The Danish Medicines Agency’s control strategy

2017 - 2021
1 Introduction

Our mission
Effective, safe and accessible medicines and safe medical devices that benefit society

Our vision
The Danish Medicines Agency: Among Europe’s best in class

This means

- Active dialogue and collaboration – value to citizens
- Quality and on-time delivery
- Professional expertise and commitment – a fantastic place to work!
- Help boost Denmark as a leading life science nation
- Driver of European collaboration and a strong international position

Our culture and values support and guide our employees towards becoming Europe’s best in class. Through collaboration, our performance and improvement culture allows us to consistently pursue our guiding values; and to be attentive, professional, efficient and European.

Our overall strategy for 2017-2021 and underlying sub-strategies describe how we will become part of Europe’s best in class.

Our goal of reaching a European best-in-class level is in many areas achieved through consolidation. It includes timely national assessment times, control and inspections at a level matching our risk-based approaches, full compliance with the pharmacovigilance standards as well as modernisation and simplification of our IT landscape. As 2018 comes to an end, we have come far with this consolidation.

The control strategy contributes to this work and is revised on an annual basis to ensure it is up to date. This present version has been updated at the end of 2018.
2 Control strategy

Medicines control comprises control in a large number of areas. We make medicines control and monitor the development of medicines in many different types of business. For example:

- manufacturers of medicinal products
- wholesalers, proprietary pharmacists and retailers
- internet retailers
- marketing authorisation holders
- sponsors/investigators of clinical trials.

The control covers an assessment of their data integrity, their systems and documentation, and the quality of the medicinal products they put on the market. We mainly control the legal chain, both nationally and internationally, but naturally also falsified and sub-standard medicines (in the following called falsified medicines) as well as illegal sale and private individuals’ import of medicines. We control the quality of medicinal products through analytical control and monitor companies’ manufacturing methods and documentation (own analyses and analysis methods). The control covers the entire medicinal product, including the packaging, the package leaflet and labelling and its life cycle. In the division of labour between the Danish Medicines Agency, the Danish Health Authority and the Danish Patient Safety Authority, the Danish Medicines Agency is not responsible for controlling how medicines are used by patients and clinics; except when we inspect clinical trials.

The basis for our control is diverse and based on legislation, guidelines mostly prepared by the EU, authorisations applied for and/or issued, pharmacopoeia monographs, standards etc.

The Danish Medicines Agency’s Laboratory and Inspection units are accredited under ISO 17025:2005 and 17020:2012, and from mid-2019, we expect to be accredited under the new version of ISO 17025:2017.

It is essential that our citizens have confidence in medicines. To some extent, this trust builds on the expectation of an efficient, proactive, relevant and timely control, which secures the quality of medicinal products and protects citizens against defective, illegal and falsified medicines.

The Danish Medicines Agency performs the control in a determined and consistent way and enforces compliance with all rules, from the early development of a medicinal product until the medicinal product is administered to a citizen. It is of paramount importance that we never compromise the safety, efficacy and quality of medicinal products and that no illegal or falsified medicines are available in the legal supply chain. We take action on relevant information that may imply a risk to the safety of citizens and a breach of the legal chain. We have a strong focus on clinical trials, bioequivalence trials in third countries, the manufacturing of medicinal products as well as the requirements that distributors have a thorough knowledge of those they do business with so that we can protect the legal chain.
As a result of our work, we have seen very few cases of falsified medicines or medicines with serious quality defects in the legal chain in Denmark. With the resources at our disposal, combined with a risk-based approach, we will do all we can to ensure that citizens can continue to have trust in medicines from the legal chain.

The companies we inspect have a legitimate expectation that the control is fair, reasonable and understandable. The framework for the control must be communicated, clear and harmonised across the EU. Moreover, we are expected to demonstrate business understanding and be attentive. Our control work is built on collaboration with researchers, companies and others to ensure the highest possible patient safety. We are working actively to gain an understanding of the terms of the party that is being controlled, and we provide guidance on our rules and practice to achieve good compliance with rules. We will continue this approach, but we do not hesitate to impose sanction measures in the event of non-compliance.

The Danish Medicines Agency performs strong control of a high quality. The quality of our control is assessed on an ongoing basis via DANAK accreditations and through the common European audit programmes, Mutual Joint Audits (MJA), covering the laboratory area, the Joint Audit Programme (JAP), covering the inspection area, and the Benchmarking of European Medicines Agencies (BEMA), covering our entire regulatory responsibilities. The general evaluation at every audit is that our control is performed with high professionalism and good quality. Our deliveries in relation to company authorisations and certificates are monitored closely, and we meet assessment times in the majority of cases.

Medicines control forms part of the international collaboration in the inspection and laboratory areas. In this field too, our efforts are appreciated and highly-regarded, and we work hard to claim that we are a driver in this collaboration. Until now, the quality of our international efforts has been on a best-in-class level, which the most recent BEMA visit and our position in the proficiency testing scheme demonstrated, but we seek to become a driver in several areas.

By keeping a persistent focus on resources and resource optimisation, our primary objectives throughout the strategy period will be to consolidate the control, develop renewed robustness, expand the scope and the academic depth of the individual controls and review our risk models, so that we can have confidence in our control work. In the same period, we will of course play an active role in the international collaboration, at least on the same level as today, but in certain areas we will increase our activities.

Throughout the consolidation period, we will increase activities and focus on more extensive international work, more communication with learning in mind, closer collaboration with stakeholders, improved data utilisation and even more targeted and risk-based controls, so that we will be able to claim that our medicines control is among the best in class.

The control strategy does not include medical devices, because this area has its own strategy.
3 Strategic challenges and answers

3.1 Increasing complexity requires efficient use of resources and due diligence

Regulatory control of the pharmaceutical area is important to secure the quality of companies’ work and the quality of medicinal products and drug development. It is important that the control has the right focus; that is in areas with the greatest risk of quality defects, and that the control serves a purpose and constantly discloses unacceptable conditions that need to be addressed. In the exercise of our regulatory functions, we use many different means to improve compliance with the rules. In most cases where companies or researchers can and will work according to the rules, our role is primarily consultative and collaborative, but we will not hesitate to take firm action and impose sanctions against companies or researchers that do not have the required will or skills. We put patient safety above all things.

It is a fact that our resources are limited, and our control is therefore risk-based because we cannot control everything. We will continue to focus our control on the areas where patient safety is most at risk, and where we suspect critical conditions. Over the years, we have had a constructive dialogue with the political level on the resource basis when even a clear-cut risk-based approach could turn out to be too lenient compared to the development of the risk scenario.

We have adopted a risk-based approach for a long time, but the risk models should be validated regularly and revised, and new models built so that new risk factors can be included and match the development in the different areas.

We have access to a large amount of data, but they are not always fully accessible and structured. We must ensure that our decisions are data-driven via efficient use of available data – both internal and external data – to ensure robust risk selection for the control and timely control. We will expand the pool of data and use it to select the data that can contribute to our risk management and risk selection. In addition, we will increasingly seek and apply postmarketing information, such as complaints about medicinal products, as relevant input for future authorisations of medicinal products and the control of them. In this context, it should also be clarified which data are available, but not to be included in our work.

Data and data integrity are an area of great importance to the Danish Medicines Agency as well as the companies, which experience increasingly complex volumes and sources of data. We therefore focus on the companies’ and researchers’ handling of data, their data integrity and their skills in this area.

In order for society to have trust in medicinal products, researchers and companies, the control must be continuously adjusted and keep up with the developments in industry, research environments and medicines. This will have an impact on the following:

- The variation and width of our controls, so that we work with planned controls, but also make regular unannounced controls, for example to disclose deliberate cheating.
- Our collaboration with other authorities in Denmark and abroad, which we will expand.
- Our collaboration with other authorities will be expanded, e.g. with the Danish Veterinary and Food Administration and the Danish Patient Safety Authority, which have interfaces to our control tasks.
- Our interactions with industry, where we will expand our collaboration with various stakeholders, such as industry associations, in the planning of our control work.

- Our development of rules, where we will use our business knowledge to influence the preparation of new rules, and we will seek a legal basis for improving our control work in areas where it may be missing.

3.2 Medicines control takes place in an international collaboration that we must make the best use of

We take advantage of the European community that we form part of and cooperate on medicines control, and we work actively for the best possible use of resources. For example via relevant EMA working groups, via participation in the Working Group of Enforcement Officers (WGEO) and via the collaboration between the European Official Medicines Control Laboratories (OMCL). The regulatory framework for medicinal products is to a high degree European, and common European control procedures are an important part of the overall European control, where we mutually recognise results across all EU countries and ensure that companies operating across borders are controlled.

We work hard to be opinion leaders in the development of common European rules and subsequent interpretations, for example through participation in controls carried out jointly with the authorities in other countries. The idea is to maintain a high professional level, to focus on the quality of medicines when new rules are prepared and to ensure harmonised conditions for industry in Europe. In addition to our participation in the relevant working groups, we have also increased our commitment by making auditors available for JAP and BEMA.

Without compromising the safety of citizens, we must, via a profound business knowledge of the controlled parties, work to ensure that the adaptation of current rules and the introduction of new rules are made with an eye for the conditions of industry and researchers – also proactively so that legislation can keep pace with developments. However, patient safety must never be jeopardised.

A growing part of medicinal products in the EU is either centrally authorised, decentrally authorised or based on a mutual recognition procedure. Consequently, we must aim to provide control work adapted to a common EU control plan. We must work actively to create a common EU overview, and we must ensure that our skills fit into a national context as well as an EU context. As regards the laboratory, in particular, we cannot maintain leading expertise in all areas of laboratory control; consequently, our expertise and methodology must be built up and maintained in a broader context, and so that we can incorporate other authorities’ analytical skills into our methodology.

As mentioned, the specialisation of the laboratory should be seen in a European context, but also reflect our specific obligations. This means that the laboratory's focus and related skills should reflect the production of Danish industry, where we have assumed the roles of either rapporteur or reference member state in connection with authorisations or where it is considered beneficial for society that we have special expertise.

Across the EU authorities, the country, in which production or release takes place, has special control obligations, and when a medicinal product is manufactured in a third country, the rapporteur or reference member state also has special obligations. When the Danish Medicines Agency assumes the role as either rapporteur or reference member state, we also assume a special control obligation for these medicinal products. This applies to cases involving quality defects or supply shortages of medicinal products. The different roles that transcend the roles as authority for marketing authorisation holders and authority for pharmaceutical players, require a comprehensive, pan-European overview of roles and responsibilities. We will work to create this overview to ensure that no control obligation falls between two stools.
In addition to the work at EU level, we also give priority to collaboration with authorities on a global level. For example, we work bilaterally with China, where it makes sense to promote patient safety in a larger context. With this aim in mind, we also participate actively in international forums, such as the WHO, the OECD, the Council of Europe’s European Pharmacopoeia, PIC/S etc.

We also carry out inspections in third countries in purely Danish teams, but also in international teams, including WHO teams. In connection with these inspections, we also try to uncover differences in practices/behaviours with learning in mind, partly for the foreign authority, partly for our own learning.

3.3 The rules are complex, so we need to communicate about our control with learning in mind

As we continue to develop the way we provide information and guidance on our rules, we continuously improve, target and to some extent increase our communication – about control campaigns, efforts and the results of the control work. Our communication must be targeted at industries, researchers, citizens and other relevant parties.

We want to communicate with learning in mind to make it easier for the recipients to comply with the rules and to strengthen citizens’ trust in the medicinal products they buy in the legal chain. To make sure that our guidance gives researchers and companies a broad and comprehensive understanding of the current rules, we must also support the overall information about the current rules, so that we support Denmark as a good place to establish and operate a life science business.

3.4 New markets and new distribution channels

Medicinal products are distributed via an increasing number of channels, including over the internet. Consequently, we want to focus on illegal distribution, particularly illegal online sale of medicines.

Positive effects, such as increased availability of medicines, should be promoted, while the risks of buying medicines via illegal channels and buying counterfeit/falsified medicinal products must be contained.

Thus, we will make efforts in a number of areas. First, we need to ensure that it is easy for citizens to buy medicines safely online via pharmacies or other legal distributors. We must communicate regularly and targeted to citizens about the opportunities and especially the pitfalls of buying medicines online. We need to collect information about citizens’ online shopping so that we can target our campaigns at citizens via various media.

And by monitoring the illegal online sale of medicines and sale via other channels, we will protect citizens against illegal distributors as well as protect the legal chain from illegal and falsified products, e.g. through participation in Operation Pangea activities. We will report illegal distributors and control products suspected of being illegal or falsified medicinal products.

Finally, we will warn citizens against illegal products and/or illegal distributors. We will continue to gather knowledge from our control and monitoring of this field to follow the development in medicines in demand online, and then use it in our future control. We will continuously explore new opportunities to protect citizens from illegal or defective medicinal products.
3.5 The control work brings important knowledge to be used by the entire Danish Medicines Agency

Increasing complexity due to the development in regulation, technology, industry structure and market etc. is a challenge for the Danish Medicines Agency's control work, because it is becoming increasingly difficult to obtain material for control, to keep track of the control area's overall risk, and thus the risk profile we have to apply in each area. The increased complexity makes it difficult even for companies to maintain an overview of their own organisation, contractual relationships, division of responsibilities and supply chain. It is of great importance to the medicines control that we have clear structures, to the extent possible, so that we will be able to implement control measures that reflect the existing risks as accurately as possible.

In our control work, we often disclose and uncover challenges of complexity, for example through our work with authorisations, inspections and laboratory controls; subsequently, we have an obligation to communicate this knowledge, both internally and externally. We work to ensure that this communication is accurate and timely by being a driver in the multidisciplinary and cross-organisational knowledge sharing, for example through competence teams. This is to align expectations between divisions, establish a reasonable practice and ensure that we appear as a unified agency.

3.6 New trend of deliberate circumvention of the rules

We have decided to perform our controls by a risk-based approach. This ensures that we focus our controls on areas where we see that patient safety is the most at risk and where we suspect critical issues. However, we note overall that the companies and persons we inspect generally endeavour to satisfy and comply with the rules in force.

Over the last few years, we have nonetheless observed several cases of non-compliance within both the GMP and GCP areas where we clearly suspect rules were circumvented deliberately. We have seen this mostly with foreign companies, but also Danish companies have come under review.

The main issues we have identified are:

1) Inspections of clinical trials and manufacture in third countries have provided evidence that rules were deliberately breached. This has led to the withdrawal of both marketing authorisations of medicines and the recall of batches of medicines from the Danish market.

2) A number of falsified medicines have found their way to the legal supply chain in Denmark, leading to the recall of batches of medicines from the market.

3) A number of Danish companies, pharmacies included, have deliberately tested or crossed the boundaries of the applicable law.

There is no indication that there will be fewer of these incidents, and we therefore need to find the leeway and possibilities of expanding our control. In our control activities, for example, we could implement new tools to increase our ability to uncover deliberate malpractice, and we could expand the international collaboration with our sister authorities.

The Danish Medicines Agency will throughout the strategy period work on a number of fronts to reverse the trend of deliberate circumvention of the rules. The expected actions to be taken will include:

- Development and training of the inspector team with the aim of improving the skills needed to detect deliberate circumvention of the rules
- A wider focus during relevant inspections aiming to inspect other areas and IT systems than those inspected routinely
- Acquisition of new IT systems for the processing and comparison of large volumes of data with the intention of uncovering manipulated data
- Review of the legal basis to carry out inspections in new places and in new ways

4 Overall delivery plan in the strategy period

- In the year 2021, we play an even more important role in the common European control work and we have been working actively on optimising the use of resources across the EU.
- In the year 2021, we use all available and relevant data in the best possible way to select control elements. We achieve this through systematic and repeated checks of our risk models.
- In the year 2021, we provide relevant and focused information on our control results in a way that makes it easier for the recipients to understand and comply with the rules.
- In the year 2021, we have expanded our collaboration with various stakeholders, such as industry associations, in the planning of our control work.
- In the year 2021, we have intensified our efforts within illegal distribution of medicines with a focus on useful communication to citizens about the pitfalls of buying medicines via the internet.