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: Evidence on the agenda

By Thomas Senderovitz, Director General at the Danish Medicines Agency

Under the headline "Do you know your evidence?", the Danish Medicines Agency, DKMA, together with the Danish Health Authority and Videnskab.dk (science news) invited journalists and communicators to an event in the beginning of March.

Journalism and science do not always see eye to eye. The personal story is important in journalism, and a moving case story can easily fill an entire newspaper article. But if we look at things from a scientific angle, isolated stories do not carry much weight. Isolated stories are placed at the very bottom of the hierarchy of evidence, and they are often referred to as "anecdotes" in scientific circles.

It seems that the gap between journalism and science has grown wider in recent years. Feelings on the one hand are answered by sometimes hard-hitting facts on the other. In this context, communication from the authorities might seem arrogant and stand-offish. And there is no doubt that we as an authority can learn to communicate better in emotional debates. But it can be very difficult to communicate that we fully acknowledge a person's experiences while insisting that we cannot conclude anything or take any measures on the sole basis of individual reports. The challenge is the same whether the case stories concern positive or negative effects of a certain medicine. As an authority, we need to take the scientific high ground in order that both the authorisation and the monitoring of medicines can rest on an informed basis for the sake of society and our citizens.

Thomas Senderovitz

> Health is everywhere in the media these years – and I thoroughly believe that it is positive that patients and citizens are actively involved in their own health, disease prevention and treatment, and that they look for information. But it makes it all the more important that journalists are equipped to assess the knowledge they present to their readers.

Editorial

Health is everywhere in the media these years – and I thoroughly believe that it is positive that patients and citizens are actively involved in their own health, disease prevention and treatment, and that they look for information. But it makes it all the more important that journalists are equipped to assess the knowledge they present to their readers.

From our viewpoint, the evidence-based work methods cannot be disputed. This is how we work with the authorisation of medicines – and these are the methods we must continue to develop and refine.

But perhaps we have neglected the opportunity to tell our surroundings how scientific evidence comes into existence. Remarkably many journalists express openly that they do not feel well prepared to assess validity when researchers approach them with new studies and seek publicity.

We do not want to the gap between science and journalism to grow wider. Instead we want to contribute constructively by showing how to raise the bar in Danish health journalism. We therefore took a somewhat untraditional approach by inviting the media to join a presentation of the evidence hierarchy (or evidence pyramid) in the beginning of this month.

There was a time when we would never have thought it possible that the media would show up on a Wednesday afternoon at the agency for a three-hour meeting with no news whatsoever on the agenda. Fact is that 55 journalists and communicators turned up! They were genuinely interested in the topic – and I will admit that I also learn something every time I discuss news, significance and relevance with journalists.

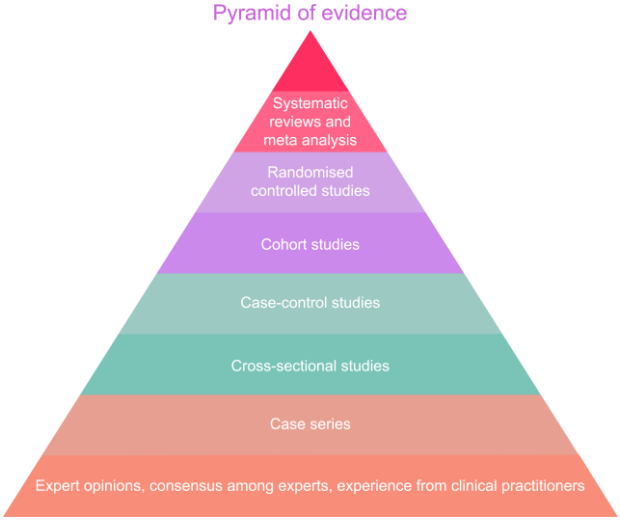
From the evidence meeting at the Danish Medicines Agency on 7 March 2018.

> An isolated result is often just a small piece of a much larger puzzle. It will usually take numerous studies before the authorities will change the summaries of product characteristics and recommendations. The researchers' press releases should reflect this as well.

There was plenty of lively debate on the concept of evidence highlighted by examples from many months of media coverage of various "ground-breaking" studies on adverse reactions from vaccines, contraceptive pills, hydrochlorothiazide, Ibuprofen and much more. We can give endless examples because the DKMA is frequently asked to respond to various new research results – often provided by Danish researchers by the way.

Editorial

The fact that researchers go to the media to talk about their research is fundamentally good. This is how the Danish people generally gain knowledge about new research. And we should appreciate that we live in a society with freedom of speech and where the authorities are challenged by the researchers. Having said that, journalists should be able to sense how ground-breaking a study really is when they present it to their readers. Is it a collection of case series placed at the bottom of the evidence hierarchy – or is it a major double-blinded placebo-controlled study, which offers some of the most valid evidence there is. And is it the only study in the area, or are the study results to be included in already existing knowledge.



We started this year with this evidence event for journalists – and the first ideas to improve communication with researchers are now also on the drawing board. An isolated result is often just a small piece of a much larger puzzle. Usually, it takes numerous studies before the authorities will change the summaries of product characteristics and recommendations. The researchers' press releases should reflect this as well.

I sense good intentions from the authorities, researchers and the media to do better moving forward. There is a lot of reflection going on in journalist circles, for example about constructive journalism. The universities have created guidelines on press releases about research, and Videnskab.dk (science news) has just launched a new initiative to strengthen expert communication. And we the authorities are also working in many ways to rethink our communication, and we are becoming more and more visible, also on social media.

There is agreement throughout that the citizens should receive information on health matters on an informed basis. And we have planned several initiatives here in 2018.

It can only mean one thing: The communicative outlook is getting brighter.

Thomas Senderovitz

The SmPC for tramadol to be changed

The risk of dependence on tramadol will now be written more clearly in the product information.

In the past couple of years, the media and expert forums have extensively debated pain treatment in general and more specifically the dependence potential of tramadol.

The authorities agree that the consumption of tramadol is very high, and several initiatives have been launched to reduce consumption. At the DKMA, we have changed tramadol's dispensing group to its current A§4, which means that prescriptions for tramadol can be monitored just like other types of opioids.

Several experts have reported in the media that they find that tramadol is more addictive than expressed in the summary of product characteristics (SmPC). For this reason, the DKMA has also focused on the SmPC and has thoroughly reviewed the scientific literature in the area. At present, there are no scientific data to warrant the setting of a different frequency than the one in the SmPC. However, we have introduced stricter reporting of adverse reactions from tramadol for a period of two years, which means doctors now have a duty to report all adverse reactions from tramadol. In this way, we hope we will be able to contribute to the future collection of valid data to provide a more accurate assessment of the dependence potential of tramadol.

The case also gave us good cause to look at whether there are other ways in which we can improve the SmPC of tramadol with respect to the information about dependence.

As a result thereof, we proposed the following changes to the SmPC to the European Medicines Agency (EMA).

1. **A recommendation is inserted to taper the tramadol dose gradually to prevent symptoms of withdrawal.**
   This insertion means that the SmPC of tramadol is brought in line with the recommendations of the other opioids.
2. **The wording of the current SmPC that tramadol has a low dependence potential is removed.**
   This correction can be made because the new guidelines on SmPCs provide that recommendations may not make comparisons to other similar medicines. The current wording thus conflicts with the current guidelines, and we therefore recommend to remove it.
3. **It becomes more clear that dependence and tolerance not only can occur in long-term use.**
   We have assessed that new adverse reaction data warrant this change.

At the monthly meeting in the European Pharmacovigilance Risk Assessment Committee in January 2018 it was finally decided to update the SmPC for tramadol in line with the Danish proposal. The SmPC for tramadol is therefore expected to be updated with the final wording during the course of 2018.

Inspection of the sale of over-the-counter medicines outside pharmacies

The DKMA regularly inspects shops that are authorised to sell over-the-counter (OTC) medicines. It could be supermarkets, convenience stores at filling stations, kiosks, pet shops, etc. The purpose of the inspections is to check if the shops adhere to the applicable rules, checking for example if they have medicines on the shelves, if the use-by date is exceeded, if medicines are stored correctly, and if the shops systematically measure the temperature where medicines are kept.

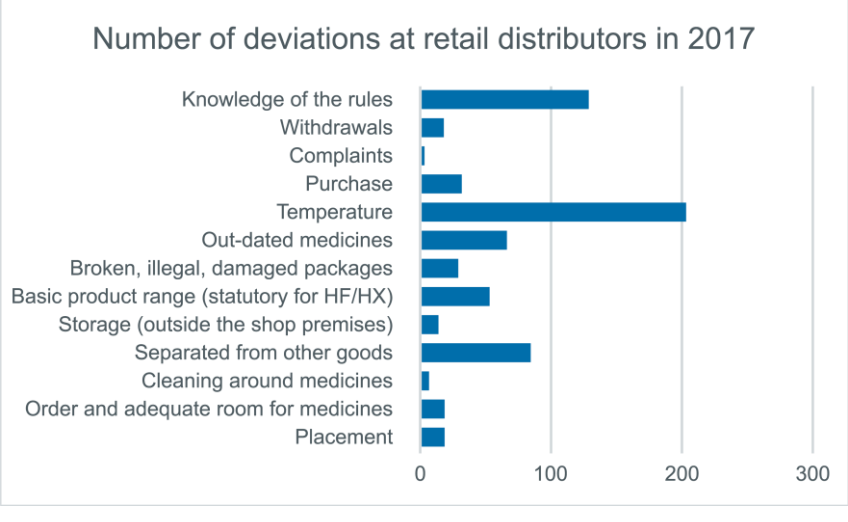
In addition, the DKMA checks websites (online retailers) that sell OTC medicines. Several shops engage in both retail distribution and online sale.

To achieve greater openness and transparency about the inspections, the DKMA published an overview in 2017 for the first time, presenting the results of our inspections for each shop selling OTC medicines. Previously, the inspection results of the individual shops were anonymous and only reported on a yearly basis.

The results of the inspections of the individual shops can be found on the website of the DKMA here: Overview of inspections of retail distributors and online retailers (Excel), in Danish only.

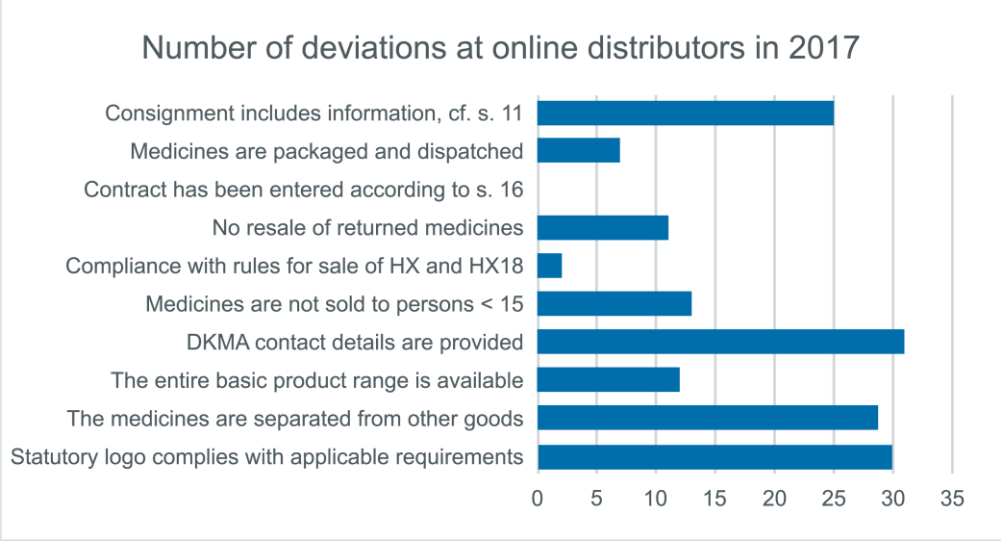
The overall results of the DKMA's inspections in 2017
In 2017, the DKMA carried out altogether 634 inspections of which 40 inspections involved only websites (online sale).

There were most temperature-related deviations since many were unable to present documentation of temperature measurement. Temperature measurement is a new requirement that was introduced from 1 January 2017. But also knowledge of the rules applicable to medicine sale was limited in many of the shops. See the total results in the figure below.



In autumn 2017, the DKMA inspected nearly half of the websites that sell OTC medicines. These inspections focused solely on the companies' websites and whether the rules on online sale of OTC medicines were observed.

The most frequent deviation at these inspections were missing contact details for the DKMA, incorrect or missing statutory EU logo as well as the placing of OTC medicines together with other goods.



Police notifications in 2017

In case of particularly serious or repeated violations of the rules, the DKMA can report a shop to the police for imposition of a fine. Causes that may lead the DKMA to request the imposition of a fine are findings of out-dated medicines, findings of opened medicine packs or if OTC medicines have been placed in areas freely accessible to customers[1].

The vast majority of the cases that the DKMA reports to the police involve findings of out-dated medicines.

We requested the imposition of a fine in 39 cases; 32 of them involved out-dated medicines.

[1] From 2018, it became possible to place certain OTC medicines in self-selection areas.

No withdrawals of authorisations to sell OTC medicines in 2017
In case of serious breaches, the DKMA can withdraw a shop's right to sell medicines. A withdrawal implies that the shop is no longer allowed to sell OTC medicines. There were no withdrawals of authorisations in 2017.

New rules on the sale of OTC medicines outside pharmacies from 1 January 2018
As of 1 January 2018, new rules on the sale of OTC medicines outside pharmacies became effective. The new rules were introduced in light of the new self-selection scheme, which means that some types of OTC medicines may be placed on shelves in the shops so consumers will not have to ask for them. In continuation of the new rules, the DKMA has updated the e-learning modules to be used in connection with applications for authorisation to sell OTC medicines and for training of shop assistants who sell OTC medicines.

The new e-learning modules give a thorough introduction to the dispensing rules among other things. The e-learning can also be completed on a smartphone or tablet. The e-learning is in Danish and can be found here: E-learning on the sale of OTC medicine.

As part of the Danish government's decision to relocate state workplaces, the tasks of inspecting shops authorised by the DKMA to sell OTC medicines will be transferred from the DKMA to the Danish Safety Technology Authority from the beginning of 2019. The DKMA will, however, still be handling a number of functions in the area.

Do not use Xofigo for treatment of prostate cancer in combination with Zytiga and the anti-inflammatory agents prednisone/prednisolone

In response to a possible increased risk of bone fractures and death, the European Pharmacovigilance Risk Assessment Committee, PRAC, has resolved that Xofigo must not be used together with Zytiga and prednisone/prednisolone.

The DKMA sent out notifications about Xofigo on 9 March 2018 with recommendations to patients and doctors. A Direct Healthcare Professional Communication will also be sent out to relevant doctors with the recommendations.

To patients

- If you are treated with a combination of Xofigo, Zytiga and prednisone/prednisolone, your doctor will put you on a different treatment.
- Both of the products Xofigo and Zytiga can be used separately according to their respective guidelines.
- If you take Xofigo, we advise you to consult your doctor about any questions you may have.

To doctors

- Xofigo in combination with Zytiga and prednisone/prednisolone must not be used to treat patients with prostate cancer with metastases to the bones.
- We emphasise that the safety and efficacy of Xofigo in combination with second-generation androgen receptor antagonists such as Xtandi (enzalutamide) have not yet been established.
- Both of the products Xofigo and Zytiga can still be used separately as monotherapy according to the guidelines appearing from the summaries of product characteristics of the two products.

These recommendations are temporary in the interest of patient safety until the ongoing in-depth review of the benefits and risks of Xofigo is complete. An update will be provided when the ongoing review of clinical data has been concluded.

Background
The PRAC has reviewed the preliminary data from an ongoing clinical study involving patients with metastatic prostate cancer. The PRAC has assessed that bone fractures occurred more frequently with Xofigo combinations compared to patients who did not receive a combination with Xofigo. In view of the seriousness of the reported cases of bone fractures, the PRAC recommends to introduce a temporary ban against using Xofigo in combination treatment in the interest of patient safety while an in-depth review of the benefits and risks of Xofigo is ongoing.

See the announcement on the website of the DKMA (in Danish only): New recommendations on the use of the prostate cancer medicine Xofigo.

Rare but possible risk of liver injury in the treatment of fibroids with the medicine Esmya

In February, the DKMA raised awareness about a rare but possible risk of liver injury in medical treatment of fibroids with Esmya. The following recommendations were therefore sent out:

Recommendations for doctors

- Do not start any new patients on Esmya (ulipristal)

Recommendations for patients

- Patients treated with Esmya who experience signs of impaired liver function, e.g. nausea, vomiting, lack of appetite, upper or right belly pain, yellowing skin or eyes, or itching should contact a doctor immediately.

The recommendations are made because the European Pharmacovigilance Risk Assessment Committee, PRAC, has gathered reports of five patients throughout Europe who developed serious liver injuries after treatment with Esmya. Some of the affected patients have previously had liver problems or have taken other types of medicines, which makes it

uncertain to what degree Esmya has anything to do with the liver injuries. Nonetheless, the measures taken are always cautious and thorough, and this safety update is made as a result.

Read the announcement on the website of the DKMA: Be aware of rare but possible risk of liver injury in medical treatment of fibroids.

Multiple sclerosis medicine Zinbryta removed from the market

Cases of suspected serious inflammatory brain disorders in patients who were treated with Zinbryta (daclizumab) have led to the withdrawal of the product from the market.

The DKMA sent out a notification about Zinbryta on 7 March 2018 with the following recommendations to patients and doctors:

To patients:

- If you are being treated with Zinbryta, contact your doctor to discuss your treatment.
- Do not take another injection of Zinbryta.
- Tell your doctor immediately if you have or experience symptoms such as persistent high temperature, severe headache, nausea (feeling sick), tiredness, yellowing of the skin or eyes and vomiting. These could be signs of a reaction to Zinbryta.
- Your doctor will carry out regular blood tests for up to 6 months after stopping treatment to check for side effects.
- If you are in a clinical study with Zinbryta, contact the doctor treating you in the study.

To doctors:

- Do not start any new patients on Zinbryta.
- Contact your patients currently being treated with Zinbryta as soon as possible and stop their treatment. Consider alternative treatments as appropriate.
- Patients stopping treatment should be monitored at least monthly and more frequently as clinically indicated for up to 6 months after the last dose of Zinbryta.
- Advise patients to immediately report symptoms of liver injury such as prolonged fever, severe headache, tiredness, jaundice, nausea or vomiting. These reactions can occur for 6 months after treatment has been stopped.
- Zinbryta has been recalled from pharmacies and hospitals.

Zinbryta is available as an injection pen for self-injection once a month. Zinbryta is dispensed only in hospitals. In Denmark, Zinbryta has been dispensed to a total of 43 patients.

The European Pharmacovigilance Risk Assessment Committee, PRAC, has reviewed 12 cases of inflammatory brain disorders in patients treated with Zinbryta. Most cases occurred within 8 months of starting treatment.

Available data also indicate that treatment with Zinbryta may also have caused other immune-mediated disorders, such as liver injuries, blood disorders, thyroiditis and inflammation of the kidneys.

See the announcement on the website of the DKMA (in Danish only): Patients receiving Zinbryta for treatment of multiple sclerosis to stop treatment.

New status report on biological medicines and biosimilars

No safety problem signals observed for selected biological medicinal products, so shows the DKMA's most recent status report on reports of suspected adverse reactions of selected biological medicines and biosimilars and their consumption.

In spring 2017, the DKMA published its first report on selected biological medicinal products and biosimilars as part of the action plan for better monitoring of biological medicines. Because new biological medicines and biosimilars are put on the market regularly, it was decided that strict monitoring of adverse reactions of biological medicines was to be a focus area for the DKMA moving forward. Status reports on these medicines are therefore published biannually.

The biological medicines and biosimilars included in the analysis are dynamic. New biological medicines will be included as they are introduced on the market. When a new biosimilar medicine is marketed, both the medicinal product and the reference medicinal product are added to the list. In addition, the DKMA will regularly assess if medicines should remain on the list. After a period with no signals and/or only very few ADR reports compared to a certain consumption level, we will remove medicines from the list – although not until two years after marketing. The list applicable at any time can be seen on the website of the DKMA.

In this report, we reviewed the consumption and ADR reports from 1 July to 31 December 2017. We identified no signals of safety problems related to biological medicines or biosimilars – which includes switches between biological medicines and biosimilars.

Infliximab-containing medicines were available in 2017. Inflectra won the tender in autumn 2017 and has been cheaper than Remsima since 1 October. The Danish regions were to switch from Remsima to Inflectra as of 1 October 2017. Remsima and Inflectra are made by the same manufacturer and are the same medicine. Only the names and packaging are different.

We have analysed consumption of the medicines from 1 July to 31 December 2017. In the second half of 2017, Inflectra accounted for 50% of infliximab consumption, and in the last quarter of 2017 it accounted for 96% of total consumption. The consumption data thus show that the Danish regions have followed the recommendation from the Danish Medicines Council[2] to switch from Remsima to Inflectra.

The DKMA has received information about batch numbers for 72% of the ADR reports linked to medicines on the list. No connection between batch numbers and reported suspected adverse reactions has been identified.

The report is available here in Danish only: ADR reports on and consumption of selected biological medicinal products – March 2018 (PDF).

[2] Before 2017, the Danish Council for the Use of Expensive Hospital Medicines (RADS)

Scientific advice to promote research and innovation

The Danish Medicines Agency will soon launch a new national scientific advice concept for companies, hospital researchers and others who require advice on requirements for marketing authorisations or clinical trials.

The Danish government has clear ambitions to boost the Danish life-science sector in order to generate growth, strengthen research and innovative treatments as well as increase exports by 2025.

One of the initiatives in this connection is to strengthen the DKMA to place us at the very front when it comes to giving more prioritised and competent scientific advice.

Read more on the website of the DKMA: New concept for national scientific advice.

Short film about the medicinal cannabis pilot programme

The DKMA has produced a short infographic film about the medicinal cannabis pilot programme. The film gives a brief introduction to the programme and is intended for sharing on social media.

The film is available from the DKMA's Facebook, LinkedIn and Twitter profiles, YouTube Channel and website. On YouTube you can switch on subtitles in English.

The film will also be offered to hospitals, general practitioners, patient organisations, etc. for displaying on for example their info screens.

Click below to see the film, and read more on our website: Infographic on the medicinal cannabis pilot programme.