LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Annual OMCLReport 2019-2020

Lægemiddelstyrelsen / Danish Medicines Agency
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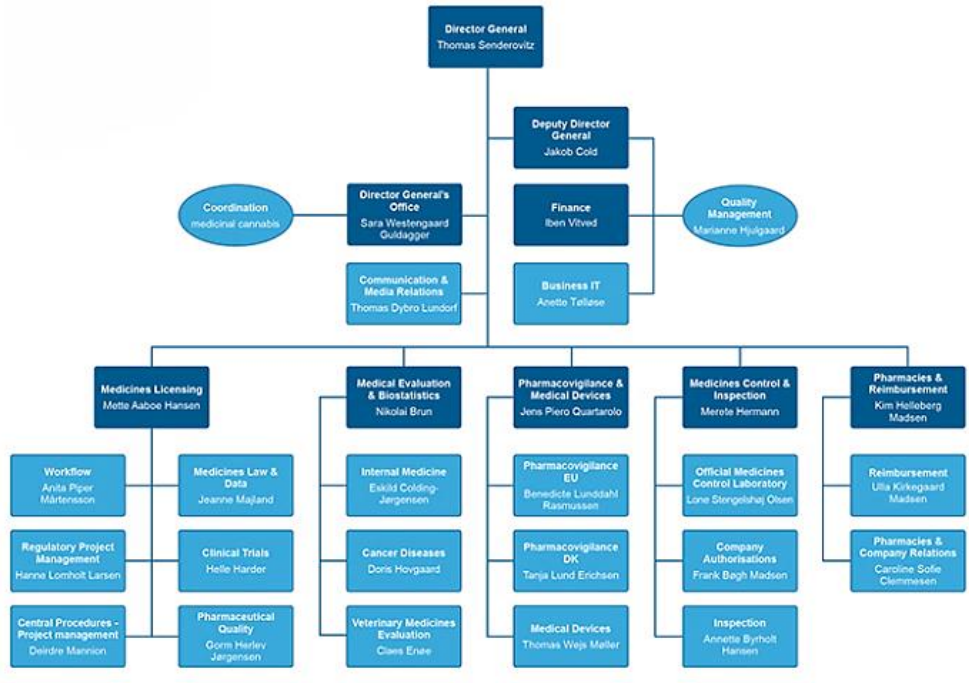
OUR MISSION

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

Indhold

1
Organisation of the Laboratory

1.1 General structure of the Danish Medicines Agency



The Danish Medicines Agency has around 500 employees, and the five largest professional groups in our organization are pharmacists, administrative assistants, physicians, lawyers and masters of social science. We perform most of our tasks in close collaboration with colleagues from regulatory authorities and organizations in the other EU countries.

The Danish Medicines Agency

- authorizes and inspects pharmaceutical companies and licenses medicinal products on the Danish market
- monitors adverse reactions from medicinal products and authorizes clinical trials

- monitors medical devices available in Denmark and supervises adverse incidents involving medical devices
- appoints proprietary pharmacists, organizes the pharmacy structure and supervises pharmacies and retailers.

In 2016, The Danish Medicines Agency launched a new strategy for 2017-2021: Among Europe's best in class. In general, the strategy emphasizes our commitment to both public health and growth in Denmark and describes a number of focus areas built on the five points of our vision (see next page).

In addition to the overall strategy for 2017-2021, we have prepared specific strategies: a licensing strategy; a pharmacovigilance strategy; an availability strategy; a control strategy; and a strategy for medical devices. We have also developed cross-functional strategies: a strategy for employee and manager development; a quality and delivery strategy, an IT strategy; and a communications strategy. These specific strategies and cross-functional strategies provide the basis for planning the coming year's focus areas on an operational level.

OUR VISION

- 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

1.2 The Division for Medicines Control and Inspections

The division “Medicines Control and Inspections” is responsible for the Danish Medicines Agency's regulatory duties with respect to laboratory testing and monitoring of medicinal products. The division handles complaints and reports about quality defects in medicinal products as well as any related recalls. The division supervises and is responsible for company authorizations for handling and manufacturing medicinal products and psychoactive substances.

1.2.1 The Control Strategy for the agency

Medicines control is a task of the European and other international authorities. In order to fulfill our vision to become a driver of international collaborations, we want to increase our efforts in the international arena and make use of recognition across borders to make medicines control more efficient. This means that we have been putting efforts into establishing a mutual recognition procedure with the USA, and the Danish inspectorate achieved recognition in November 2018.

We are seeking dialogue and offering guidance in our control, but we also act decisively when patient safety is at risk. We put a high priority on securing the quality of legal medicinal products, but we also want to warn citizens against illegal and falsified medicinal products. We want to increase our focus on illegal distribution, particularly illegal online sale of medicines.

Moreover, we carry out risk-based control adjusted to the individual situation. Risk models and the tools we use in the control of medicines must be dynamic in order to prevent them from becoming predictable. Consequently, we plan to revise and expand our risk models and toolbox. The OMCL has been working extensively with a model for scoring risk parameters based on available data and the model will be evaluated and optimized accordingly.

In 2020, a brand-new initiative, the Data Analytics Centre (DAC) of the Danish Medicines Agency was launched. DAC will enable the Danish Medicines Agency to offer new types of scientific advice to the pharmaceutical companies on the development of new medicines, including medicines for people with rare diseases. DAC will also develop new methods for optimized real time drug safety surveillance.

At the OMCL, we have utilized the computational resources at DAC to establish an updated list of prioritised medicines selected for control. This selection has been based on many different parameters, such as time elapsed since last control, novelty, complaints from patients as well as medical professionals, and findings during previous controls.

The complexity and the number of control points mean that we cannot check each control point every time. Thus, the use of communication to promote learning and improve compliance with rules is very important. We want to increase communication about our expectations and learning points before, during and after our control.

The Lean transformation was launched in the Danish Medicines Agency in 2017. The Lean transformation is driven by an ambitious goal of optimizing operation and internal processes of the Agency. During 2020 the Corona-situation forced us to rethink our way of planning and work with LEAN. Since more colleagues were working from home the physical boards needed to be replaced by an electronic solution. After reviewing the market and talking to the internal LEAN group we decided to work with the online system Klartboard.

Once this was decided we began working with the Klartboard organisation to design a solution that could manage both long term overview and weekly and daily planning of projects and tasks. This work took place over a couple of months and finally the solution was presented to the group. After some training sessions the system is implemented and has now replaced the physical whiteboards previously used for planning activities in the laboratory.

In addition to OMCL activities, the laboratory performs tasks in connection with the elaboration of monographs for Ph. Eur.

A separate Annual Report on OCABR activities is provided.

1.2.2 Personnel matters

The Biological and Chemistry & Radiochemistry Laboratories had 30 employees and 31 employees in 2019 and 2020 respectively. The staff distribution according to role is presented in Figure 1.

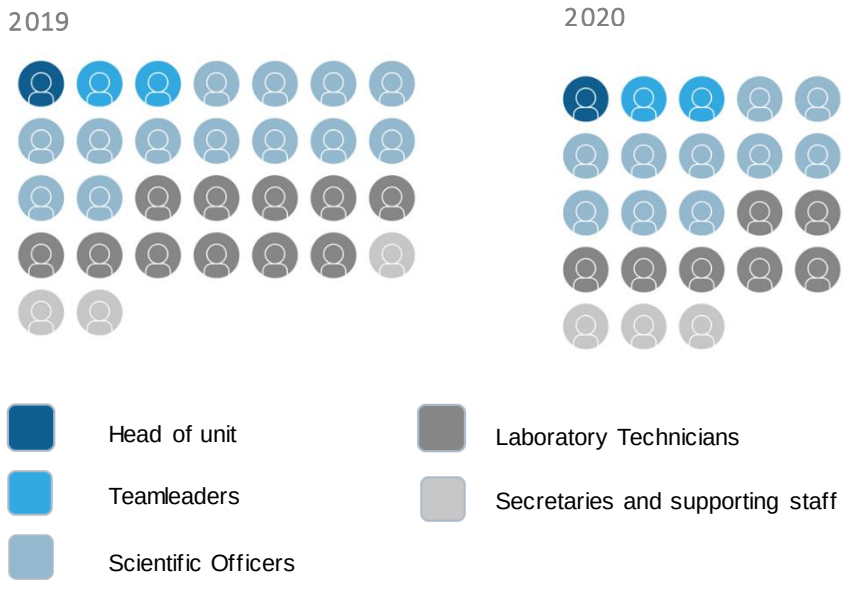


Figure 1. Staff distribution based on roles in 2019 and 2020

1.2.3 Quality Management System

Since 1995, the Laboratory has been accredited according to the requirements of ISO 17025 and has been subject to a regular independent surveillance programme. In 2006, the accreditation included a flexible scope accreditation. The accreditation of the Laboratory was renewed in April 2020.

The scope of the accreditation is testing of pharmaceutical products and active ingredients and is linked to a specific list of methods mainly from Ph. Eur. and list of methods/techniques authorized by the accreditation board.

Our national accreditation body for the Laboratory is DANAK.

Types of testing:

- **Biological and biochemical**
- **Chemical testing**
- **Radiochemistry and radiation**

The Laboratory received the first MJA attestation on February 2011. The specified field of activity for the Laboratory is "Testing of pharmaceutical products and API (biological, chemical and radiopharmaceutical); Market surveillance testing and screening for illegal products. Elaboration of standards and reference materials to Ph. Eur.; Participation in PTS, CAP, BSP and MSS". The previous MJA (06/15) was successfully carried out in collaboration with DANAK. The MJA in 2019 was a re-assessment audit joint with the DANAK accreditation.

A DANAK audit team successfully audited the Danish OMCL in September 2020. Due to the current pandemic, part of the audit was conducted virtually.

2
Activities related to the National Market

2.1 Legal Supply Chain (Authorised Medicines)

The Laboratory carries out analyses on a range of medicinal products both according to the authorised dossier of the marketing authorisation holder as well as in-house (validated and non-validated) methods. In general, selected testing which typically includes appearance, physical tests such as uniformity of mass and hardness, assay of active ingredient(s) and impurities is performed. Furthermore, the laboratory performs supplementary tests for specific products or drug substances. These investigations review the labeling, batch protocol and/or specification compliance, without the typical analysis performed in the laboratory.

2.1.1 Sampling approach

With the introduction of DAC (see 1.2.1), the process of selecting medicines for control have been updated and utilizes powerful computational resources to include several parameters, such as time elapsed since last control, novelty, complaints from patients as well as medical professionals, and findings during previous controls. Liaising with DAC, has enabled the Danish OMCL to establish updated lists of prioritised medicines or groups of medicines for control.

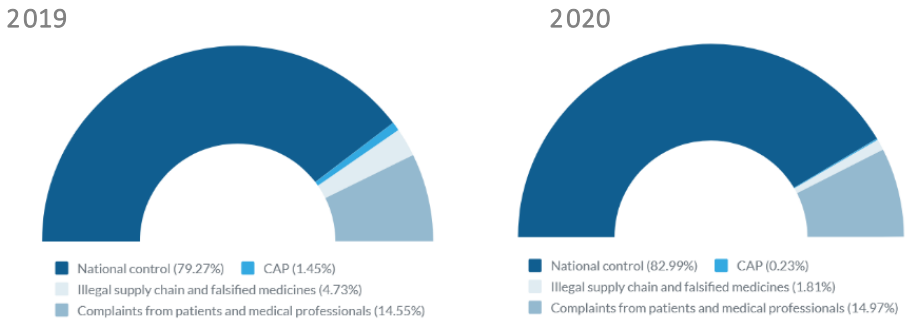


Figure 2. Cases handled by the Danish OMCL divided by the nature of the tasks for 2019 and 2020.

A total of 158 and 201 finished products and APIs were controlled in 2019 and 2020 respectively, see Figure 2. A significant number of the products tested (48 % for 2019 and 52 % for 2020) led to additional enquiries with the marketing authorization holder or manufacturer concerning labelling, analysis methods, validation of analysis results as well as specifications and stability issues.

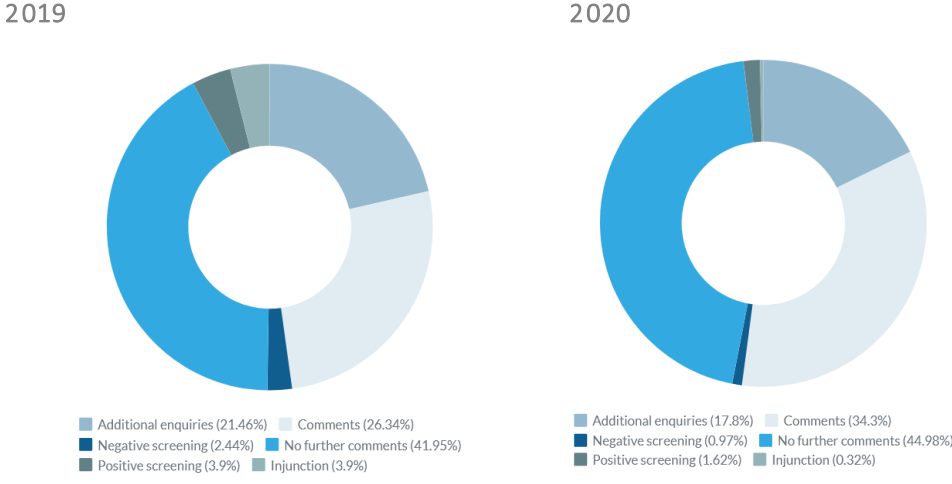


Figure 3. Case outcome for 2019 and 2020

The Danish OMCL received 40 and 66 complaints of the pharmaceutical products from pharmacies, healthcare professionals and patients in 2019 and 2020 respectively. In 2019, nine samples were analysed in the laboratory and in 2020, seven samples were analysed in the laboratory (see Figure 4). For the remaining complaints, labelling controls were performed.

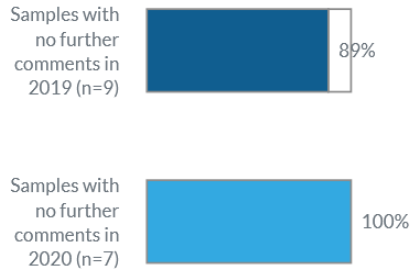


Figure 4. Complaint samples with no further comments in 2019 and 2020 respectively.

2.1.2 Results, details/technical issues

See Appendix 1.

2.2 Legal Supply Chain (suspected samples)

The Danish Medicines Agency did not carry out any analysis on counterfeit medicines during neither 2019 nor 2020 (see Table 1).

2.3 Illegal Supply Chain

The OMCL works closely with Danish customs to control medicine imports, ordering the return or destruction of illegal packages as well as with other agencies such as the National Food Institute and Anti-Doping Danmark (ADD) in order to investigate seized packages for suspected illegal substances.

Samples arriving at the OMCL are primarily analysed by liquid chromatography coupled to a high-resolution mass spectrometer (LC-HRMS). This initial analysis is sometimes complemented by infrared (IR) analysis. In general, a vast majority of the samples arriving at the laboratory can be divided into three subsections; slimming products, pain killers and medication used to treat erectile dysfunction. The illegal products imported to Denmark is usually concealed as dietary supplements, for instance as Vitamin C and herbal supplements. Some seized products consist of tablets and capsules; however, other seized products contain sometimes large amounts of powder. The largest seized products, certainly in terms of amount of the product, in the period of 2019-2020 can be contributed to pain killers. For instance, in 2019 the OMCL analysed roughly 4000 undeclared, high-dosage tramadol tablets.

The number of positive samples analysed by the Danish OMCL in 2019 and 2020 is presented in Table 1.

Table 1. Total number of samples tested in the legal and illegal supply chain in 2019 and 2020 respectively.

		2019	**2020**
Total number of suspected counterfeit samples	a	0	0
Total number of confirmed counterfeit cases of licensed medicines in the legal supply chain	b	0	0
Total number of suspected illegal samples tested	g	13	8
Total number of illegal samples identified (other than counterfeit samples)	c+d+e+f	8	5

Key Issues 2019-2020

COVID 19

Map and secure medicine availability as well as test vaccines

Nitrosamines

Develop a validated analysis method for nitrosamines in API's and finished products.

Counterfeit products

Continue the work on analysing falsified medicines and suspicious unknown products.

Allergen products

A standardized, competitive ELISA has been developed for testing medicinal products

Cooperation with Chinese Authorities

The Danish OMCL has initiated a collaboration with Chinese Authorities to investigate radioactive pharmaceuticals

3
Activities related to the Network

In this section, we report some of the highlights from the OMCL's activities related to the network in 2019-2020.

MSS on Sildenafil finished products and Sildenafil citrate API (MSS058 and MSSFP004)

The focus on the MSS on Sildenafil was to analyze finished products and Sildenafil citrate API (MSS058 and MSSFP004).

Finished products were initially analyzed by the generic methods described in the BP monograph, where the following analyses were performed on 26 samples from the Danish market: Assay (HPLC), Related Substances (HPLC), Dissolution. Upon reviewing the results of the HPLC assay, 9 out of the 26 samples were OOS. All 9 samples were subsequently retested with the MAH method and all complied with specifications. All results from Related substances (HPLC) and Dissolution did not give rise to comments.

For the API Sildenafil citrate API samples, The API Working Group had decided to launch an atypical Market Surveillance Study (MSS) as a part of the API Fingerprint project (MSSFP004) in which the API sildenafil citrate was analysed. 70 samples were received from EDQM, and Raman, Residual Solvent and Water Content were performed on selected samples.

Additionally, five of the API's was analysed for residual solvents based on a GC-MS method described in "A validated GC-MS method for the determination and quantification of residual solvents in counterfeit tablets and capsules". *J Pharm Biomed Anal*. 2012; 70:64-70. The results from the Danish OMCL were compared to results from the Norwegian OMCL with good correlation between the reported results from the analysis of residual solvents.

Moreover, thirteen of the finished sildenafil products were analysed using GC-MS. None of the finished products contained residual solvents above the threshold specified in *Ph. Eur*.

Crude Heparin testing

The Danish OMCL participated in the Crude Heparin testing campaign of the OMCL Network that is coordinated by the Irish OMCL. The Crude Heparin was sampled from two Chinese manufacturers during inspection. The Crude heparin was tested in several OMCL´s including the Danish OMCL. The Danish OMCL tested the crude Heparin samples by PCR and SAX-HPLC and results was reported to the Irish OMCL.

Suspicious Unknown Products (SUP)

The OMCL regularly participates in the yearly EDQM SUP analysis. This exercise simulates an unknown sample, for instance a customs seizure, arriving at the OMCL for analyses such as identification and quantification.

In 2019, the received SUP-009 was a mixture of the two antibiotics Benzylpenicillin sodium and Ampicillin. Due to issues with the stability of the substances during normal LC-HRMS conditions, the substances were identified by LC-HRMS and quantified using LC-UV/Vis. When comparing the results obtained by the Danish OMCL to the other participating OMCLs, it was concluded that this strategy of quantifying by LC-UV/Vis was highly successful.

However, the received SUP-010 for 2020, was challenging and resulted in an incorrect identification of the substance. The main component in the SUP-010, Agmatine sulphate, is an extremely polar compound that posed a challenge to analyse using the conventional techniques, such as LC-MS, LC-UV/Vis and IR, normally utilised by the Danish OMCL in SUP cases. Some of the other participating OMCLs successfully identified the main component using Raman and/or NMR.

CAP testing of DaTSCAN

In 2019 a CAP testing of DaTSCAN was performed. DaTSCAN is a solution for injection containing the active substance ioflupane (I-123). DaTSCAN is used for diagnosis of loss of nerve cells in the stratium area of the brain. The preparation is for example used for distinguishing between essential tremor and diseases related to Parkinsons Disease. The testing of DaTSCAN was challenging because of a short shelf-life. The preparation was delivered in the morning with reference time at 12:00 o'clock and with expiry at 19:00 o'clock, so all the tests related to content of radioactivity and radiochemical purity should be performed within a few hours.

Planned CAP testing of Zevalin

CAP test of Zevalin was planned for 2020. Due to shortage for Zevalin on the market and non-availability of reference materials the CAP project was postponed to 2021. In 2021 the project was further postponed to 2023 due to shortage of the drug substance (the antibody ibritumomab).

The collaboration with the German OMCL_BBB regarding testing of selected ROTOP products continued in the period. The analytical control on the individual products was shared between the two OMCLs, in other words the Danish OMCL has only performed the methods including radioactivity.

As always, further details regarding our control and the outcomes are available at EDQM. Analytical control on Radiopharmaceuticals licensed according to the MRP/DCP procedure, like Renoscint MAG3 are included in the MRP/DCP database in line with other Pharmaceuticals.

4
Method related activities

In this section, we report some of the highlights from the OMCL's method related activities in 2019-2020.

The COVID-19 Taskforce

During early stages of the pandemic, a COVID-19 Taskforce for supply of medicines was a cross functional group responsible for securing availability of medicines during the global pandemic. Staff from the OMCL participated in the taskforce's highly prioritised job to map and secure medicine availability during these unprecedented times. Any signal of a possible lack of medicine investigated in order to clarify the criticality and initiate mitigating actions.

Another task was to represent DK in the Single Points of Contact (SPOC) Network to ensure medicine supply on a European level. The SPOC network is a pilot programme initiated by the HMA/EMA Task Force on the Availability of Authorised Medicines for Human and Veterinary Use for the purpose of improve information sharing between Member States, EMA and the European Commission on important medicine shortages of human and veterinary medicines and to organize actions to help prevent and manage shortages.

Developing an allergen standard

According Guideline on Allergen Products – Production and Quality Issues" (EMEA/CHMP/BWP/304821/2007) *-the content of relevant allergens should be measured by validated assays using certified reference standards or biological reference preparations and assays validated in international standardization programmed whenever possible*.

Standardisation of allergen testing in medicinal products has traditionally been very difficult because of the complexity of the finished products. During 2019-2020, the Danish OMCL developed a competitive ELISA with some of the WHO allergen standards, which can be used for standardization of medicinal products on the Danish market.

Nitrosamines

Developing analytical testing techniques for nitrosamine testing were a priority for the Danish OMCL in the period 2019-2020. Following the initial reports of nitrosamines in sartans, other active substances, such as metformin, have been suspected of being contaminated with nitrosamine. Initially, the instrument chosen for developing a method for detecting nitrosamines in medicines was a GC-MS. Twelve nitrosamines (N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosoethylisopropylamine (NEIPA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA), N-nitroso-N-methyl-4-aminobutyric acid (NMBA), N-Nitrosodipropylamine (NDPA), N-Nitrosomethylethylamine (NMEA), N-nitrosopyrrolidine (NPYR), N-nitrosopiperidine (NPIP), N-nitrosomorpholine (NMOR), N-Nitroso-diphenylamine (NDPhA)) were selected for analysis.

After initial analyses, it was decided that the instrument was not suitable for analysing such low levels with the specificity and sensitivity that is required by an OMCL laboratory. This is because the method that has been used by the Swiss OMCL the Danish OMCL based the method on uses a GC-MS/MS, while the Danish OMCL only has access to a GC-MS. Most of the nitrosamines selected for testing are small molecules that generates even smaller fragments during the ionisation process. When analysing these small fragments by MS, the background was deemed to high.

Comparison of monocyte activation test (MAT) and Limulus endotoxin test (LAL)

The Danish OMCL have compared monocyte activation test (MAT) with classical Limulus endotoxin test (LAL), both tests performed as described in *Ph.Eur*. In total, 14 chemical products and 11 biological products were tested. All products were within the approved specification using LAL test. Six of the chemical products had a stronger response than the specification approved (LAL) when compared to the MAT results, and two products (vaccines) had a stronger response in the MAT test than in the LAL assays. Moreover, three products blocked the TNFα, thus MAT therefore could not be used for these samples.

Inter-laboratory comparison testing with NIFDC (China)

The collaboration with the Chinese Authority, National Institutes for Food and Drug Control (NIFDC) continued in 2019. As NIFDC also perform analytical control on Radiopharmaceuticals, an inter-laboratory comparison testing would be of great benefits to both parties. During visits, interchange of information and experiences we learned, that the laboratories were quite similar in the field of radioactivity regarding equipment and testing methods, type of radionuclides allowed to handle and type of Radiopharmaceuticals authorized.

In spite of challenges in handling radioactivity and in testing Radiopharmaceuticals we succeeded to find suitable methods and a suitable sample for the testing. Methods like radioactive concentration, radionuclidic identy and purity were chosen. Due to the willingness from a manufacturer to help with sample preparation and export of the Radiopharmaceutical despite the physical distance between the laboratories, we agreed to continue.

The protocol for inter-laboratory comparison testing was finalized at a face to face meeting at the Danish OMCL in summer 2019 and the inter-laboratory testing took place in November 2019. Reporting and evaluation of results took place in spring 2020. In conclusion, the results were comparable and the inter-laboratory comparison testing on the Radiopharmaceutical *Sodium I-131 iodide for injection,* was a success.

5
Future Planning

5.1 National

One of the groups of medicines highlighted by the updated list for prioritising national control campaigns was medicines used to treat ADHD. It is therefore the focus for the coming year to initiate documentation and laboratory control. Another focus for the future will be the continuous work to improve the analysis methods as well as analyse samples suspected to belong to the illegal supply chain.

In December 2020, the Director General announced a largescale restructuring of the entire Danish Medicines Agency to be implemented in 2021. These changes will be presented in more detail in the subsequent annual report for 2021.

5.2 Network

In the future, one of the main priorities for the Danish OMCL is to develop a LC-MS based method to identify and quantify nitrosamines present in very low concentration in medicines. The laboratory has in close collaboration with the instrument vendor Waters developed a testing strategy that will be tested and, if successful, implemented in 2021.

Moreover, the Danish OMCL is in the midst of developing an optimised quantitative/semi-quantitative GC-MS method for the analysis of residual solvents in finished products and API's. The aim is for the method to be optimised and fully validated by the end of 2021. Another future aim for the Danish OMCL is to develop a sample preparation method for cremes.

After the successes with MSSMSS058 and MSSFP004 on sildenafil APIs and finished products, the Danish OMCL also plans to participate in future MSSs such as the coming MSS059 and MSSFP005 concerning tadalafil APIs and finished products respectively.