LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

DKMA Update is an electronic newsletter intended for anyone who work with medicines either clinically or in the pharmaceutical industry or the retail industry and people who would like to gain an insight into our work and get the most recent updates on medicines and medical devices. The newsletter contains information about current medicine issues, the most recent safety updates and reimbursements.

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Editorial

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Editorial: Have a nice summer!

By Thomas Senderovitz, Director General at the Danish Medicines Agency

The People's Political Festival in Allinge on Bornholm is a sure sign that summer is around the corner.

This year, we participated in ten debates at the People's Political Festival. I get just as excited every year about how directly I can talk to citizens and stakeholder organisations when I am over there. Both at the big debates in the tents and when individual citizens reach out to me after a debate, wanting to discuss a question face to face without the big audience.

If you look at the themes of this year's Political Festival, you will get a pretty good idea of what is happening in society right now. For instance, 2017 was the year we really started to debate fake news, misinformation and journalism versus science. This debate is far from over. In fact, like the year before quite many wanted to discuss health journalism and the use of anecdotes and cases against strong evidence, and I am happy to see that the media industry is still reflecting on the press' responsibility – for example for the decline in participation rates for the HPV vaccine (which luckily is now turning!).

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The debate dominating this year's Political Festival was no doubt data – data safety, data protection, data ethics, the state's use of the citizens' data, the companies' use of the citizens data and the possibilities and risks of big data. More than 50 debates addressed the use of our data. And with good reason. Denmark has just adopted a new act on the

National Genome Centre, and surely we must have a thorough democratic debate about how our data are to be stored and used and for what purposes.

It is a debate that the Danish Medicines Agency is watching closely. The new National Genome Centre is a good basis for Denmark to take a leading position in the development of precision medicine. Precision medicine is medicine that is developed and tailored to the individual person, so that the efficacy is optimised, and the risk of adverse reactions is reduced. In the longer term, the potential of this new type of treatment is big – but it also challenges the way we have so far imagined authorisation. Very simply, we are facing a new authorisation paradigm whereby medicine in the future is most likely authorised in trials with fewer patients who in return will be monitored for longer periods – and far more intensively – after authorisation. It will be necessary to start using new analytical methods, and Denmark is in a strong position to exploit this opportunity.

There is another reason why we are following the data debate closely: as an authority, we also regulate medical devices, and medical devices are becoming increasingly advanced and data-driven. More and more devices are being linked to the internet, and in the future, we will see several types of medical devices using artificial intelligence. It will make it possible to collect huge amounts of data that can be used to both diagnose and monitor diseases. Obviously, it will also make our society more vulnerable if those data get in the wrong hands. We must also consider how to best ensure that artificial intelligence is used correctly and thus also how to validate these new methods in the best possible way.

I am sure this autumn will hold many new exciting tasks for us. We will still be working on the medicinal cannabis pilot programme, the government's Growth Plan for Life Science, exciting tasks with foreign authorities (including our collaboration with the USA, Japan, Brazil and China), and we will maintain our focus on positioning the Danish Medicines Agency among Europe's best in class.

But first, I would like to wish you all a very happy summer.

Thomas Senderovitz

New rules on private individuals' import of medicines

With the summer holiday just around the corner, the Danish Medicines Agency will almost certainly receive many questions about the rules on brining medicines purchased abroad back to Denmark. On 1 May 2018, new rules on the import of medicines were introduced, among other things, making it clear that medicine purchased abroad may only be imported if it is sold legally in the country it comes from.

The new rules imply the following:

- It is legal to import medicine for your own personal use either when it is posted to you or you take it home in connection with travelling to another EU/EEA country provided the medicine is sold legally in the country where it was bought or dispatched from.
- You are allowed to buy medicine for a maximum of three months' use from countries outside the EU/EEA.
- Medicine containing euphoriant substances must not be sent by post no matter which country it comes from. This means you are not permitted to buy medicine containing euphoriant substances online and have it posted to you.
- You are allowed to bring medicine containing euphoriant substances from another country if the medicine appears on the Danish Medicines Agency's list of euphoriant substances subject to control in Denmark (schedules B, C, D, E, or if the euphoriant substance is listed as no. 1 on schedule A) – however, corresponding to no more than 30 days' personal use, irrespective of the country you are bringing the medicine home from.

Danish Medicines Agency is hosting European effort to reduce animal testing and enhance animal welfare

On 25 and 26 June, veterinary pharmaceutical experts within immunology, toxicology and animal testing from across Europe will meet at the Danish Medicines Agency to discuss how a coordinated European effort can help reduce the number of animal trials and ensure the best possible animal welfare.

The work to reduce the number of animal trials and improve and replace animal testing with other alternatives has been going on for several years under the heading Replacement, Reduction and Refinement (3R) and is coordinated by food authorities, drug regulatory authorities and the industry throughout Europe. Besides finding alternatives to animal testing, the focus has also been on improving the conditions for test animals in general.

A total of 50 experts from Europe will meet in the Danish Medicines Agency to obtain more knowledge about the areas below and more:

- Animal models and cell cultures
- Statistics and changed expectations from the surrounding communities
- The European collaboration on alternatives to animal testing
- The work in the EDQM on ongoing changes to the requirements of the European Pharmacopoeia
- The work in the Danish 3R-Center
- The concrete work with 3R in practice in animal testing and medicinal product testing.

The meeting will be conducted as course sessions. The educational materials used for the course sessions will be made available electronically on the drug regulatory authorities' joint network for training and education to ensure as many as possible will benefit from the teaching.

The meeting is organised by the European Committee for Medicinal Products for Veterinary Use (CVMP).

Danish Medicines Agency key driver in European solution for complex clinical trials

The Danish Medicines Agency is heading a working group formed by drug regulatory authorities in the EU. The working group is to establish the framework for and ensure a high quality and safety of complex clinical trials involving new and advanced medicines. The purpose is to pave the way for the development of new medicines for patients with serious diseases and limited treatment possibilities.

In step with the development of personal medicine, clinical trials of medicines are becoming more complex – from relatively simple randomised trials in which the effect of a new treatment is examined against standard treatment in a larger group of patients to several trials with fewer patients recruited based on e.g. changes in the DNA. These new complex trials offer the basis for developing new medicines that can be targeted at the individual patient with a specific gene type. The development of this type of medicine is especially seen in the cancer area.

The increased complexity can expose the patient to a greater risk, just as the quality of data can be deteriorated, and the trials can become difficult to comprehend. Because of this, the Danish Medicines Agency has taken up a leading role in the preparation of common European guidelines on complex trials in the EU for applicants such as doctors, pharmaceutical companies and researchers. These common guidelines is intended to contribute to harmonisation and optimisation of the procedures for the conduct of complex trials through which to establish a framework for the best solution to bring complex trials in the EU under conditions that will continue to ensure a high patient safety and data quality of the trials.

Great increase in the number of clinical trial applications in Denmark

The Danish Medicines Agency received a total of 324 applications for clinical trials last year. The number of applications thus increased by 13 per cent on 2016 even though the total number of applications in the EU is decreasing. It is both the number of applications for clinical trials sponsored by the pharmaceutical industry and the non-sponsored clinical trials that have increased in Denmark, so shows the Danish Medicines Agency's annual report on clinical trials 2017.

The increase in the number of clinical trial applications may partly be ascribed to the recent years' intense focus on clinical research, which in various ways may have given clinical trials a boost in Denmark.

Among other things, the Danish government established a growth team in June 2016, which was to publish recommendations on how to strengthen the framework conditions for pharmaceutical research in Denmark, and clinical trials played an important role in the recommendations of the growth team. The Minister of Health's Growth Plan for Life Science from spring 2018 also shows strong political support for ensuring good conditions for clinical trials in Denmark.

Read more here in the annual report: Great increase in the number of clinical trials in Denmark.

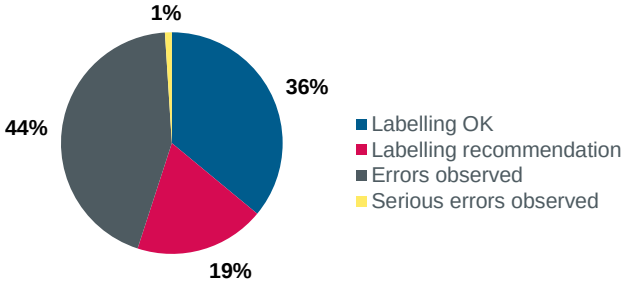
Clinical trials involve testing in human beings and are intended to show how medicine works, what adverse reactions it causes, and how it is metabolised in the body. The medicine tested in these trials can be new medicine, but it can also be known medicine that is already on the market in Denmark.

Controls performed on the labelling of medicine packs

The Danish Medicines Agency regularly checks medicine packs to ensure they are labelled with the information required by law. The Danish Medicines Agency has now started publishing the results of these controls.

According to the executive order on labelling, medicine packs must include information such as name, pharmaceutical form, strength, method of application and storing conditions. In case medicine packs have not been labelled with this information, the Danish Medicines Agency will initiate dialogue with the companies concerned about how to improve the labelling.

The results of the Danish Medicines Agency's labelling control from 2013 to 2017
The Danish Medicines Agency conducted a total of 688 labelling controls in the period 2013 to 2017. 243 of these controls (36%) satisfied the requirements. In 132 of the cases (19%) of the labelling controls, the Danish Medicines Agency offered suggestions to the companies concerned on how to improve the labelling. In 304 of the controls (44%), errors involving the packaging and packaging material were observed, whereas nine controls revealed serious errors or omissions related to labelling.



In those cases where the labelling did not meet the requirements of the executive order on labelling, the company concerned was contacted and requested to remedy the observed deficiencies.

General observations made in the labelling controls
The Danish Medicines Agency generally observed deficiencies in connection with the labelling of:

- **Labelling of single dose blister packs**
  In case of single dose blister packs, each individual blister pack must be labelled. Read about 'Labelling of unit-dose blisters (single dose blister)'.
- **Clear indication of pharmaceutical form**
  The executive order on labelling states that strength and pharmaceutical form must be indicated after the name of the medicine. The pharmaceutical form together with the strength and the name are important to identify the medicine, and it is therefore important that the pharmaceutical form appears clearly in connection with the name and strength.
- **Risk of confusion**
  The labelling must be such that it cannot be confused with other medicine, pharmaceutical forms or strengths. The majority of confusions between medicines involve products of the same product family and same company because of design/layout; products that have been confused with others share many similarities of design, font and choice of colours.

  To prevent medicines from being confused with others, it is a good idea to use colours and typography to highlight important information and to differentiate products. In addition, it is advisable to put information such as name, strength and pharmaceutical form on several sides of the pack.

Renewed focus on IT tool to facilitate the reporting of adverse reactions

In 2014, the Danish Medicines Agency launched a new web service intended to make it easier for healthcare professionals to report adverse reactions of medicines, but there is limited awareness of the web service. The Danish Medicines Agency is therefore putting renewed focus on the service.

Since the web service was made available, three of a total of eight medical practice systems (WinPLC, Ganglion and EG Clinea) have implemented it. This is less than the Danish Medicines Agency had hoped for, and it also seems that awareness of the solution is generally limited. The Danish Medicines Agency is therefore continuously working to spread and improve knowledge of the web service.

Many doctors and healthcare professionals refrain from reporting adverse reactions (ADRs) to the Danish Medicines Agency because it is time-consuming and laborious and requires the manual entering of a line of details from the patient's medical record into a form placed on the website of the Danish Medicines Agency. The web service offers the possibility of technologically embedding ADR reporting in the local practice systems directly, implying that healthcare professionals do not have to leave their own system to submit an ADR report, and that makes it easier and quicker to report adverse reactions.

Besides giving healthcare professionals the possibility to report directly from, for example, an electronic patient record at a hospital or a medical practice, the web service means that you do not have to enter a number of basic information manually. The web service in fact auto-fills parts of the report by transferring data form a patient record, or other, directly to the report. This could be information about the patient who experienced the adverse reaction, details about the medicine the patient is taking, as well as the doctor's own notes and details, all of which constitute mandatory information in an ADR report.

More information about the web service is available in Danish from the National Service Platform (NSP): Adverse reaction reporting (Danish title: Bivirkningsindberetning (BivWS)).

Doctors, dentists and midwives have a duty to report all serious or unexpected adverse reactions to the Danish Medicines Agency as well as all adverse reactions of new medicines during the first two years of marketing. You only need to have a suspicion that an adverse reaction has occurred to report it.

ADR reports are important and are included in the assessment of the safety of medicines on the market.