LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

DKMA Update
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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

Latest news about medicines safety and medical devices

An insight into the work of the Danish Medicines Agency in 2018

Two projects with focus on companies

Short news

Editorial: The safety of medical devices is strengthened

By: Pierre Quartarolo, Director of Division of Pharmacovigilance & Medical Devices

In recent weeks, Danish national TV, the newspaper Politiken and journalists across the world have put focus on the regulation of medical devices, implants in particular. Media from all over the world, the Guardian, BBC, Süddeutsche Zeitung, the TV channel ABC Australia and many more, brought stories of patients who had been harmed or left worse off after placement of an implant. On social media, the topic has been debated under the hashtag #ImplantFiles.

> But even though several rules are tightened in the field of medical devices, it is important to keep in mind that the CE-mark on a specific medical device does not give you any details about who the product is intended for and to what extent it should be used. Even the most tried-and-tested devices can be used in the wrong way or be the wrong treatment for a specific patient.

In Denmark, it is the Danish Medicines Agency that is responsible for medical devices, and we have therefore followed the world-wide media coverage keenly as well as given interviews to several Danish media. It has been important for us make absolutely clear that medical devices is a term that is used broadly for all products used to diagnose, prevent, alleviate or treat disease, disability or injury. There are more than 500,000 different types of medical devices out there, and they help lots of people every day as it could be anything from wheelchairs, thermometers and glasses to pacemakers, mobile phone apps and state-of-the-art surgical equipment. When medical devices are used in the right way, they are generally safe, and injuries caused by defective devices are fortunately rare, but if an accident does happen, it can be a very serious matter.

That said, it is no secret that both politicians and the drug regulatory authorities in the EU have worked determinedly in recent years to conclude a new common European medical devices regulation. There is broad consensus that the development within medical devices

has evolved rapidly over the past years, which has made it necessary to bring legislation in line with the challenges facing us now and in the coming years.

The new EU regulation on medical devices generally enters into force on 26 May 2020 – and there is no doubt that it will greatly improve patient safety.

Stricter documentation requirements

The new regulation introduces stricter requirements in regard to the manufacturers' clinical evaluation, including stricter requirements for the documentation of equivalence. Equivalence means that a manufacturer may refer to the results of published studies, surveys and clinical experience of corresponding devices to document the safety and performance of a device.

In practice, if a manufacturer was to produce a hip prosthesis that has been lawfully marketed according to the rules of the directive and which has the same purpose, design, materials and function as another hip prosthesis that has been subject to clinical investigation, then the manufacturer is not required to submit results of new clinical investigations if the existing data represent sufficient documentation. Thus, the manufacturer can build on the clinical data that are already available.

It is a principle that we know from the pharmaceutical area. Completely newly developed medicines must be tested in a long and thorough process – first in laboratories, later in animal trials and finally in human trial subjects, before they are allowed on the market. In the years after, companies that manufacture "copies" of that medicine, also called generic medicines, may to some extent refer to the trials already conducted with the original product when they submit documentation on the efficacy and safety of the new generic medicines.

As for medical devices, it is of course essential that the companies can submit documentation to prove that their product *is in fact* equivalent to another product (the reference product), and that the manufacturer can submit data documenting the safety and performance of the reference product. If the manufacturer fails to do so, then the product, for obvious reasons, cannot be certified on the basis of the principle of equivalence. This is also the case today, but when the EU regulation enters into force, the regulation will specify more clearly the requirements to be fulfilled if the manufacturer intends to apply the principle of equivalence.

The new regulation thus contains requirements for the technical, biological and clinical specifications in regard to being able to document equivalence and more detailed requirements for the overall clinical evaluation. It is a requirement that the characteristics (technical, biological and clinical) applied to document equivalence are similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device.

If, for example, it is a new type of hip prosthesis and the clinical data are insufficient, it is required that clinical investigations be conducted to document that the device fulfils the safety and performance requirements.

Requirements are tightened for notified bodies

Another improvement area of the new medical devices EU regulation is the tightening of the requirements imposed on notified bodies. Notified bodies are usually private companies that have been designated by the authorities to review the documentation for medical devices. The regulation imposes stricter requirements for the designation of notified bodies, including stricter requirements for qualifications, procedures and decisions on the issuance of certificates to manufacturers, and stricter requirements for the authorities' surveillance of notified bodies. Notified bodies intending to carry out tasks under the medical devices regulation must be designated according to the rules of the regulation. For this reason, the rules on the designation of notified bodies entered into force as early as 26 November 2017.

The authorities in the EU are presently working to finish the review of applications for designation of notified bodies. The Danish Medicines Agency has provided experts to participate in the common European assessment team which is to help the member state authorities assess if applicants fulfil the requirements of the regulation.

Manufacturers of medical devices in medium- and high-risk classes must perform an assessment of conformity with the involvement of a notified body. The notified body issues a certificate if the manufacturer and the device fulfil the requirements of the legislation. Hereafter, the manufacturer can affix the CE marking to its device, and it can be marketed throughout the EU/EEA.

An assessment procedure will also be introduced whereby an expert panel appointed by the European Commission can provide a scientific opinion on a notified body's assessment of the clinical evaluation that has been conducted by the manufacturer. This is relevant for implantable devices in class III or class IIb active devices that are intended to administer a medicinal product. The assessment procedure takes place before the notified body can decide to issue a certificate, and the purpose of the expert panels is to ensure the provision of a high and uniform level of performance by notified bodies.

Post-market surveillance

The new regulation also contains stricter requirements for the surveillance of the safety of medical devices after marketing. For example, the manufacturers of medium- and high-risk devices must prepare periodic safety update reports for use by the notified bodies and the authorities in their regular assessment of the products' safety. A new requirement is introduced, whereby manufacturers must now report trends if they become aware of statistically significant increases in the frequency of incidents, that are not serious, that could have a significant impact on the benefit-risk ratio.

The European Commission is also in the process of establishing a new common European database on medical devices. The database will include reports on serious incidents, reports on trends, field safety corrective actions, field safety notices and periodic safety updates. The Commission must, in collaboration with the member states, put in place systems and processes to actively monitor the data held in the database. Accordingly, the database is to be used actively in the surveillance of the safety of medical devices.

Along with the above-mentioned tightening of rules at EU level, we have also launched initiatives in Denmark that will improve patient safety in the field of medical devices. Most importantly, we have established a national implant register, which, moving forward will

give us a much better overview of the implants used in Denmark and of the individuals who have them implanted. We are also working to improve the registers of the types of medical devices on the market and of the incident reports we receive, and we are enhancing the reporting system to make it more user friendly and easier to submit reports.

But even though several rules are tightened in the field of medical devices, it is important to keep in mind that the CE-mark on a specific medical device does not give you any details about who the product is intended for and to what extent it should be used. Even the most tried-and-tested devices can be used in the wrong way or be the wrong treatment for a specific patient. Doctors need to consider all the relevant treatment options available for the specific conditions they are treating. The availability of implants does not necessarily make it the right treatment for everyone. There are lots of ways to treat different diseases, e.g. with medicine, surgery, implants or changes in lifestyle, and we maintain that the treatment of human beings should rest on an individual medical evaluation adjusted to the individual patient's situation.

The Danish Medicines Agency takes pride in contributing to the availability of a large selection of effective products with acceptable risk profiles, allowing doctors to choose between a number of treatment alternatives, be it medicines or medical devices. No treatment or product is completely risk free, so it is absolutely essential that doctors can access reliable adequate information about the efficacy and risks of the products, enabling them to make informed choices and plan the best possible treatment in partnership with the patient.

Further restrictions on the use of valproate

The use of valproate for treatment of epilepsy, migraine and bipolar disorder is further restricted for women of childbearing potential. The restrictions follow from a review showing that earlier restrictions on its use were insufficient.

In 2014, the warnings and restrictions on the use of valproate in women and girls were tightened to minimise the risk of congenital malformations and development disorders in children exposed to valproate in the womb.

The European Pharmacovigilance Risk Assessment Committee (PRAC) has now evaluated the effect of these restrictions. It concluded that the restrictions had not been sufficiently effective to raise awareness of the risks and reduce the use of valproate during pregnancy according to the specified precautions.

PRAC has therefore introduced new precautions.

The new restrictions include, for example, the placement on the medicine pack of a visual warning against use during pregnancy and that an efficient pregnancy prevention programme must be in place.

In November 2018, a letter was sent out to relevant healthcare professionals with important safety information and educational material, emphasising the following:

- Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.
- Foetuses that are exposed to valproate are at high risk of serious development disorders in up to 30-40% of cases as well as congenital malformations in about 10% of cases.

A number of contraindications in women of childbearing potential and during pregnancy have also been implemented:

Treatment of epilepsy

- Valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.

Treatment of bipolar disorder

- Valproate is contraindicated in pregnancy
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled

Further, the treating specialist should at least annually review whether valproate is the most suitable treatment. The treating specialist should also ensure that the women receiving treatment have understood and acknowledged the risks of congenital

malformations and neurodevelopmental disorders in the event of pregnancy. Women receiving treatment must annually acknowledge that they have received information about the above in an annual risk acknowledgement form. If a woman is planning to become pregnant or becomes pregnant while using valproate, she should consult her doctor.

Pharmacy staff dispensing valproate must make sure to provide the patient with a patient card and must remind the patient about the precautions for use and the need for highly effective contraception.

The letter sent out to doctors can be found here: Valproate: New restrictions on use of the medicine; prevention programme to be initiated (in Danish only).

Risk of suicide to be reflected in the product information of contraceptive pills

In October, the European Pharmacovigilance Risk Assessment Committee (PRAC) completed its review of two Danish ADR signals involving contraceptive pills. The two signals concerned contraceptive pills and the risk of suicide and contraceptive pills and the risk of breast cancer – both signals were raised on the basis of Danish registry studies.

The review of the two studies concluded that there was insufficient evidence to establish an association between the use of contraceptive pills and the risk of suicide and breast cancer, respectively. Because the risk of depression is a known adverse reaction of contraceptive pills and can be a very serious matter – and thus a risk factor for suicidal behaviour and suicide – the PRAC decided that the risk of suicide should be reflected in the product information for contraceptive pills. In regard to the risk of breast cancer, the pharmaceutical companies that market contraceptive pills were requested to monitor this risk carefully.

Restricted use of antibiotics with quinolones and fluoroquinolones is advised

Potentially disabling and possibly permanent adverse reactions have led to suspension or restrictions of quinolone and fluoroquinolone antibiotics after a hearing in the European Medicines Agency (EMA). Some new studies have also shown an increased risk of aortic aneurysm or dissection after use of quinolone and fluoroquinolone antibiotics given by inhalation, mouth or injection.

The EMA has therefore decided that the marketing authorisations for products containing cinoxacin, flumequine, nalidixic acid and pipemidic acid should be suspended and that the use of the remaining quinolones and fluoroquinolones should be limited.

As a result, the product information for healthcare professionals and information for patients must in future describe the potentially disabling and possibly permanent adverse reactions of quinolones and fluoroquinolones.

More specifically, quinolones and fluoroquinolone should:

- not be used to treat infections that most likely will get better without treatment, e.g. such as throat infections;
- not be used to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
- not be used for preventing traveller's diarrhoea or recurring lower urinary tract infections (inflammation of the bladder);
- not be used to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

Patients who have previously had adverse reactions after treatment with quinolones and fluoroquinolones should as far as possible not be treated with quinolones and fluoroquinolones. Particular caution is advised in the treatment of elderly patients with kidney disease or patients who have had an organ transplantation because these patients are at a higher risk of serious injury. Concomitant treatment with a corticosteroid and a quinolone/fluoroquinolone should be avoided due to the increased risk of adverse reactions.

Stricter dose warning on the package of the arthritis and psoriasis medicine methotrexate

A special warning will now be placed on the packages of the arthritis and psoriasis medicine methotrexate to ensure correct dosing. The change is prompted by the reporting of several cases of overdose.

A red warning box will now be placed on the methotrexate packages to emphasise that the medicine must only be taken once a week in the treatment of psoriasis and arthritis.

Campaign targeting nursing staff

In the beginning of December, the Danish Patient Safety Authority and the Association of Danish Pharmacies launched a campaign targeting the nursing care sector to prevent dosing errors with methotrexate. The campaign material consists of a warning card on the risk of overdosage and posters to be placed in the medicine rooms at nursing homes. When a pharmacy receives an order for methotrexate for handling by staff in the nursing care sector, it can place the warning card in the bag with the medicine to ensure the nursing staff take extra care to give the correct dose.

New biosimilar medicines for Humira

On 1 November this year, three new biosimilar medicines containing adalimumab became available in Denmark. The three new biosimilar medicines are authorised for the treatment of e.g. psoriasis, different rheumatic disorders and inflammatory intestinal conditions (ulcerative colitis, Crohn's disease), just like Humira, which is the biological reference product of the three biosimilar medicines.

Remember to report all suspected adverse reactions
Ever since the first biosimilar medicines were marketed in Denmark in 2015, the Danish Medicines Agency has paid attention to biological medicines and biosimilars to ensure a targeted and product specific surveillance of these medicines and ultimately a safe and secure treatment of patients.

To support these efforts, doctors are subject to stricter reporting requirements for two years for biological medicines when biosimilar versions of existing biological reference products become available. This means that all doctors must submit an ADR report to the Danish Medicines Agency if they suspect an adverse reaction of either of the medicines has occurred.

Patients and relatives can also report suspected adverse reactions to the Danish Medicines Agency. The more ADR reports we receive the better, because it improves our total basis for assessing the safety of the medicines.

The Danish Medicines Agency keeps a record of selected biological medicines whose name and batch number must be indicated, if possible, when ADR reports are submitted to the agency. The Danish Medicines Agency pays special attention to reactions potentially occurring when a switch is made between a biological medicine and a biosimilar.

Adverse reactions can be reported to the Danish Medicines Agency at www.meldenbivirkning.dk (report a side effect).

Same efficacy and effect
A biosimilar medicinal product is a new version of an existing biological medicinal product (the reference product) which must have been authorised in the EU for at least 10 years. A biosimilar medicine may have minor molecular differences compared to the original version of the medicinal product, but these differences have no bearing on the medicine's efficacy and safety (adverse reactions). In other words, the biosimilar medicine has the same efficacy and safety as the biological reference product.

In regard to Humira, some of its biosimilar versions could have an injection pen/syringe that is different. The vast majority of patients who receive adalimumab take the medicine at home without assistance. Patients who switch from Humira to a biosimilar version may therefore need to be thoroughly informed and instructed on its use to make them comfortable and to ensure a proper treatment.

Read more about Biological and biosimilar medicinal products on our website.

New growth plan boosted the Danish Medicines Agency's ambition to join Europe's best in class

At the beginning of 2018, the government launched an ambitious Growth Plan for Life Science. The plan contains a total of 34 initiatives within the areas of the Ministry of Health, the Ministry of Foreign Affairs of Denmark, the Ministry of Industry, Business and Financial Affairs and the Ministry of Higher Education and Science.

Several of the initiatives of the growth plan are to be launched in the coming years by the Danish Medicines Agency, some of which include:

- Strengthening of the international collaboration between authorities
- Strengthening of the Danish Medicines Agency's engagement in the HMA network (European network of national medicines agencies)
- Continuation of the Danish Medicines Agency's strengthened involvement in the EMA (European Medicines Agency)
- Initiatives to strengthen the Danish Medicines Agency's efforts in the area of medical devices, among which an analysis of the establishment of notified bodies in Denmark.
- Removal of fees for Phase I clinical trials
- Testing of a new concept for scientific advice from the Danish Medicines Agency given to life science companies in regard to e.g. clinical trials.

Growth plan puts the Danish Medicines Agency on course for Europe's best in class (in Danish only)

Danish Medicines Agency part of inspection agreement between EU and the USA in 2018

In November, the U.S. Food and Drug Administration, FDA, completed its review of the Danish Medicines Agency's company inspections, which means Denmark is now covered by the mutual inspection agreement concluded by the EU and the USA.

The inspection agreement entails that the drug regulatory authorities in the USA and the respective EU countries mutually recognise and rely on each other's inspections of pharmaceutical manufacturers and share information on for example quality issues identified at the companies. The agreement also means that the EU and the USA mutually recognise each other's rules on good manufacturing practice (GMP).

Denmark covered by inspection agreement between the EU and the USA (in Danish only)

Concerted campaign on safe online shopping received with great interest

In autumn, the Danish Medicines Agency and 12 other regulatory authorities joined forces to put focus on safe online shopping. A safe online shopping portal was created (Nethandel #heltsikkert) to offer consumers advice on how to find products that are safe and how to pay safely online.

Our advice is to look for the EU logo whenever you buy medicines online. The EU logo is your assurance that the online shop you are using is selling medicines legally, so you avoid being cheated or getting medicine that does not work as promised or, in the worst-case scenario, is highly dangerous.

Simple advice for safe shopping online (in Danish only)

Impurities found in several batches of blood pressure lowing medicine valsartan

One of the cases that kept us busy in 2018 was the finding of impurities in valsartan that potentially could cause cancer. The fist findings originated from a Chinese factory. Later, batches with the same impurities originating from an Indian company were also made. All sale of the affected medicines was therefore stopped from Danish pharmacies. When the fist findings of impurities were made, about 1500 patients in Denmark were treated with valsartan.

Together with researchers from the Department of Clinical Pharmacology and Pharmacy at the University of Southern Denmark, the Danish Medicines Agency launched a registry study to investigate if the cancer incidence rate is higher among people receiving valsartan. The study concluded that there is presently no indication that the incidence of cancer is higher among the patients who were treated with valsartan. However, the study does not remove concerns about potential long-term consequences resulting from certain specific valsartan products that may have been contaminated. Further studies are required to monitor patients over several years and to investigate more specifically the incidence of the individual cancer forms.

Recall of valsartan blood pressure medicine

A Danish registry study found a small increased risk of two forms of cancer with the use of hydrochlorothiazide

In late October, the European Medicines Agency (EMA) completed a review of studies on the anti-hypertensive hydrochlorothiazide and the risk of two forms of cancer.

The EMA concluded that long-term use of hydrochlorothiazide may increase the risk of the skin cancer types of basal cell carcinoma and squamous cell carcinoma. There have been no observations of malignant melanoma.

Following the decision made by the EMA, the increased risk will be reflected in all package leaflets (the product information) of hydrochlorothiazide-containing medicines.

Small increased risk of certain types of skin cancer associated with the use of hydrochlorothiazide

High turnout for theme events at the Danish Medicines Agency

Debating event on how to communicate research results
On 1 October, the Danish Medicines Agency and the Danish Society for Pharmacoepidemiology invited researchers, doctors and communication managers from research institutions across Denmark to a debate on the most responsible way to communicate new health research results to the media.

The debate will culminate in a white paper for researchers to be published in 2019.

Theme event on big data
Patients and citizens will in future have quicker access to new medicines, and the drug regulatory authorities will be forced to rethink the way medicines are authorised. These are some of the consequences expected from the development of big data in the pharmaceutical area. The Danish Medicines Agency therefore invited a number of stakeholders to a theme event on big data and medicine on 20 November this year.

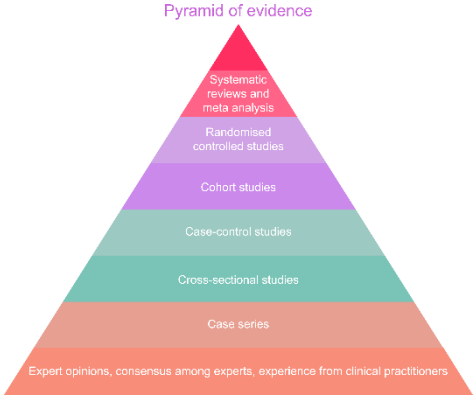
Among the speakers were representatives from the U.S. Food and Drug (FDA), Administration, the European Medicines Agency (EMA) and Novo Nordisk. It was a full house at the Danish Medicines Agency's premises, and we were unable to seat everyone.

Both meetings were streamed live on our Danish Facebook profile and our English twitter profile and were followed keenly.

Expert forum on medicine and evidence
In March, the Danish Medicines Agency together with the Danish Health Authority and videnskab.dk (science news) invited journalists and communicators to an event on evidence.

The event's main subject was the question of how many investigations it takes for the authorities to decide that the evidence is sufficiently strong to support a treatment or an adverse reaction.

At the expert forum, the Danish Medicines Agency and the Danish Health Authority wanted to put focus on the criteria based on which the authorities' work to ensure the availability of effective and safe medicines and treatments. The attending audience was presented with the evidence pyramid.



Debate on research dissemination at the Danish Medicines Agency

Theme event on big data and medicine

Expert forum on medicine and evidence (in Danish only)

Tonnes seized in global operation against illegal online sale of medicines

Illegal sale of medicine is a growing problem often taking place online and across national frontiers. To tackle the problem, several countries around the world join forces every year in a comprehensive operation against illegal online trading and import of medicines. The operation is called Operation Pangea, and this year, it took place for the eleventh time.

Operation Pangea 2018 involved 116 countries. Worldwide, the operation resulted in 859 arrests and further investigations of individual persons, and more than 30 organised crime groups or networks were investigated and dissolved. More than 542,300 parcels with illegal medicines were seized, combined representing more than 10 million units of potentially life-threatening medicines. More than 3,670 websites were closed down or had their payment functions removed, and 1,300 websites are still being investigated.

Tonnes seized in global operation against illegal medicines (in Danish only)

Danish Medicines Agency strengthened its international collaboration

Visit from China
In September, the Danish Medicines Agency welcomed a delegation from China to discuss clinical trials, drug monitoring and the possibility of staff exchanges between the Danish Medicines Agency and its Chinese counterpart with a view to skills development within various pharmaceutical areas.

Exchange of data with Japan
In May, the Danish Medicines Agency welcomed leading representatives from the Japanese Pharmaceuticals and Medical Devices Agency and the Japanese Ministry of Health, Labour and Welfare. The intention of the meeting was to enter into a collaboration agreement and exchange knowledge and experience in relation to regulatory procedures in the pharmaceutical area. The primary focus was how new technologies for the collection and analysis of health-related data can enhance the possibilities of developing and designing new innovative medicines while strengthening the monitoring of the efficacy and safety of medicines. The Japanese authorities have extensive knowledge of and experience in collecting and using patient data that may document how medicines work when used to treat patients in everyday clinical practice.

Drug agency from China visits Denmark

Danish-Japanese collaboration on better use of health data

Danish Medicines Agency represented at World Economic Forum

The development of future medicines imposes a number of requirements on the authorities, which become more and more dependent on new tools and new competences to categorise, read and analyse the new data for the benefit of people.

The Danish Medicines Agency participated at this year's World Economic Forum in China, among other things with input to the general principles of the new global Precision Medicine Global Council (PMGC). Rather than being developed as standard medicine for a larger population, precision medicine is to a much higher degree developed for smaller, defined groups of patients and, by comparison, takes into account the individual's lifestyle, genes, genetics variations as well as the intake of other medication to a much higher degree.

Medicines of the future in focus at World Economic Forum

Top marks for the Danish Medicines Agency in European survey

In the spring of 2018, the Danish Medicines Agency was evaluated in the joint survey European Benchmarking of European Medicines Agencies (BEMA), and in September, we received the score of 4.5 out of a possible 5.

Since the re-establishment of the Danish Medicines Agency in October 2015, the agency has been supported by a political goal of positioning the agency among Europe's best in class. Our BEMA performance shows that we are well on the way to reach our goal.

Danish Medicines Agency launched a new concept for national scientific advice

On 31 August 2018, the Danish Medicines Agency launched a new concept for national scientific advice where companies, hospitals and others can request advice on clinical investigation and marketing authorisations for human and veterinary medicines.

The new concept constitutes one of the elements of the Danish government's Growth Plan for Life Science, and the aim is to offer applicants more prioritised and competent national scientific advice in order to ensure high-quality applications to the authorities, a fast process for pharmaceutical development, and ultimately, medicines that reach patients faster.

To start with, the Danish Medicines Agency scientific advice will focus on applications for marketing authorisations and applications for clinical trials within both the human and veterinary fields. The Danish Medicines Agency will offer advice aimed at exploiting already achieved investigational results and at future development programmes.

Over time, the concept will be expanded to cover other areas such as medical devices, precision medicines and guidance on good manufacturing practice (GMP).

Fee for scientific advice
The new concept will be financed through cost-oriented payment by the company/applicant. Thus, payment will vary according to the nature and extent of advice requested by the company/applicant.

Read more about fees and National Scientific Advice.

Danish Medicines Agency launches new concept for National Scientific Advice

Work began on a new register of medicinal products to benefit patient safety

The Danish Medicines Agency began building a new national register of medicinal products which holds data on the medicine's active substances, packs and companies, etc. These data are important for the work with surveillance, control and patient safety.

The register of medicinal products is built on a standard platform on the basis of the European pharmaceutical terminology to facilitate efficient communication with other similar systems in the EU. The new system will ensure a faster, safer and simpler exchange of data on new medicines between the EU countries, which will benefit pharmacovigilance for example.

The system will modernise the present register of medicinal products, which will be phased out once the new system is operational. We expect this to take place by the end of 2019.

A new register of medicinal products for the benefit of patient safety is being constructed (in Danish only)

Major efforts for safer prescription of blood thinning medicines

In 2018, a collaboration between pharmaceutical companies, pharmacies and authorities succeeded in reducing the number of adverse events with medicines – including dosing errors involving blood thinning agents.

In collaboration with two pharmaceutical companies, the Danish Patient Safety Authority and the Danish Medicines Agency completed in 2018 a comprehensive project to change the determination of strength of blood thinning agents, which are typically used by hospitals. The change has implied that a previously frequent cause of dosing errors has been eliminated.

Later in the year, an analysis of adverse events reported to the Danish Patient Safety Database of the Danish Patient Safety Authority showed that there had been a fall in the number of reports of adverse events involving prescription mix-ups. Although data from the Danish Patient Safety Database cannot be used specifically to measure the number of mistakes being made, the recorded fall in the number of errors is significant enough to clearly indicate that the changed labelling has had an effect.

Safer prescription of blood thinning agents

Better conditions for clinical trials in Denmark

In 2018, the conditions for clinical trials improved in Denmark. This was the result of the Budget for 2018, when the government decided to remove the Danish Medicines Agency's fees for non-commercial (research-initiated) clinical trials of medicines, implying that non-commercial sponsors of clinical trials of medicines will not have to pay a fee for authorisation to start a clinical trial, make substantial amendments or to pay annual fees.

As part of the Growth Plan for Life Science and to strengthen research in general, commercial sponsors were exempted from all fees for phase I trials of medicines and are therefore not required to pay a fee for authorisation to start a trial or to pay annual fees.

Better conditions for clinical trials in Denmark

European top post for Thomas Senderovitz

In March, Director General of the Danish Medicines Agency, Thomas Senderovitz, was elected Chairperson of the HMA Management Group. HMA is the network of the heads of the national drug regulatory authorities in Europe.

The HMA together with the European Medicines Agency (EMA) and the European Commission represent the European medicines regulatory network. The HMA develops a common strategy, and the purposes include coordination, knowledge sharing and worksharing on regulatory activities among the national drug regulatory authorities at the European level.

The work of the HMA has great benefits for the Danish Medicines Agency, both when it comes to improving patient safety and when it comes to influencing the EU strategy in the pharmaceutical area, which helps to strengthen Danish life science.

European top post for Thomas Senderovitz

Medicinal cannabis pilot programme entered into force

On 1 January 2018, the medicinal cannabis pilot programme entered into force. The programme allows doctors to prescribe a new type of cannabis product, which was not legal in Denmark before.

The purpose of the pilot programme is to offer patients a lawful way of testing treatment with medicinal cannabis if they have experienced no benefits from authorised medicines.

During the course of 2018, more special funds were allocated to carry out research on the efficacy and safety of medicinal cannabis, which, along with the pilot programme, will provide a better basis to evaluate the use of medicinal cannabis.

Medicinal cannabis pilot programme

Pharmaceutical companies must ensure people have access to package leaflets on www.indlaegsseddel.dk

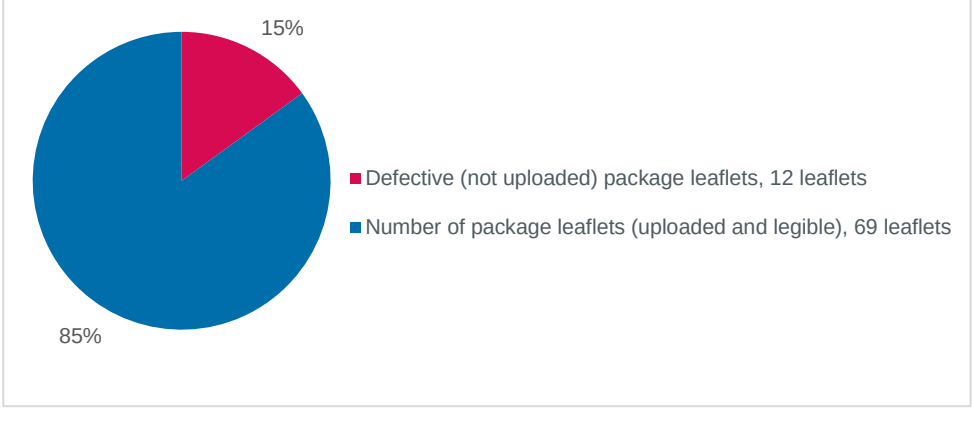
The Danish Medicines Agency regularly monitors the database of package leaflets www.indlaegsseddel.dk on DKMAnet. The purpose is to check if the pharmaceutical companies upload their package leaflets to the portal so medicine users can access them. Our control has shown that several package leaflets are missing.

The Danish Medicines Agency has recently finished a sub-project investigating the pharmaceutical companies' upload of package leaflets to DKMAnet.dk for radiopharmaceuticals.

When a patient is treated with a radiopharmaceutical, it takes place in hospital, and the patient is therefore not given a medicine pack with a package leaflet. For this reason, it is important that patients and relatives can access all package leaflets at www.indlaegsseddel.dk.

The Danish Medicines Agency performed a control of 81 package leaflets on www.indlaegsseddel.dk of radiopharmaceuticals for diagnostic and therapeutic use.

The result showed that 12 of 81 package leaflets (15%) had not been uploaded to the portal.



The Danish Medicines Agency has previously reviewed the entire database www.indlaegsseddel.dk.

It revealed that 10% of all package leaflets were either missing or contained errors.

Requirements for pharmaceutical companies
All pharmaceutical companies who hold a marketing authorisation for a medicine must ensure that the package leaflets currently in force are uploaded to DKMAnet and available at www.indlaegsseddel.dk.

Companies are required to submit the current package leaflet to the Danish Medicines Agency. The package leaflet must

- be text based
- be easy to read on screen and on printed A4 paper
- be readable by common screen reading tools, cf. section 59(1) and (2) of the Danish Medicines Act
- be uploaded to the Danish Medicines Agency's portal DKMAnet – Package Leaflets.

It is the marketing authorisation holder's responsibility to ensure the package leaflet has been uploaded at the time of marketing (cf. section 1 of Executive order no. 426 of 6 May 2011 on submission of package leaflets to the Danish Medicines Agency).

The Danish Medicines Agency regularly performs spotchecks on www.indlaegsseddel.dk of selected groups of medicines.

Please also see: Uploading package leaflets to the Danish Medicines Agency's portal DKMAnet – Package Leaflets.

Major European review of the subdivision of tablets

A common European review of tablet scoring shows that not all tablets live up to the European drug standards on the subdivision of tablets. In some cases, the responsible pharmaceutical companies were cautioned.

The Danish Medicines Agency took part in a common European project aimed at investigating the subdivision of tablets. 27 regulatory laboratories from 22 European countries participated in the project, which examined a total of 675 tablets. All tablets that were examined had either a score line or a cross-score break line intended to divide the tablets into equal halves or equal quarters.

European rules on the subdivision of tablets
When tablets have a score line or a cross-score break line, it does not necessarily mean that the tablets can be divided into equal parts. A score line may serve two purposes:

1. to divide the tablet into equal parts
2. to divide the tablet to help the ingestion of the tablet.

It is described in the medicine's product information – the summary of product characteristics for healthcare professionals and usually also the package leaflet – if the score line can be used to divide the tablet into equal parts, and likewise if the tablet must not be divided.

Special requirements apply to tablets which are intended to be divided into two/more equal doses. These requirements appear from the European drug standards (European Pharmacopoeia). But as the common European review showed, not all tablets meet these standards.

Of the 675 samples included in the European project, 17% had a score line which failed to divide the tablet into equal halves as otherwise described in the product information. 107 samples were subjected to a subdivision test to see if the tablets could be divided into quarters, and 30% of them failed to meet the requirements for subdivision.

In the project, the Danish Medicines Agency in Denmark subjected 36 different tablets to a subdivision test, two of which failed to meet the requirement for subdivision. The Danish Medicines Agency has therefore contacted the companies marketing the tested products, one of the results being that the score line will be improved for one of the products. In addition, the text in the package leaflet for four products was corrected or elaborated to clarify how to divide the tablets.

Tablet breaking

It is important to check the package leaflet to see if the tablet can be divided, and if so to see if it is described how to divide the tablet.

The technique used to subdivide a tablet may decide if a tablet is divided into equal parts and thus if the receiver gets the right dose.

If a tablet which should not be divided is split into smaller parts, the active substance might be released too early and might potentially lose its effect. For prolonged-release tablets, which are absorbed more slowly in the body, the effect could be that the entire content is released at once in a dose that is too high.

New front page for our website

In 2019, the website of the Danish Medicines Agency will be improved. The planned improvements include entry points based on target groups, more themes on the front page and direct access to our Facebook and Twitter profiles. The aims are to ensure better information and increased user-friendliness as well as to give our users the possibility of following our social media posts without having a profile.

Take at sneak peek at the theme-based front page with our social media profiles. See: www.dkma.dk

Brexit page on the website of the Danish Medicines Agency

We have created a Brexit page on our website. We will use it to make sure we keep a strong focus on ensuring that the common European drug regulatory network and the pharmaceutical companies in the EU achieve a successful Brexit transition in order to ensure the continued supply of medicines for the benefit of patients. We participate actively in the Brexit-related considerations and preparations that have been going on in the pharmaceutical area for quite some time.

Read more on Brexit page.

Major international focus on the reporting of suspected adverse reactions

For the third time, the Danish Medicines Agency together with a number of other countries put focus on the reporting of suspected adverse reactions of medicines. This year, particular attention was given to families with children and expecting women on the occasion of the UN's Universal Children's day.

From 19 to 23 November, we raised awareness with three animated movies which 32 drug regulatory authorities around the world shared on their social media platforms, the Danish Medicines Agency included.

You can watch the films here:

Help to make medicine safer (in Danish only)

Are you pregnant or breastfeeding? (in Danish only)

Together we can make medicine safer (in Danish only)

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Thank you for your dedication in 2018!

We look forward to resuming our achievements in 2019

Fruitful collaboration and close dialogue between us and our surroundings are essential for us to fulfil our tasks intelligently and efficiently, and to do our very best every day to ensure safety for humans and animals alike.

2018 offered us many exiting challenges. And even though we are well on our way to achieving our vision of becoming Europe's best in class, we still have many important tasks ahead of us. Among them are the development of a stronger market surveillance and stronger medical devices regulations. And the fight to ensure the Danish population has access to objective and factual evidence. These are tasks we can only fulfil when we pull together.

Fortunately, we are on firm ground and have achieved many results in 2018: We scored 4.5 out of a possible 5 at the latest BEMA survey (benchmarking of European medicines agencies), and the FDA has acknowledged our excellence of inspections so that we are now covered by the inspection agreement between the EU and the USA. We also have fruitful bilateral collaborations with our sister authorities in for example China, Japan and Brazil – collaborations that have been strengthened further in 2018.

At home, we have launched the medicinal cannabis pilot programme, and we have contributed to the government's Growth Plan for Life Science and delivered on several of the plan's initiatives. We have achieved all of this in interaction with our surroundings – for the benefit of patient safety and growth in Denmark.

In the spirit of collaboration, I am wishing you and your family a truly merry Christmas and a prosperous New Year!

Yours sincerely

Thomas Senderovitz, Director General