

Conference Report

Research in Rare Diseases in Denmark: Barriers and Prospects

Report from a conference in Copenhagen
on 26 February 2004



Danish Alliance of Rare Disorders

Research in Rare Diseases in Denmark: Barriers and Prospects



Conference report:

Research in Rare Diseases in Denmark: Barriers and Prospects.

ISBN: 87-989614-3-8

A report of the conference "Research in Rare Diseases in Denmark: Barriers and Prospects", held in Copenhagen on 26 February 2004.

The report is available from

Danish Cancer Society

Strandboulevarden 49

DK-2100 Copenhagen Ø

Tel. +45 3525 7500

web: www.cancer.dk

KMS

Danish Alliance of Rare Disorders

Frederiksholms Kanal 2, 3. sal

DK-1220 Copenhagen K

Tel. +45 3314 0010

web: www.kms-danmark.dk

Editorial staff

Dorthe Lysgaard, KMS

Iben Holten, Danish Cancer Society

Poul Riese, KMS (editor)

Poul Eik Jørgensen, KMS (proof reader)

Text

Journalist Anne Birkelund

Translation

Malene Markussen

Design

Rumfang 04147-44

Photos

Mads Meinertsen, Stilleben

Preface

Under the heading “Research in Rare Diseases in Denmark: Barriers and Prospects” the Danish Cancer Society and the Danish Alliance of Rare Disorders (KMS) held a conference in Copenhagen on 26 February 2004.

The conference gathered 120 participants who represented a wide range of scientists, health care professionals, patients’ organisations, Danish pharmaceutical and biotech companies, authorities and politicians.

As it appears from this report the participants were eager to discuss what Denmark can do to encourage research in rare diseases.

Need for a national strategy

The conference illustrated that Denmark has a fine potential for research in orphan medicinal products. We have well functioning biobanks and registers, many dedicated people among scientists and other parties, a strong international cooperation and a lot of knowledge.

But the conference participants equally agreed that special initiatives and support will be necessary to increase the Danish potential. Therefore, there is a need for a national strategy for research in rare diseases, for strengthening the research environments and for increased participation in international networks.

Now the challenge is to turn the words into action – for the benefit of Danish researchers, health care professionals, pharmaceutical companies and, especially, for the Danish patients.

Anne Thomassen
Chairman

Torben Grønnebæk
Chairman



Kræftens Bekæmpelse
Danish Cancer Society



Danish Alliance of Rare Disorders

The organisers thank the sponsors who made this conference a reality:

- The Danish Ministry of Science, Technology and Innovation
- Novo Nordisk A/S
- AstraZeneca A/S
- Roche Diagnostics
- Bristol-Myers Squibb
- Swedish Orphan A/S
- HemeBiotech A/S

Programme

Panel

Facilitator: *Ms. Connie Hedegaard (reporter and host on national television 2)*

9.00 Registration and breakfast

9.30 Welcome

Ms. Anne Thomassen, Chair of the Danish Cancer Society

9.40 Introduction

Ms. Hanne Severinsen, (MP, Liberals), Chair of the Parliamentary Committee for Science and Technology

Barriers og problems

9.50 Research in Rare Diseases: a European Perspective

Mr. Terkel Andersen, President of the European Organisation for Rare Diseases (EURORDIS)

10.05 From Bottlenecks to Solutions in Clinical Trials

Mr. Brendan Buckley (DMSc.), Director of the European Institute for Clinical Trials in Rare Diseases. University College Cork, Ireland

10.35 Scientific Evidence and Research in Rare Diseases

Mr. Ulrik Lassen (Staff specialist, MD), Department of Clinical Oncology, Copenhagen University Hospital

10.50 Challenges to Research on Orphan Drugs in Denmark

Mr. Jens Fogh, CEO, Hemebiotech

11.05 A Cost/Benefit Analysis Applied to the Development of Orphan Drugs

Ms. Dorthe Gyrd-Hansen, (Professor, PhD), Institute of Public Health – Health Economics, University of Southern Denmark..

11.25 Discussion and summing up

12.00 Lunch

Possibilities and solutions

10.50 The Role of Patients' Organisations in Promoting Research

Mr. Torben Grønnebæk, Chair of the Danish Alliance of Rare Disorders (KMS)

13.00 The Dutch Experience

Mr. Harrie Seeverens (MD) Internist and policy advisor at the Dutch Ministry of Health, Welfare and Sports. Member of the Dutch Steering Committee Orphan Drugs.

13.30 Taking Part in International Research

Ms. Karen Brøndum-Nielsen (Professor, DMSc.) Head of Institute, J.F. Kennedy Institute. Member of the Danish Medical Research Council.

13.45 Opportunities and Conditions for Research in Rare Diseases

Ms. Merete Reuss, Head of Department, Ministry of Science, Technology and Innovation.

14.00 Public-Private Sector Cooperation

Mr. Mogens Kruhøffer (Associate Professor, PhD), Molecular Diagnostic Laboratory, Aarhus University Hospital. Manager R&D, Aros Applied Technologies

14.15 Coffee Break

14.45 Panel Discussion and Summing Up

16.00 End of Programme

Ms. Hanne Severinsen

(MP, Liberals), Chair of the Parliamentary Committee on Science and Technology

Ms. Sophie Hæstorp Andersen

(MP, Social Democratic Party), Member of the Parliamentary Committee on Health

Mr. Torben Grønnebæk

Chair of the Danish Alliance of Rare Disorders (KMS)

Mr. Ulrik Lassen

(Staff specialist, MD) Department of Clinical Oncology, Copenhagen University Hospital.

Ms. Karen Brøndum-Nielsen

(Professor, DMSc.) Head of Institute, J.F. Kennedy Institute. Member of the Danish Medical Research Council.

Ms. Ebba Nexø

(Professor, DMSc.) Chief Physician. Chair of the Danish Cancer Committee

Ms. Merete Reuss

Head of Department, Ministry of Science, Technology and Innovation.

Mr. Jens Fogh

CEO, HemeBiotech

Summary

Background

Around 20-30,000 people in Denmark suffer from rare diseases. The majority of the diseases are serious or even life threatening and in most cases no therapy exists.

Still, research and development of drugs for rare diseases, the so-called "orphan drugs", is a neglected area. One of the reasons is that the number of patients is so small that most pharmaceutical companies are reluctant to initiate development of drugs for them. There may be problems with conducting clinical trials, problems with maintaining a community of competent scientists and establishing new research environments, poor conditions for cooperation and limited research funds.

On this basis, the EU adopted a regulation in 1999, which stresses the obligation of the member states to support research and development of drugs for rare diseases. A number of countries have already taken steps in this field, but so far nothing has been initiated in Denmark.

In Denmark it is necessary to work out a joint strategy for research and development of drugs for rare diseases. One of the first steps is to map existing research and knowledge in the area. There is also a need for special initiatives in the form of economic support and incentives – and for the various actors in the area to work closer together.

Those were some of the conclusions from the conference about research in rare diseases held on 26 February 2004 in Copenhagen.

Conclusions from the conference

The conference gathered a number of scientists, health care professionals, patients' organisations, Danish pharmaceutical and biotech companies, authorities and politicians. The purpose was to discuss barriers and prospects for research in and development of orphan drugs in Denmark.

The conference had around 120 participants and was organised by the Danish Cancer Society and The Danish Alliance of Rare Disorders, KMS.

Orphan drugs

The term orphan drugs comes from the United States. Some diseases are so rare that there are not enough incentives for the pharmaceutical industry to develop drugs for them. This led to the American Orphan Drug Act in 1983. It gives the companies exclusive rights to seven years marketing of drugs developed for diseases with less than 200,000 affected people, plus a number of other advantages. Today around 900 drugs are authorized as orphan drugs, of these 238 are authorized for marketing. Also countries outside the United States and Europe have taken steps to strengthen research and development of drugs for rare diseases. These include Japan, Singapore and Australia.

EU-regulation on drugs for rare diseases

On 16 December 1999 the EU adopted a regulation on orphan medicinal products ((EC) No 141/2000). The objective was to strengthen research and development of drugs for patients with rare diseases. The means are free protocol assistance for companies developing orphan drugs, a faster market authorisation procedure and lower fees. Moreover, the companies will have up to ten years exclusivity on the European market once the drug is authorized.

The regulation also stresses the obligation of the individual member states to support research and development of drugs for rare diseases.

So far, 189 products have been authorized as orphan drugs, out of which 14 are authorized for marketing. Some have been developed for rare cancer diseases; an example is Glivec, which is used for chronic myeloid leukaemia and GIST. But also drugs for rare metabolic disorders such as Fabry and Gaucher have been authorized.

The regulation on orphan drugs has been followed by another regulation from 27 April 2000, which, among other things, specifies the criteria for the authorization of pharmaceutical products as orphan drugs. Both regulations may be found at:

<http://europa.eu.int/scadplus/leg/en/lvb/l21167.htm>

Barriers for research in rare diseases



There are many barriers when it comes to research and development of drugs for rare diseases: There are problems with conducting clinical trials, problems with maintaining a community of competent scientists and establishing new research environments, lack of overview, poor conditions for cooperation and limited research funds. Moreover, the number of rare-disease patients is so small that most pharmaceutical companies are reluctant to initiate the development of drugs for them.

In the EU a disease is defined as rare if it affects no more than 5 out of a population of 10,000 people. There are more than 6,000 rare diseases which together affect around 25 million Europeans. The latest research indicates that there are far more subtypes of each disease than previously known. This also applies to some of the more common diseases which may be subdivided into many rare diseases with individual needs for tailored therapy.

In spite of their extent, a considerably smaller amount of research is being carried out in the small disease groups than in the large ones, as was pointed out by Anne Thomassen, President of the Danish Cancer Society. And this is due to many reasons.

Scientific evidence as a barrier

Scientific evidence is needed for the introduction of new kinds of therapy. This means that the effects must be well documented before the drug can be used. However, scientific evidence may be difficult to obtain when it comes to rare diseases because the number of patients is often too small for randomized tests to be carried out.

– Thus the question is whether it is realistic to demand all research and therapy be based on scientific evidence, said Ulrik Lassen, Ph.D. Section for Experimental Cancer Therapy at the Copenhagen University Hospital (Rigshospitalet). Naturally, it should always be the aim to obtain scientific evidence and let this form the background for the therapy. But it should not be at the expense of the individual rare-disease patient. The consequence of limited resources is that well documented research receives the highest priority, and patients with rare cancer diseases often cannot receive therapy in Danish hospitals. If a doctor treats these patients, he or she may fear violating some rules or restrictions because the research or therapy is not based on scientific evidence.

Ulrik Lassen therefore called for tools and a framework for the non-evidence based therapy and research in rare diseases. At the same time he was critical of the new EU-directive 2001/20/EC which came into force on 1 May 2004. The directive lays down rules and procedures for the clinical trials but will, according to Ulrik Lassen, limit the scientists' possibilities for launching projects on their own initiative.

Small patient base

There are other barriers in connection with clinical trials. According to Brendan Buckley, Director of European Institute for Clinical Trials in Rare Diseases, data from the clinical trials are often inadequate and of poor quality. According to him this is due to the small number of rare-disease patients in the individual countries. Furthermore, 80% of the companies that apply are small and often from one country. A large part of the companies have only limited experience with clinical trials and with the procedures of approval in the other countries. This means that the market authorisation procedure for orphan medicinal products may be difficult. Consequently, it would be natural to carry out clinical trials across the countries in Europe.

This, however, is complicated because of differences in the individual countries' health care systems, ethical rules, legislation and culture. Furthermore, financing projects across countries is complicated, and the countries' research funds normally only support national projects.

The price of orphan drugs

Another barrier for research and development of drugs for rare diseases lies with the pharmaceutical industry.

– The industry is basically conservative and chooses the safe areas, said Dorte Gyrd-Hansen, Professor at the



Institute for Health Services Research at University of Southern Denmark. Instead of trying new fields, the industry goes for familiar and tested products.

At the same time, resources for the health care system are limited. When money is channelled to one place in the system, it is at the expense of other areas. Thus the question is to which degree society is willing to pay the price for orphan drugs.

A number of participants at the conference objected to this analysis. Arne Rolighed, Managing Director of the Danish Cancer Society, did not know of any examples of authorized and beneficial therapy methods being disfavoured at the benefit of others. Likewise, Terkel Andersen, President of the European Organisation for Rare Diseases (Eu-rordis), found that society has already proved its readiness to pay with the orphan drugs regulation. He also emphasized that the social sector may save large amounts from treating rare diseases which often cause severe handicaps.

Less focus on drugs

Terkel Andersen pointed out some of the more traditional barriers. One of the characteristics of research in rare diseases in the Scandinavian countries has been the connection between the social efforts and the pharmaceutical area. He emphasized this as a positive aspect.

The social consequences of rare diseases have received more attention than their causes. And this has made the need for the development of a joint research strategy in the medical field less obvious.

- More knowledge of the pathology of the diseases, epidemiological data and special grants regarding clinical trials are still necessary, he said.

Also Torben Grønnebæk, President of the Danish Alliance of Rare Disorders (KMS), regretted that up till now the initiatives on rare diseases have had insufficient focus on research. According to the EU-regulation on orphan drugs member states should introduce measures to support research. France, Spain, Italy and The Netherlands have made the first moves, but nothing has been initiated in Denmark.

Little public funds for research

A complete overview of Danish research in rare diseases does not exist. But it is quite modest according to several

participants at the conference. This is also reflected in the figures from The Danish Medical Research Council which allocate a large amount of the public research funds to the health care area.

In 2002 and 2003 around 1,200 project applications were considered. 35-40% received grants but only 10-15% of the total amount applied for was granted. From the 1,200 projects about 1% went to projects on rare diseases. This is a relatively small number considering the fact that in its national strategy for health sciences from 1995 the Danish Ministry of Science, Technology and Innovation had given priority to areas that play a central role as to rare diseases. This includes neuroresearch, genetics and therapy methods. The small number is due to the tough competition, said Karen Brøndum-Nielsen, Professor, MD, and member of the Danish Medical Research Council.

Only 5% of all public research funds are allocated by the EU. But it requires a lot of resources applying for these funds from the EU, one participant from a small Danish biotech company told the conference. They had spent a whole year preparing one application.

Glue on the hands

The scant resources in the area also mean that it is difficult to maintain a community of competent scientists and establish new research environments.

- If one wants to make a career as a research scientist it is much easier to head toward the resources, said Ulrik Lassen. This means that the scientists are pressured into directing their research to the areas where the money is.

A number of the participants drew attention to the poor relationship between doctors at the regional level and the university hospitals. One participant found that international cooperation on rare diseases was better than the national cooperation. According to Arne Rolighed one of the reasons is that some doctors and scientists find it difficult to send their patients elsewhere in the health care system – and some have a “bit of glue on the hands”.

So there are several barriers for research and development of orphan medicinal products. But Denmark also has some advantages and this means that the task is not impossible.

Prospects for research in rare diseases

Denmark has a solid foundation for research and development of orphan drugs: well functioning biobanks and registers, dedicated scientists, international collaboration programmes and a large amount of knowledge. But the conference agreed that it takes special initiatives and support to develop the Danish potential. There is a need for improvement of the research environments, more participation in the international networks, and a national strategy.

Since 1981, all newborns in Denmark have had a blood test which is being kept at the State Serum Institute. The purpose is to prevent and treat certain genetic diseases such as Phenylketonuria (PKU). This register is often referred to internationally. However, several other registers and biobanks exist across the country and they are significant tools for research in rare diseases. On this basis, Denmark is quite advanced when it comes to the genetic mapping of rare diseases. Denmark is also ahead when it comes to therapy of certain rare diseases. Most often, however, the work is carried out by a small number of dedicated scientists, but it provides a foundation for further exploration – also in the research field.

Cooperation across boundaries

Commercially speaking, several companies in Denmark already do research in orphan drugs. Although most of them are small, this is not a barrier in itself, says Jens Fogh from HemeBiotech. His company develops drugs for three rare metabolic diseases in close cooperation with a number of international research groups and networks.

The Danish participation in international networks was also emphasized by others. Generally, cooperation is fine; 40% of the Danish health articles are written in cooperation with either the United States, Sweden, Britain or Germany, Karen Brøndum-Nielsen informed the conference.

Even though cooperation at national level was criticized by a number of participants, the conference offered several examples of good cooperation between the public and the private sector. One example is the Danish company Aros Applied Technologies which is a collaboration between university, county and private investors in the city of Aarhus.

Many participants at the conference requested an overview or a database of the existing research and knowledge about rare diseases in Denmark. In this connection attention was drawn to the considerable amount of knowledge and competence in the Danish patients' organisations.

Framework for research

At the turn of the year a new system of research councils was introduced in Denmark. The new system will make it easier to monitor and coordinate Danish research. Additionally, in 2002 the KOF(cancer plan and research)-committee was set up, as a follow up to the Danish National Cancer Action Plan. One of the committee's tasks is to examine how Danish cancer research may be best supported, including research in rare cancer diseases. So far, the work has been directed towards the cross-disciplinary research groups, the regional infrastructure and public financing. And according to the chairman of the committee, Ebba Nexø, the work of the committee can be used as a model for other disease areas.

International models

An example to be followed could be the one set by the Netherlands who already in 1997 took the initiative of developing a rare disease policy. Since then, a steering committee with representatives from the pharmaceutical industry, patients' organisations, universities, hospitals and other institutions has been established. They have held conferences, published information material and produced an overview of parts of the existing research. Moreover, the steering group is working on a proposal for a Dutch research programme for orphan drugs. France is also among the countries which may be a source of inspiration for Denmark. In its new health care plan the French government has included rare diseases as one of



five focus areas. Moreover, they have the clear target of turning the increasing amount of knowledge about human genetics into new therapy methods for rare diseases. In this connection, a number of so-called "génopoles" – gene metropolises have been established across France, bringing together French universities and biotech industries.

Towards a Danish strategy

Thus some countries have taken central initiatives in order to strengthen research and development of orphan drugs. A number of the participants mentioned that this is also necessary in Denmark. Special incentives are required if rare diseases should be able to manage the tough competition for research grants.

Hanne Severinsen (MP, Liberals) was not unresponsive, although she did not offer any promises either. She referred to the government's action programme "New Ways between Research and Industry" from 2003, which aims at strengthening interaction between public research and industry:

- This programme has encouraged an open discussion about which research areas are important. And I believe that this area (development of orphan drugs) is important. The new research structure aims at supporting good ideas and research projects that may also be beneficial for the advances in therapy for rare diseases, said Hanne Severinsen.

- Now it is time for a discussion of which areas to give priority; this may well be a strategic choice. But a decision will be made in the next Finance Act, she said.

Arne Rolighed picked up the thread and suggested the building of a strategy focusing on the areas in which Denmark already is in a strong position. He also assessed that 2-3 million Euros will be necessary to establish three to four Danish centres of excellence.

Need for a persistent effort

Also Torben Grønnebæk found that a national strategy for research in rare diseases should be developed.

- We would be pleased to present a proposal to the Danish Council for Strategic Research. Between 6-8% of the population are affected by rare diseases. In 2001, public expenditures on health research amounted to

around 335 million Euros. If 6% of this amount were allocated to rare diseases it would equal 20 million Euros. And this is considerably more than the amount which is presently allocated to research in rare diseases, he said. Karen Brøndum-Nielsen stressed that a single economic boost is not enough. It is important to establish an infrastructure to ensure ongoing research. The effort should be persistent for the sake of international research cooperation: To participate in the cooperation everybody must contribute.

Hanne Severinsen emphasized the importance of basic research in relation to rare diseases:

- One can envisage the development of orphan drugs as a niche production to be exported worldwide. But basic research is also important because it is the means of finding causalities which were not considered previously – contrary to the applied research, she said. There were also warnings against the selection of specific areas which may result in other areas being neglected. This may, however, be prevented by appointing a public institution such as the Danish Medicines Agency to be responsible for this.

Towards a proposition

At a more concrete level, Sophie Hæstorp Andersen (MP, Social Democratic Party), health policy spokeswoman and member of the Health Parliamentary Committee, promised to follow up on the Orphan Drugs Regulation from 1999. She found it important that a suitable structure is made for Denmark so that there will be less barriers in the future.

She also found that a better overview of the costs and benefits should be established, possibly by including Institute for Rational Pharmacotherapy in order to benefit the most from the therapy.

Moreover, Sophie Hæstorp Andersen found that the possibilities for tax exemptions for the companies should be considered more closely and that other incentives that may encourage development should be provided.

Hanne Severinsen did not disagree that this was feasible. But she also emphasized the politicians' possibilities for favouring research in rare diseases with the new research advisory system. She also found the Dutch experience interesting.



- › – I will not rule out that we could work out something like that. One of the consequences of this conference could very well be that a proposition is made, said Hanne Severinsen, thereby making an open invitation.

There was general agreement among the conference participants that a joint strategy for research and development of drugs for rare diseases should be worked out. Mapping of existing research and knowledge in the area is one of the first steps. Other needs are special initiatives in the form of economic advantages and incentives – and that the various actors in the area work closer together, internationally as well as in Denmark. Now the challenge is to turn words into action.

There is a need for a national strategy for research in rare diseases. This was one of the main conclusions at the conference "Research in Rare Diseases in Denmark: Barriers and Prospects", held in Copenhagen on 26 February 2004.

The English edition of the report summarises the main conclusions from the conference. The conference counted 120 participants – representing scientists, health care professionals, patients' organisations, pharmaceutical- and biotech companies, authorities and politicians.

Further copies are available from:

Danish Cancer Society
Strandboulevarden 49
DK-2100 Copenhagen Ø
Tel. +45 3525 7500
web: www.cancer.dk

KMS
Danish Alliance of Rare Disorders
Frederiksholms Kanal 2, 3. sal
DK-1220 Copenhagen K
Tel. +45 3314 0010
web: www.kms-danmark.dk