiations and that have inadequate price ideas. Sometimes we almost have to teach them how the process works, what they can and can’t do.” – CCO1

“I’ve seen drugs used to treat rare diseases where molecules were initially used for mold prevention, where the kilo price was almost nothing, but when the same molecules were used for medicine it was all of a sudden thousands of SEK per milligram.” – CCO1

“Many of the companies have as a strategy to first receive orphan drug designation and then expand the medication to more diseases. All of a sudden, they’re treating hundreds of patients but want the same price. Can’t work that way, can’t come in through orphan drug designation and then stay there even with an expanding patient group they’re treating.” – CCO2

“The companies are thinking, well 2 million SEK, that’s nothing for your budget. However, we have to try to make them understand displacement, it’s a reality today and will only get worse if we don’t keep these unjustifiably, as we believe, high prices down.” – CCO2

“It is the biggest obstacle we are facing today to introduce drugs for treatment of rare diseases, companies’ price setting” – CCO2

As mentioned earlier, the process of centralization has also helped with these challenges. Deals and negotiations have benefited from a more central process. Price controls have been added where there previously were none and a larger number of economic decisions are being based more on evidence than previously.

“TLV has said they want to take responsibility so this process is more and more happening on a national level with national deals and negotiations and that’s very reasonable I think, there are such small number of patients and so it’s important there’s equal distribution of costs.” – CCO1

“The prices are now the same, we have national agreement for several orphan drugs.” – CCO2
“Some of those working with pharmaceuticals are critical because we’re slowing down their decision-making process, but the budget can’t allow for everything. Drugs have been allocated initial budgets without proper evidence basis.” – SCCO

Informants also discussed how the process was evolving and how work was being done to actively reign in and keep down costs. The ultimate goal is to allow patients to get access to the treatment they need but within budget and at reasonable prices.

“If the drug has good effect but is simply too expensive, we try to negotiate a lower price. If the price is not negotiable we must consider a negative recommendation” – CCO2

“We have to ensure we get reasonable prices . . . we are willing to pay more for an orphan drug, but not at the excessive prices the companies are charging.” – CCO2

“The wet dream for companies would be that we gave up and said ‘We’ll buy all the drugs regardless of price’, but we try to set up alternatives while we wait out companies to meet us halfway when it comes to price negotiations.” – CCO2

**Challenges & Difficulties**

There are many and varied challenges when it comes to orphan drugs. While there is supposed agreement on adhering to the three ethical principles set out in 1996, many of the necessary tools, structures, and processes are still lacking. Several informants expressed the need for continuously evaluating and striving for improvement in multiple areas.

“Everyone says they stand behind the three ethical principles but why isn’t the outcome then equal and good healthcare without weird instances? It’s clear that there is some resistance that resource evaluation should occur this way . . . tools, processes, knowledge, and organizational culture are needed to handle these questions.” – SCCO

“It’s also important that we can remove things . . . we need to press even more that we should get better at removing things, that old disappears. It’s an education question to those prescribing medicines.” – LP1

“The national prioritization model is smart, the best there is . . . I think it has good valuing basis, the model holds and I think it should be used.” – SCCO

One particularly difficult aspect with orphan drugs is the number and wide array of rare diseases. It’s difficult to standardize a process for all orphan drugs as well to evaluating them against each other.

“We need to be able to compare these items on a single scale regardless of technique or technology . . .” – SCCO

“Orphan drugs are a very heterogeneous group, it can range from very primitive molecules that are cheap to develop to very advanced ones that are difficult and where production costs are high.” – CCO1
“QALYs need to be interpreted differently depending on if a patient needs a medicine daily for their entire life or just needs one or two treatments. Then you have to make separate decisions for different drugs, so it’s difficult to standardize.” – CCO2

A difficult part of the process has also been clearly defining and setting criteria for the different pieces involved in approving and introducing an orphan drug. Many of the debates center on ethical concerns that don’t have clear cut answers.

“We discuss how to look at severity of the disease, what it’s about, how urgent it is, and how debilitating it is . . . How big should the effect be? Is it worth starting treatment? There are no clear answers for these questions, it’s more that we are problematizing the issue . . .” – CCO2

“We have the need and solidarity principle in combination with the cost-efficiency principle saying that we accept worse cost-efficiency for the sickest. Then the question becomes what is the limit? We don’t know, no one has tested it in that way.” – SCCO

Currently, the healthcare system in Sweden is facing many challenges, not only with orphan drugs and treating rare diseases, but also in numerous other areas such as primary care, elderly care, and more. Informants expressed the challenge in dealing with so many problematic pieces when trying to provide a working, functioning whole healthcare system.

“It’s always the case that we talk about a small piece of the whole. Orphan drugs are a part of the whole, just like a bunch of other pieces that we need to be looking at in the county council.” – LP2
Discussion

The aim of this study was to provide insights and to clarify the decision-making process and the introduction process for orphan drugs in Västerbotten County from the very people working within or supporting the processes. Through the interviews, the informants provided a much clearer picture of the local, regional, and national structures and how the cooperation between these levels is evolving. There are many challenges facing those involved in the processes, both in executing and developing the processes themselves, as well as with ethical concerns and negotiating with external actors. There was complete agreement that the centralization of these processes is a step in the right direction with benefits already being seen, and that it needs to continue. The preferred option was a mixed approach, where the strengths of pooled resources and knowledge could be combined with local specialization and responsiveness. Ultimately, the guiding principles were the well-being of the patient and the human solidarity principle. In the wide variety of issues and tough questions the informants discussed, equal treatment of patients and making the best possible care available for patients, in the best way possible, were their “lodestars” as CCO2 described it.

There has been much research done on the international level looking at financing, orphan drug policies, and the availability of orphan drugs following market authorization. Literature focusing more narrowly on the decision-making and introduction processes on a national or regional level was harder to come by. Nonetheless, there is an active debate in many circles about orphan drugs; what consequences they will have and how the processes and policies should be developed. Our results consistently mirrored the ongoing debate seen in literature, media and among the various professional groups, where ethics, costs, and centralization are the main themes regardless of geographic setting (51-61).

Most of the literature argues in favor of more centralization, not only on a national level, but also on an international level and some even on a global scale (58, 62). Several studies lend support to the notion that centralization has had, and will have a positive effect particularly concerning equal access to orphan drugs as well as both keeping prices in check and ensuring funding (56, 63). In their report for the prioritization center at Linköping University, Carlsson et al detail the specifics of why a national model is more preferable in decision-making and financing in Sweden (64). Similarly to the informants, Carlsson et al talk about alternatives with varying setups for funding and areas of responsibilities (64). Carlsson et al talks about the strengths and weaknesses of various mixed models, but overall sees centralization of both budget and processes as the way forward (64). Several researchers also discuss the inequalities that arise when member states within the EU don’t have clear centralized processes, in the same vein that the informants described in Sweden between counties and regions before centralization (53, 56, 65). Alain argues that in order to be able to take into account social considerations, cost-effectiveness, and clinical effectiveness centralization is needed (59).

One line of discussion that also arose during the interviews was the role of the pharmaceutical companies, and primarily the questioning or negative opinion on their strategy and tactics. As mentioned previously, while there are issues on specifics when it comes to standards and evaluation methods in providing orphan drugs, there is common
consensus that patients suffering from rare diseases are entitled to the same care (57). Some of the biggest issues identified were the often-held views that pharmaceutical companies are abusing the streamlined process for orphan drug introduction, abusing the orphan drug designation when said drug’s target group expands past rare diseases, and charging unwarranted exorbitant prices for orphan drugs (66, 67). The legislation that has led to increased availability of orphan drugs by supporting development and providing incentives, has simultaneously resulted in higher prices many times considered out of budget or unacceptable, as described by several of the informants in this study. It raises interesting questions, similarly to that of standardization and methodology in the decision-making process, of how to find an acceptable solution to price-setting. Should there be a cap on the profit margin for orphan drugs? Does there need to be more stringent regulation on the criteria for an orphan drug to maintain its orphan designation? Should the development and research of orphan drugs be more tied to public organizations than they currently are? Or should pharmaceutical companies be forced to present their development costs and a market analysis as member of parliament Barbro Westerholm suggests (15)? Policy makers will be treading a fine line to find a solution that continues to encourage development of drugs for rare diseases while simultaneously keeping budgets in check and keeping orphan drugs at affordable prices allowing them to be accessible to patients with rare diseases.

These interviews provided a clearer understanding of the introduction process for orphan drugs and the effects it has on accessibility to these drugs for patients with rare diseases in Northern Sweden. The information provided by the informants, in line with current literature on the topic, stressed the importance of centralization while maintaining a mixed approach where international, national, and local levels worked together. In addition, the pricing models and business strategies by pharmaceutical companies pertaining to orphan drugs was discussed as one of the major emerging hurdles by the informants interviewed for this study.

**Further Research**

This study aims to provide new perspectives on the issue of orphan drugs. While there has been much research done on the interplay with national and EU regulations and processes there is little literature published regarding how the regional and local aspects fit into this picture. This study serves as an early step in mapping out the concerns as they are seen from the bottom up, laying the foundations for more pointed studies in the future. Hopefully, it serves to offer an avenue to look more closely if the results from international and national legislation and processes actually are trickling down to patients with rare diseases and that these patients are as a result, receiving equal care, not only compared to other patient groups but also compared to other countries and regions. An understanding of the discussion and issues related to orphan drugs can serve as a guide for policy makers and officials in the future. In the interviews, CCO2 described how similar issues are and will continue to grow with, for example, medical devices as they lack adequate standardization and processes for introduction. As more diseases are discovered, new treatments developed, and budgets become more strained, the ethical and structural debates around orphan drugs will most likely be repeated in new arenas.
Limitations

Due to time constraints, the sample for this study’s data was limited to five informants. If possible, it would have added additional insights to be able to expand the setting of the interviews to include representatives from all councils comprising the NRF to get an even more complete perception of the cooperation of the Northern Councils. In addition, there were few previous studies focused specifically on the decision-making process on the local or regional levels. In the literature research, most studies were focused on the international plain or on legislation offering incentives for development of orphan drugs. Finally, with the use of self-reported data and interviews, transcribing, and coding done by the same person there is an absence of independent verification. However, the structure and defined steps in the methodology of the study do allow for the independent replication of identified themes and results by third parties.
Conclusions

The results of this study provide additional evidence and a new perspective on the issue of financing, introducing, and regulating orphan drugs and ensuring equal treatment for people with rare diseases. Centralization of standards and processes are necessary to pool resources and knowledge. Centralization is the solution if the end goal is equal quality and equal access to healthcare. There are still many questions to be answered to determine exactly how this should look and how to further standardize and objectively evaluate options while still accounting for numerous ethical dilemmas. The uniform results from this study suggest that there is broad agreement on which direction orphan drug legislation and processes should pursue, but also that there still is much debate and many questions exactly what it should look like.
Appendix A

Database Search Terms

Health Services Accessibility
Legislation
Legislation & Jurisprudence
Orphan Drug Production
Drug therapy
Rare Diseases
Methods
Health Policy
National Health Programs
Organization
Administration
Drug and Narcotic Control
Pharmaceutical
Insurance, Health
Prioritization
Decision-making for drugs for rare diseases
Economics
Jurisprudence
Drug
Organization & Administration
Insurance
Health
Reimbursement
Standards
Ethics
Development
Procedure
Pricing
Appendix B

Interview Guide

1. Hur ser beslutsprocessen ut inom landstinget angående särläkemedel?

Vet:

- Vem är det som fattar besluten?
- Vilka faktorer utgör erat beslutsunderlag?
- Vilka externa faktorer måste ni tänka på när ni fattar era beslut?
  - Budget?
  - Reglament/riktlinjer ni måste följa?
- Hur ser det ut när ett beslut väl tagits om ett särläkemedel?
  - Är det en rekommendation, regel, osv?
- Vem är beslutet riktat till?
  - Läkare, tjänstemän, osv?
  - Vad har de för möjligheter att motstrida eller motsäga beslutet?

Vet ej:

- Vilka är involverade i beslutsprocessen?
- Vet du vad de använder för kriterier för att nå fram till deras beslut?
- På vilket sätt jobbar du med beslutsprocessen

2. Hur upplever du dagsläget när det gäller särläkemedel i Västerbotten?

- Hur omfattande är särläkemedelsförskrivningen?
- Hur ser ni på kostnadsbilden gällande särläkemedel?
- Upplever ni att det finns skillnader mellan landstingen när det gäller särläkemedel?
  - Med tanke på landstingen?
  - Med tanke på patienterna?
- Hur ser diskussionen ut inom landstinget angående särläkemedel?

3. Vad tycker du om att godkännanden av särläkemedel sker på landstingsnivå?

- Vad ser du för särskilda möjligheter som följd av att det sker på lokal nivå?
- Vad ser du för särskilda svårigheter som följd av att det sker på lokal nivå?
- Vad ser du för alternativ till beslutsprocessen på regional nivå?

4. Vad har du för funktion inom landstinget?

- Hur relaterar sig din funktion till det vi har diskuterat?
- Hur har ditt engagemang med särläkemedel bildats?
  - Ansvar som en del av dit jobb?
  - Yrkeslivet bredvid politiken som lett till intresse för särläkemedel?
  - Särintresse för särläkemedel?
Appendix C
Interview Guide

1. What does the decision-making process for orphan drugs looks like in the county council?

**Knows:**
- Who makes the decisions?
- What factors constitute your decision-making basis?
- What external factors do you account for when making your decisions?
  - Budget?
  - Regulations / Guidelines you need to follow?
- What does it look like when a decision has been made for an orphan drug?
- Who is the decision directed towards?
  - Doctors, officials, etc.?
  - What possibilities do they have to argue or act against a decision?

**Doesn’t Know:**
- Who is involved in the decision-making process?
- Do you know what criteria they use to reach a decision?
- How do you work with the decision-making process?

2. How do you perceive the current situation with orphan drugs in Västerbotten?
- How extensive is the prescribing of orphan drugs?
- How do you view costs regarding orphan drugs?
- In your perception, are there differences between counties when it comes to orphan drugs?
  - In regards to the county councils?
  - In regards to patients?
- What does the discussion within the county council look like concerning orphan drugs?

3. What is your view on approvals for orphan drugs being made on the county council level?
- What advantages do you see as a result of decisions being made locally?
- What difficulties do you see as a result of decisions being made locally?
- What alternatives do you see to the decision-making process at a local level?

4. What is your function within the county council?
- How does your function relate to the topics we just discussed?
- How has your involvement with orphan drugs developed?
  - Responsibility as a part of your role?
  - Professional life outside of politics that developed your interest for orphan drugs?
  - Special interest for orphan drugs?
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