LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

REPORT 2007

Foreword

The Danish Medicines Agency is assigned a number of tasks by the Danish Parliament, and we must fulfil these tasks as an authority. The tasks encompass authorisation, granting and monitoring. But what exactly do we authorise, grant and monitor? This is captured in our vision and mission, and if you turn the page, you can see our core activities illustrated as a molecule. On the pages that follow, we take you through a few events from 2007 that demonstrate the broadness of our tasks.

We have also invited some of our employees to talk about their ongoing work with large cross-disciplinary projects and tasks built around three themes. Because, as our vision and mission indicate, we wish to use the knowledge we gather through our daily work to be proactive and open to the public. We wish

Mission, vision and values

to influence the development of medicinal products and other healthcare products. And we also wish to promote the proper use of such products.

On the theme pages, we therefore tell about projects that deal with the future of the Danish Medicines Agency, focusing on our partners in the business sector, consumers and our involvement in European development.

Enjoy

Jytte Lyngvig
Chief Executive Officer

Mission
We aim to ensure the availability of effective and safe healthcare products – medicinal products, medical devices and new therapies – and we promote the proper use of such products.

Vision
We will influence the international development of medicinal products and other healthcare products. We will focus on the health and welfare of both people and animals with due consideration to affordable and economic treatments.

Values
We are competent
We are trustworthy
We are attentive
We are receptive
We are European

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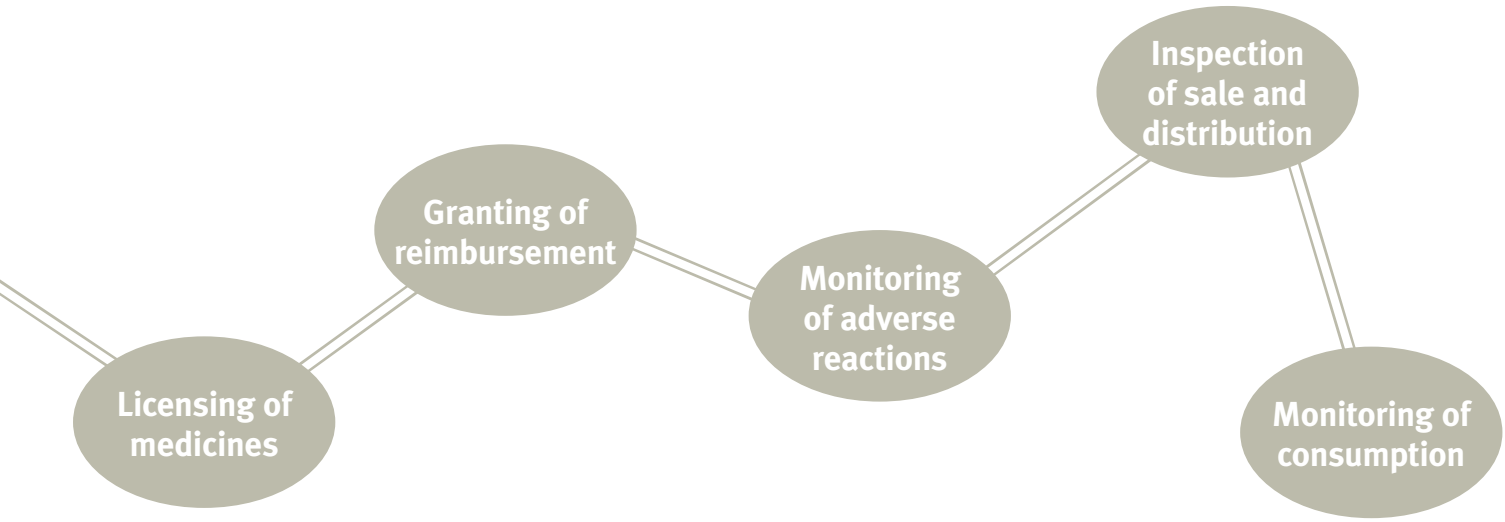
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Licensing of medicines
Monitoring of consumption

We authorise companies

Before a company may legally manufacture and handle medicines, the company's quality systems, staff competencies and premises must be authorised by the Danish Medicines Agency.

The new Danish Tissue Act

The use of human tissues and cells has given us more and better treatment options to treat infertility and a variety of diseases – it's a field within medical science which is experiencing rapid growth.

The new Danish Tissue Act from 2006 is to ensure high and consistent quality and safety standards for the handling of human tissues and cells. The act was fully implemented in Denmark in 2007.

The Danish Tissue Act derives from three European directives, which all set standards for the quality and safety of the procurement, testing, processing, preservation, storage, distribution as well as import and export of bones, cartilage, heart valves, corneas, stem cells and sperm cells, etc. – collectively referred to as human tissues and cells.

Inspection of tissue establishments
It is part of our authorisation procedure to inspect tissue establishments, and during the first quarter of 2007, we inspected all tissue establishments that had applied at the appropriate time for authorisation of tissue establishment activity pursuant to sections 4 and 5 of the Danish Tissue Act.

The inspections were carried out to ensure that hospital wards, companies and other institutions handling human tissues and cells for human application comply with the requirements of the Danish Tissue Act and any related executive orders.

These include requirements for the tissue establishments' quality control systems, staff competencies, layout of the premises and their systems for ensuring traceability of the donated material from donor to recipient.

Authorisations granted
The Danish Medicines Agency authorised more than 100 tissue establishments to handle human tissues and cells around the time when the Danish Tissue Act took full effect on 7 April 2007.

The establishments authorised were fertility clinics and gynaecologists, hospital wards, companies and laboratories.

European cooperation
Our work with tissues and cells is not confined to Denmark. We also work actively to implement and harmonise European directives in Europe and the Nordic region. For example, we are involved in the project **E**uropean **U**nion **S**tandards and **T**raining in the **I**nspection of **T**issue **E**stablishments (EUSTITE), and likewise we have established and participate in the **NOR**dic **P**artnership of the **E**ustite **P**roject (NORPEP).

Information online
On our Danish website Laegemiddelstyrelsen.dk, we have published a register of all authorised tissue establishments in Denmark. Here, we also publish relevant guidelines and forms that can be used for reporting suspected serious adverse drug reactions or unwanted incidents. This site also contains forms that tissue establishments can use when they are to report their annual activities to the Danish Medicines Agency.

What is a tissue establishment?

Hospital wards that
- store stem cells from blood and bone marrow for use in patients suffering from a serious disease,
- store bones – primarily for hip and back surgery,
- store sperm and ovaries from patients at risk of becoming infertile due to treatment of certain types of cancer; later on, men can use the stored sperm for artificial insemination, and women can regain their fertility by having the stored ovarian tissue reimplanted,
- store corneas from deceased patients for the treatment of certain eye diseases.

Fertility clinics and gynaecologists that
- perform artificial inseminations and "make" test-tube babies.

Companies that
- process and supply semen for use in artificial inseminations,
- store stem cells from umbilical cord blood from newborns, giving these children the opportunity to be treated with their own stem cells later on in life,
- process cartilage cells for the treatment of cartilage damage.

Laboratories that
- perform tests for markers of infection.

We license medicines

Before a medicine can be sold to consumers, it must be licensed by the Danish Medicines Agency or the European Commission. It must meet specific standards of quality, safety and efficacy, and there must be a favourable balance between effect and side effects.

The new Decentralised Procedure

When a medicine is to be licensed, the company behind the product must select one authorisation procedure from an alternative of procedures. 2007 was a particularly good year for the newest application procedure, the **Dec**entralised **P**rocedure (DCP).

Country by country or all at once
The DCP is the common choice when applicants (the companies behind the products) intend to sell their medicines in a number of countries from the onset. The DCP is convenient because the authorisation procedure is started at the same time in all countries where the applicants wish to market their products.

The DCP was introduced with the new medicines legislation in 2005 as an alternative to the Mutual

Recognition Procedure (MRP), according to which a product had to be authorised in one EU country before the authorisation procedure could be started in other EU countries.

A more expensive solution
When the new licensing procedure was introduced, we expected the pharmaceutical companies to approach it somewhat hesitantly, believing they wanted to gain experience with the new procedure before they would start using it actively. We expected this reaction because – unlike the MRP – the company must file applications with and pay licensing fees in all countries from the beginning. In other words, the DCP could be a more expensive solution if the company's application is turned down. But as it turned out, our expectations were by far exceeded.

Unexpected interest
In 2006, a great many applications for the licensing of medicines were submitted under the Decentralised Procedure and even more applications were submitted in 2007. In our 2006 forecast, we estimated that we would act as Reference Member State in 10 to 20 DCPs, but the actual number was 86. And in 2007, we processed as many as 218 DCPs, placing us third after Germany with 273 and England with 222 DCPs. Another very active country was the Netherlands with 140 procedures, while Sweden had 49. Together, these five countries accounted for 85 per cent of all DCPs in 2007.

There is every indication that the DCP will continue to grow in popularity in future.

– and grant reimbursement

Reassessment of reimbursement status

The first decision – after we and the Reimbursement Committee had reassessed the reimbursement status of a group of medicinal products – took effect in 2007.

The reassessment concerned the reimbursement status of cholesterol-lowering medicines, and the decision softened the reimbursement conditions for this group of medicines.

As of 23 April 2007, all lipid-lowering medicines were thus comprised by the rules on general reimbursement – conditional or unconditional.

In principle, it means that doctors no longer have to apply for single reimbursement for lipid-lowering medicines.

Decisions about the reimbursement status of medicines are no longer permanent. This follows from a decision by the Danish Parliament in 2004 based on Recommendation no. 1444 of May 2004 titled "Reimbursement and appropriate use of medicines". An extract of the recommendation reads "such reimbursement decisions must not constitute permanent decisions about the reimbursement status for these medicinal products, as the assumptions having originally led to a decision concerning e.g. general reimbursement for a medicinal product may change over time."

We inspect sales outlets and monitor medicine consumption

Traditionally, medicine is sold in pharmacies, but supermarkets, kiosks and drug stores also sell a sizeable range of over-the-counter medicines. The Danish Medicines Agency inspects sales outlets to make sure that the medicines are stored, distributed and sold according to the rules. All the while, we keep track of medicine consumption in Denmark.

The medicine settlement

On 2 April 2007, the sale of medicines for production animals was liberalised, permitting these products to be sold outside pharmacies. In this connection, the fixed-price system that applied to these medicines was abolished, making it easier to compete on price.

The liberalisation was effected for several reasons. Partly, the intention was to foster lower prices through free price formation, but a need had also emerged to tidy up the industry's various "discount schemes" and price agreements between wholesalers, manufacturers, pharmacies, etc.

Duty to ensure product availability and professional competencies
The new distributors must be authorised by the Danish Medicines Agency, which means that they must fulfil a number of requirements. For example, the distributor has an obligation to ensure the availability of products. In addition, a pharmacist must be attached to the business, and the dispensing of prescriptions must be handled as safely as at a pharmacy. Finally, the business must not sell other types of goods, such as animal feed.

We administer requests from pharmacies and others that would like an authorisation for distribution of medicine now that the new rules have entered into force. We have also changed the dispensing groups for veterinary medicines, enabling us to control which medicines are sold outside pharmacies.

Online overview
A list of dispensing groups is kept updated on our website. Together with the Danish Veterinary and Food Administration, we have also initiated a number of inspections at pharmacies and veterinarians that are active in the field.

Basically, we want to increase the safety of veterinary medicines. It is our responsibility to define the limits of when a medicine may be used in production animals and to set the so-called withdrawal periods (MRL-values) – i.e. the time that has to pass from the medicine is administered until the animal is slaughtered. In line with this, medicines for production animals were made prescription-only as of 1 January 2007.

New regional medicinal product statistics

For many years, the Danish Medicines Agency's Register of Medicinal Product Statistics has provided both national and county statistics on the dispensing of medicines in Denmark. After the transition to the new Danish administrative map on 1 January 2007, the county statistics were converted into regional statistics.

Since we keep information about prescriptions as well as the address of the prescribing doctor, pharmacy and general sales outlet, we have been able to trace back the sale of prescription and OTC medicines from the previous counties to the current regions for the years 2005 and 2006. Thus, 2005 marks the start of the regional statistics, which we have made available at Ordiprax.dk and at www.dkma.dk → Consumption and statistics → Statistics → Annual statistics.

Technological development

How do we take on tomorrow's challenges, improve cooperation with our stakeholders and stay on the leading edge of technology? We enhance and extend digitisation across our organisation and towards pharmacies and the industry.

DAHLIA – a digitisation project

DAHLIA is an acronym for '**D**igitalisering **A**f **H**ele **L**ægemiddelstyrelsens **I**nterne **A**rbejdsgange', and it refers to the digitisation of internal processes across the Danish Medicines Agency. The so-called DAHLIA programme was set up in response to a specific need to optimise a number of challenges posed by the Agency's systems. The DAHLIA digitisation project aims at equipping the Danish Medicines Agency to meet future challenges and to adapt to and solve the tasks set by the outside world.

Mette Bjørn, Programme Manager of DAHLIA, has worked intensively with the project in 2007.

What advantages will the outside world gain from the DAHLIA programme?
The DAHLIA project serves many others than the Danish Medicines Agency and our employees. It is also designed to make it easier for companies to communicate with us. For example, all relevant written communication will, in the future, take place via an electronic self-service system.

The Danish Medicines Agency thus adheres to common European standards, and the DAHLIA project helps future-proof the Agency's international and global cooperation with authorities, citizens and companies. At the same time, it helps us maintain our strong position in European cooperation on medicines.

How does the DAHLIA project affect the licensing of medicines?
When we license medicines in the future, DAHLIA will have digitised the workflow, implying that cases will be automatically processed, receipts automatically dispatched to applicants and letters of reply prepared almost semi-automatically. In other words, the project will make the licensing process run smoothly, at the same time making the documentation of each case accessible to all relevant employees. In respect of marketing authorisations, the companies themselves will benefit considerably, as they will be able to create and partly process their own cases through a portal setup.

What has the Agency worked with in 2007?
In 2007, we outlined the visions for the DAHLIA project and called for tenders for the project. The form chosen was the competitive dialogue procedure, which – after a pre-qualification process – singled out CSC, IBM and Accenture. These three companies were subsequently invited as potential suppliers for the DAHLIA programme. From August 2007 to March 2008, six dialogue meetings were held with all three tenderers, after which the best solution at the best price was to be found. In spring 2008, we chose IBM as supplier for the DAHLIA programme.

The prescription server in 2007

When a patient picks up prescribed medicine at a pharmacy, the actual prescription is often electronic. When the electronic prescription travels from the doctor to the pharmacy, it passes through the so-called prescription server, which stores all information from the prescription and makes it available to the pharmacy when the patient turns up to collect his or her medicine.

The prescription server also stores all information about prescription-only medicine purchased by means of an ordinary paper prescription form. The information stored on the prescription server can be accessed via the Personal Electronic Medicine Profile, allowing every citizen to see his or her consumption of prescription-only medicine in the past two years.

Fully implemented in 2007, the prescription server offers citizens and health professionals alike many advantages:

- Citizens have easier access to information about their own prescriptions, and they enjoy increased flexibility when picking up their medicine at a pharmacy.
- Doctors and other healthcare staff are provided with a better overview of the medicine prescribed to the individual patient, thereby increasing treatment safety.
- Pharmacies are provided with a better overview of the medicine prescribed, enabling pharmacists to advise customers on a better basis.

Every day, the prescription server plays an important role in medicine dispensing in Denmark, which is why it is both frustrating and sensitive when there are problems with the transfer of prescriptions. Unfortunately, the year 2007 did not go by without incidents. Therefore, the Danish Medicines Agency has continuously taken measures to fine-tune the engine that runs the prescription server – which has also provided increased security.

2007 therefore marks the birth of the prescription server – with successes and shortcomings alike – and we look forward to giving way to new ways of usage.

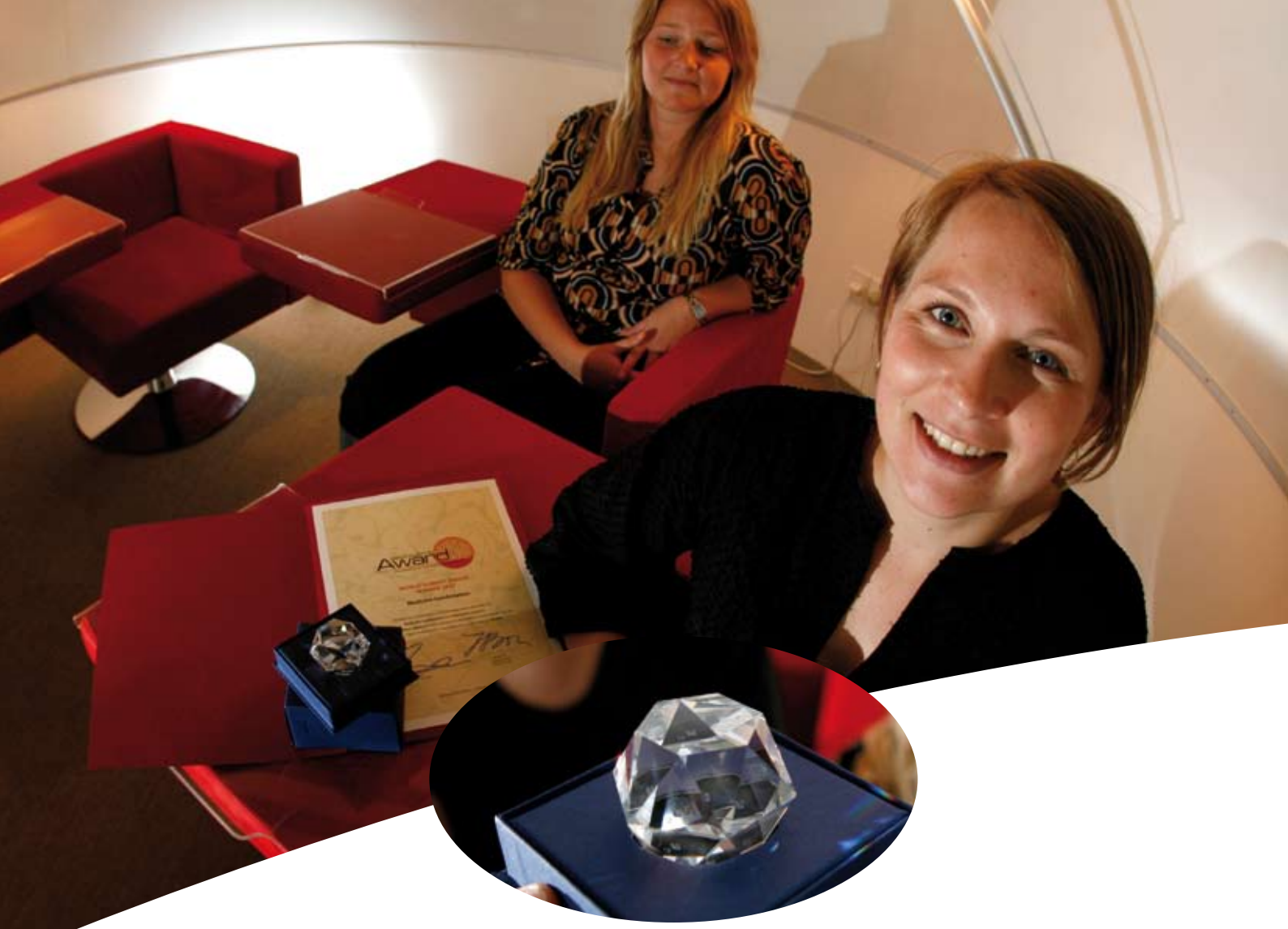
In a year, the prescription server processes some 40 million prescriptions, which corresponds to approx. 110,000 prescriptions every day – or about 203 prescriptions every minute during pharmacy opening hours.

Medicine Prices

In 2007, Medicine Prices (Medicinpriser) was converted from a printed version to an electronic platform (www.erhverv.medicinpriser.dk). Before, the print version was released every fortnight simultaneously with an abridged electronic version.

The problem with the old solution was that the data – due to the production time – were not always correct on the day of publication, e.g. with respect to reimbursement prices and deleted medicinal products.

The new electronic version, which replaces the paper version, ensures that subscribers always have an updated version with current data at their disposal. In addition, the electronic version provides a better overview and offers more information than the paper version did.



Consumer information

How do we promote the proper use of medicines? Among other things, we develop websites that increase openness and spread knowledge about medicine and websites that ease the handling of reimbursement granted to citizens in Denmark.

Medicinkombination.dk

In 2007, Danish consumers were given a unique opportunity to check how different kinds of medicine interact with each other. In cooperation with the Association of Danish Pharmacies, we launched the website Medicinkombination.dk, which simplifies complex information about different types of medicine and how they interact, thereby making it comprehensible to all. The website was very well received by Danish consumers and patient organisations alike, and it received a World Summit Award in November 2007 for being among the world's 40 best e-service solutions in the category e-Health.

Communications Officer Nina Vucina Pedersen and Project Manager Pia Elgaard were the primary driving forces behind the development of the new website.

Why did we make this new website?
The Danish Medicines Agency decided to develop Medicinkombination.dk, recognising that consumers have generally become more interested in keeping themselves updated on their own health and the medicine they take. Today, many people therefore search the internet for information about diseases and medicine. With Medicinkombination.dk, consumers have a new gateway to easily available

medical knowledge written in a language anyone can understand.

What kind of knowledge is available at Medicinkombination.dk?
Most consumers are aware that the possible side effects from a specific type of medicine are written in the package leaflet that comes with the medicine. But when the medicine is taken together with another medicine, herbal remedies, strong vitamins or minerals, the products may interact by either changing the effect or enhancing the side effects of one another to a greater or lesser extent.

One example that has taken many people by surprise is the fact that grapefruit juice and medicine can be a problematic combination. Many Danes drink grapefruit juice for breakfast, but if they drink it while being on buspirone-containing medicine, there is a great risk that the sedative effect of buspirone is enhanced. Obviously, this does not mean that grapefruit juice is harmful, but merely that it may have an unfortunate effect when combined with certain types of medicine.

Who is the website for?
The website is directed at people who take two or more medicines at the same time and people with a general interest in knowing how one type of medicine can interact with another. In brief, the website is for all.

Can all medicine interactions be found at Medicinkombination.dk?
Currently, the website contains approximately 3,000 descriptions of combinations of different medicines. In some cases, a search can result in no hits. The reason for this is that the recommendations on the website solely stem from scientific articles based on trials where medicine has been tested in humans. If consumers are unsure about a certain combination, it is important that they consult their general practitioner or local pharmacy.

Who is responsible for the content of the website?
The information at Medicinkombination.dk is retrieved from the Danish Medicines Agency's Drug Interaction Database, which is directed at doctors and other healthcare professionals. A scientific medical board has the overall medical responsibility for the recommendations and conclusions contained in the Drug Interaction Database, and the Danish Medicines Agency's Consumer Safety Division is in charge of maintaining and updating the database regularly.

Before the recommendations from the Drug Interaction Database are published at Medicinkombination.dk, they are rewritten and translated from medical jargon into general Danish by a communications officer to ensure that they are written in a language that does not require any prior medical knowledge.

How do you reach the conclusions shown at the website?
The answers you get when you search the website are the result of thorough assessments of scientific articles and conclusions from trials of medicine in humans.

Does Medicinkombination.dk replace a GP visit?
No. The website is not supposed to be a substitute for a regular doctor's visit – it is only intended as an additional source of information. It is important that medicine users consult a doctor or a pharmacy if they have any questions about the medicine they take or if they are concerned about the combination of medicines they are taking.

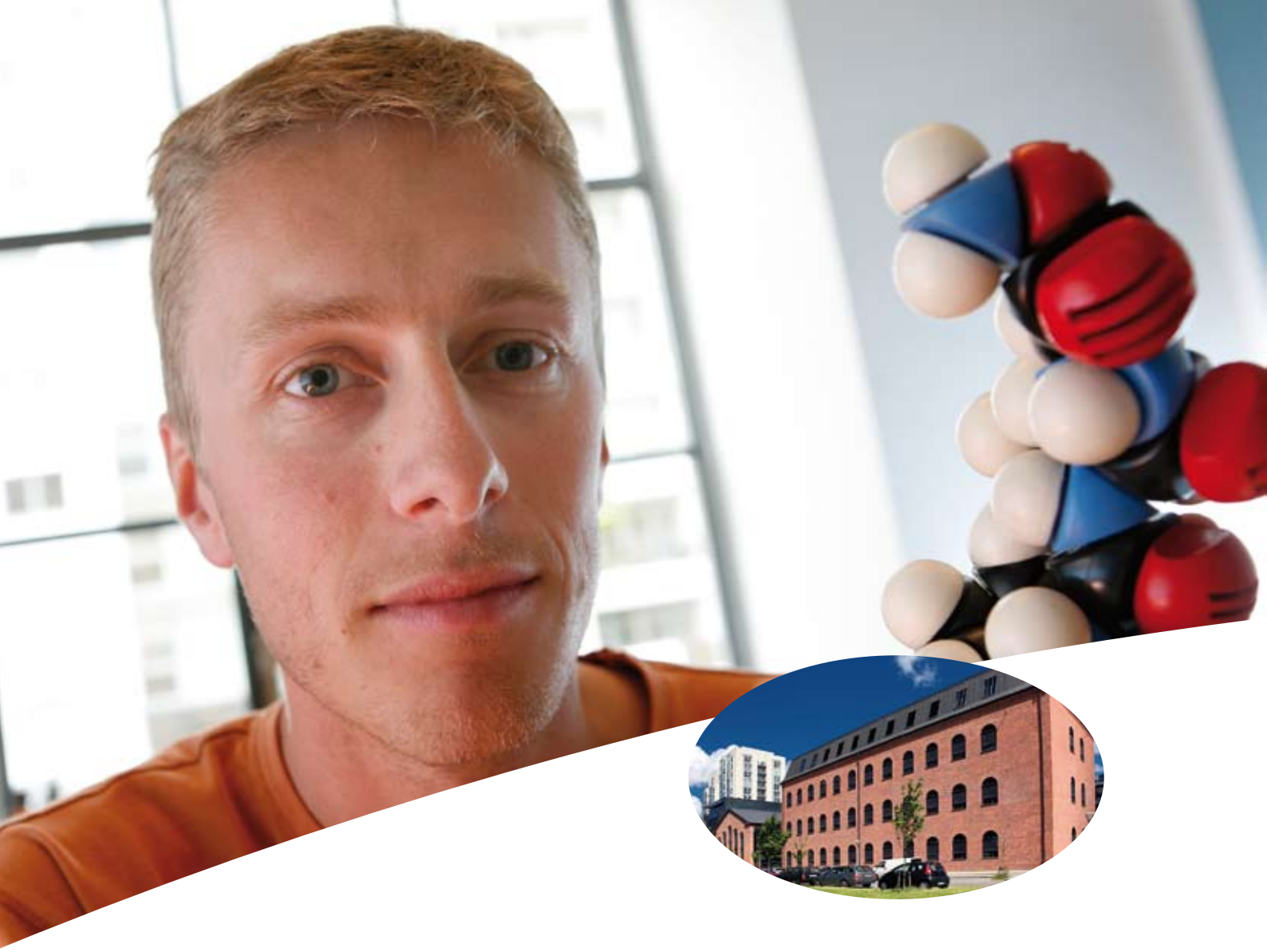
What should I do if I am taking a combination which Medicinkombination.dk tells me is problematic?
You should always contact your doctor or your local pharmacy. There may very well be a good reason why you are on that particular combination.

The Central Reimbursement Register is upgraded

In 2007, the Danish Health Act introduced a new legal provision which obligates the Danish municipalities to electronically report and continuously update information in the Central Reimbursement Register (CTR) concerning health allowances granted pursuant to the Danish social legislation.

In May 2007, we upgraded the CTR to enable pharmacies to see information about individual citizens' municipal health allowances on a par with information about other reimbursement grants. Hereby, we have taken a significant step closer to gathering information about basically all citizens' reimbursement grants in one place.

We expect this initiative to significantly ease the administrative burden on municipalities, pharmacies and medicine users. We also expect that pharmacies will be able to prevent mistakes and minimise the administrative difficulty of handling health allowance cards as well as prevent abuse of withdrawn health allowance cards and remove any doubts about validity of the cards.



International cooperation

How do we influence the international development of medicines and other healthcare products? Among other things, we participate in collaborative research, in EU projects dealing with the safety of medicines, and we also host international conferences.

BioSim

BioSim (Biosimulation – a new tool in drug development) is an EU funded research programme, which the Danish Medicines Agency actively participates in.

The project spans five years and was launched in December 2004. The European Commission has granted 10.7 million euros to the project. Headed by Professor Erik Mosekilde from the Technical University of Denmark, the project brings together research groups from 26 EU universities along with nine small and medium-sized pharmaceutical companies and one large one (Novo Nordisk). The medicines agencies from Denmark, Spain, the Netherlands and Sweden also join in the research programme.

Tue Søeborg is a PostDoc, and he works on the BioSim project for the Danish Medicines Agency.

What is biosimulation?
Biosimulation is a kind of computer modelling that can be used to extract more information from the experiments performed when new medicines are developed. The pharmaceutical area of today is characterised by skyrocketing research and development costs, while the number of new medicines is stagnant or even falling. It is often necessary to stop the development of new medicines fairly late in the

process due to too many side effects or inadequate effect, at which time several hundred million Danish kroner may have been invested.

Why are "ordinary" trials no longer sufficient?
One reason is that the many clinical trials involving a large number of patients and test subjects are not utilised optimally. Over the past years, computer modelling has proven extremely useful in extracting not only more but also more reliable information from the experiments conducted. This means that the development of unsuitable medicines can be stopped at a much earlier stage, and that more reliable knowledge about the effect of suitable medicines can be gained. At the same time, it is possible to predict or explain side effects to a greater extent.

Biosimulation will also enable a more widespread use of patients' DNA profiles for predicting whether certain patients will benefit from a given medicine or whether they may expect side effects and should therefore not be treated with that product.

What is your role in the BioSim project?
As part of the Danish Medicines Agency's involvement in the BioSim cooperation, I was employed as a PostDoc Researcher in 2007, partly to work at the Agency, and partly to work and study at other organisations, for example at the Department of Physics at the Technical University of Denmark and at Novo Nordisk.

Is biosimulation only in focus in Europe?
No. In the USA, the **F**ood and **D**rug **A**dministration (FDA) promotes that modelling should be used to a far greater extent than what is the case today. And the FDA even offers to evaluate whether it would be expedient to use modelling in the development of any new medicinal product. The FDA does so in cooperation with health research institutes.

We have therefore contacted the FDA and have scheduled a study visit in the USA. The future perspective suggests a closer collaboration between the FDA and the pharmaceutical authorities in the EU on computer modelling as a tool for the assessment of new medicines.

Coordinated endeavours towards greater medicinal product safety

All pharmaceutical companies must regularly draw up reports with the latest knowledge about the safety of their products – the so-called periodic safety update reports (PSURs).

A PSUR for each medicinal product must be submitted at a specific point in time relative to the time when the product was approved in the country concerned. If there are many generics with the same active substance, the national authorities in the EU will therefore receive many PSURs from different companies and according to different time schedules. All of these PSURs have so far been evaluated separately, although the content frequently overlapped a great deal. This has made the assessment of PSURs time-consuming and ineffective.

Enhanced efficiency at EU level
Therefore, the EU authorities have worked to make the PSUR assessments more efficient based on a voluntary division of labour. The aims are that the quality of the assessments should be improved, that the work involved for authorities and companies should be eased and that the safety information for products containing the same active substance should be standardised.

One authority – all PSURs
Now, the companies are encouraged to submit all PSURs with the same active substance in the same time period, i.e. to let the PSUR submission take place synchronously in all countries and for all companies. One authority is then in charge of assessing all PSURs with the same active substance and of communicating with the companies in question. The products have been distributed between the authorities, and the time limits for submitting PSURs have been set for products with an active substance authorised the first time after 1976. This scheme does not, however, apply to centrally authorised products.

After several years of preparatory work, the project was successfully launched in 2007. The project has not been anchored in any legislation yet, but it is expected that the new PSUR procedures will be made statutory in connection with the development of the new pharmacovigilance legislation, which is currently under way.

Topra

In October 2007, Copenhagen hosted a conference for **T**he **O**rganisation for **P**rofessionals in **R**egulatory **A**ffairs – TOPRA. The Danish Medicines Agency co-organised the annual conference, which was TOPRA's most ambitious conference yet. The conference lasted three days.

The main topic of the conference was regulatory challenges up until 2010. Some of the topics discussed were risk management, clinical trials, the new variation regulation, the challenges for the national agencies, harmonisation and the Pharmaceutical Forum.

Among the participants were prominent persons from the different European medicines agencies, the EU Commission, EMEA as well as pharmaceutical companies.

Financial highlights

In 2007, the Danish Medicines Agency achieved a surplus for the year of DKK 20.3m against a forecast deficit of DKK 2.9m. The surplus may primarily be ascribed to a higher inflow of fee-generating cases than expected.

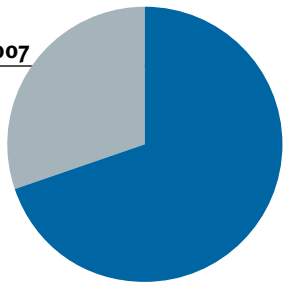
We find the overall results for 2007 satisfactory. We intend to use the surplus for the year to finance development projects and a number of unprocessed cases.

Total income from fees and annual charges, etc. amounted to DKK 251.3m in 2007, up from DKK 211.5m in 2006, corresponding to an increase of DKK 39.8m or 19 per cent.

Finances 2007	DKK
Operating income	280.0m
Operating costs	341.4m
– of which staff costs	186.1m
Result for the year before net funding	-61.4m
Net funding	81.9m

Staff gender distribution 2007

Men	30.1 %
Women	69.9 %



Staff turnover 2007	
New employees	134
Resigned employees	97

The Agency in figures

No. of inspections abroad	30
Total no. of reports (inspections)	1,218
No. of serious adverse drug reaction reports	2,307
No. of periodic safety assessments	462
Total no. of applications for general reimbursement for medicinal products	25
Granted	15
Rejected	10

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