LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Danish Medicines Agency
Medicines Control and Inspection

Annual Report of activities concerning the

OMCL-cooperation 2018

Chemical, Biological and
Radiopharmaceutical Products

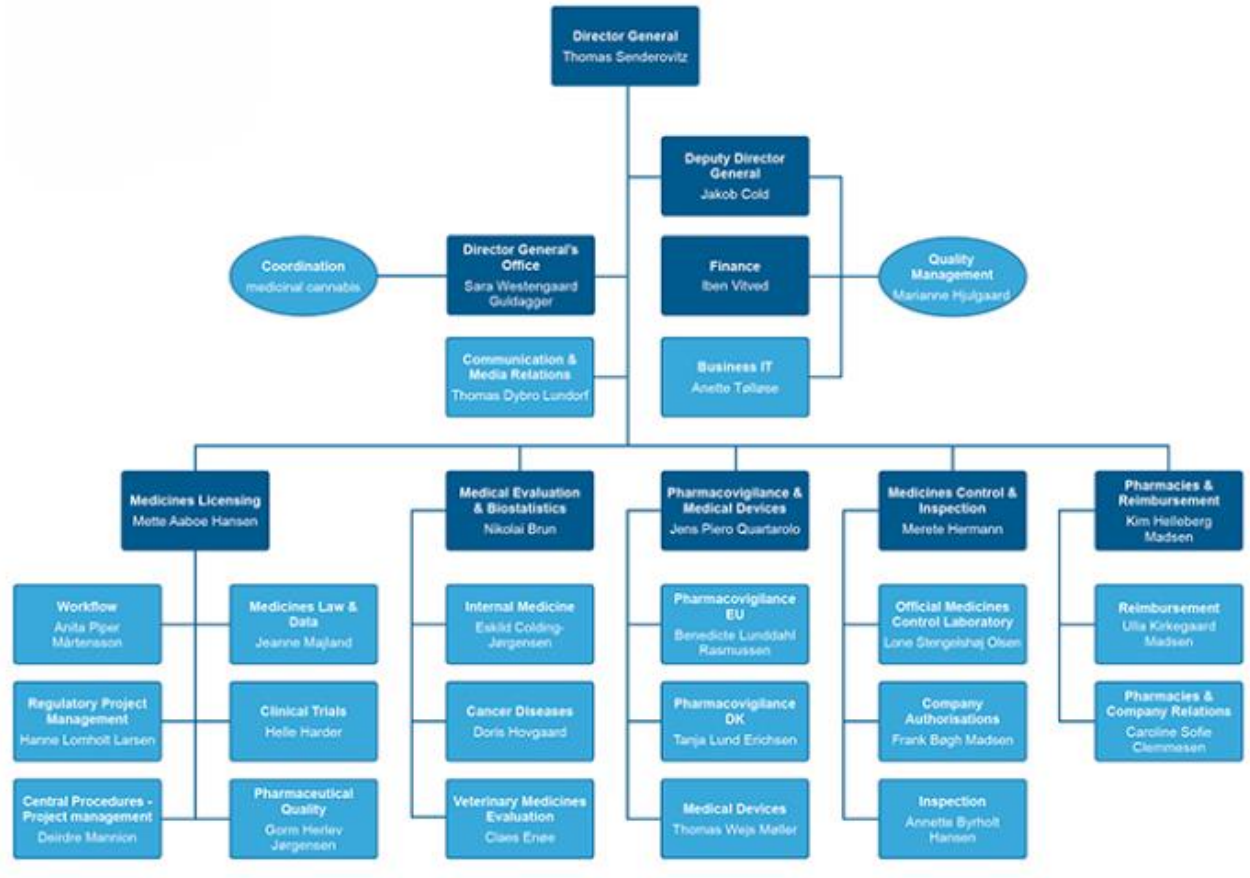
This document is for National Control Authority use only

Lægemiddelstyrelsen
Axel Heides Gade 1
2300 København S
Denmark
T +45 44 88 95 95
E dkma@dkma.dk
LMST.DK

A.1. Organization of the laboratory

A1.1 General structure

Danish Medicines Agency



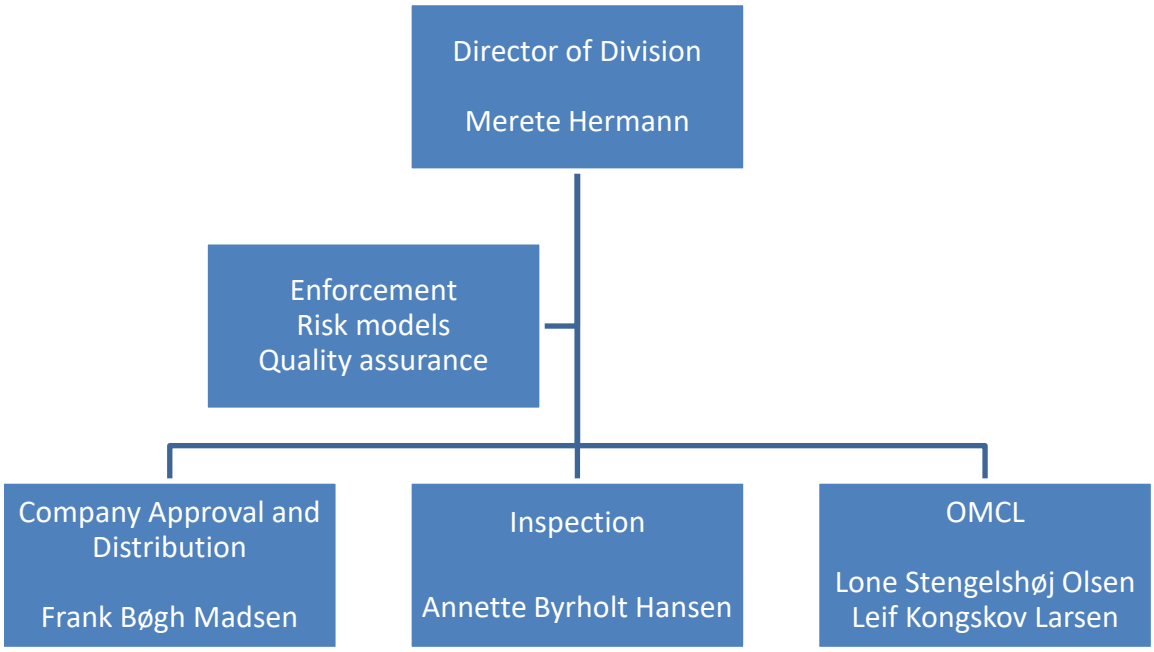
The Danish Medicines Agency has around 450 employees, and the five largest professional groups in our organization are pharmacists, administrative assistants, physicians, lawyers and masters of social science.

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.

We perform most of our tasks in close collaboration with colleagues from regulatory authorities and organizations in the other EU countries. In 2016, The Danish Medicines Agency launched a new strategy for 2017-2021: Among Europe's best in class! 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.

Medicines Control and Inspection



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.

Leif Kongskov Larsen (Head of Unit) was absent from work from August 2018 and terminated his employment at the agency in December 2018.

The Control Strategy for the agency

Medicines control is a task of the European and other international authorities. 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.

We carry out risk-based control adjusted to the individual situation. Risk models and the tools, we use in the control must not be static, because that would make them 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 in 2019 and optimized accordingly.

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. By the end of 2018, the OMCL is working along with most of the Agency with:

- Setting standards - Delivering right quality at the right time and reducing costs.
- More efficient processes - to work with fewer stations and shifts to reduce throughput times in the projects.
- Workflows - to create dedicated time for case management and to reduce distractions.
- Increase customer satisfaction by being specific about our needs so that customers deliver the right materials the first time in order to get the results from our control faster.
- Visualization by the use of project board management - to create overview, prioritization, productivity, progress and quality improvements, etc.

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.

A. 1.2 Personnel matters

Unfortunately, The Danish Medicines Agency had to lay-off several people in May 2018. The implications for the OMCL were that two vacant positions were not filled; two employees made use of a voluntary retirement scheme, and two employees reduced their working hours.

The Biological and Chemistry & Radiochemistry Laboratories had 31 employees and 2 students during 2018:

Heads of Unit	2
Scientists	16
Laboratory Technicians	11
Assistant/secretary	2

A. 2 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 February 2018.

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.

Type of Testing:

- Biological, biochemical,
- Chemical testing, Analytical chemical,
- Radiochemistry, radiation.

Our national accreditation body for the Laboratory is DANAK.

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 radio-pharmaceutical); Market surveillance testing and screening for illegal products. Elaboration of standards and reference materials to Ph. Eur.; Participation in PTS, CAP, BSP and MSS". An audit team successfully audited the Danish OMCL in June 2015 consisting of a Mutual Joint Audit (MJA) team and DANAK. Another mutual Joint audit is planned for April 2019.

B.1 Activities related to the national market

B.1.1 Legal Supply Chain (authorised medicines)

The Laboratory carries out analyses on a range of medicinal products according to the authorised dossier of the marketing authorisation. In general, selected testing is performed, which typically includes appearance, identification of constituents, assay of active ingredient and impurities. In addition, 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.

A total of 423 medicinal products and APIs were controlled. A significant number of the products tested (62 %) led to additional enquiries with the marketing authorization holder or manufacturer concerning labelling, SOPs, as well as specifications and stability issues. Some of the projects are highlighted below:

Labelling
A project regarding updating the labelling of products containing bubivacaine has been finalized in 2018. The background for the project was, that the Danish Patient Safety Authority had received an increasing number of reports where patients received the local anesthetic bupivacaine injected intravascularly. All companies was asked to include "Do not use intravascularly" on the front of the packages. All seven companies complied.

The Danish Medicines Agency has examined the DKMAnet Package Leaflets portal (www.indlaegsseddel.dk) in order to check if any leaflets are missing as well as the readability. Two ATC-groups have been examined. For the ATC-group V08 and V09 there was 15% missing leaflets/not readable. For the ATC-group N05, A, B, C there was 13% missing leaflets/not readable. All companies concerned was contacted and they all rectified the leaflets.

Testing of radiopharmaceuticals
The analytical control of radiopharmaceuticals in 2018 was triggered by different channels

- complaint from a hospital,
- request from other OMCL´s and
- our in-house testing plan with focus on radiopharmaceuticals, which have not been tested previously.

The outcome of the analytical control was in general that the results comply, but issues were identified to be discussed with the marketing authorization holder. For further details, please refer to the relevant folder in the OMCL database.

A presentation was given at the OMCL meeting in 2018 regarding the control of radiopharmaceuticals and the findings at the Danish OMCL in the years 2010-2017. Many of the control projects have been performed in cooperation with other OMCL´s either where the batches from the OMCL´s were sent to Denmark or test reports from the Danish batches were sent to other OMCL´s. An example of a CAP test of the radiopharmaceutical Quadramet in 2017 was presented. The timeline for the planning and testing was described together with special arrangements for the testing of Quadramet (Sm-153). General challenges for testing radiopharmaceuticals was also given.

In a sub-group of group 14 a document concerning validation of radiopharmaceutical methods was finalized. The document was merged with the style guide to a new guide for elaboration of monographs on radiopharmaceutical preparations and published in the 2018 edition.

The collaboration with the Chinese Authority, National Institutes for Food and Drug Control (NIFDC) started in earnest in 2018 and interchange of information, face-to-face meetings and the inter-laboratory comparison test will continue in 2019.

B.1.2 Legal Supply Chain (suspected samples)

The Danish Medicines Agency did not carry out any analysis on counterfeit medicines during 2018.

B.1.3 Illegal Supply Chain

The laboratory continues to analyze products suspected of containing undeclared APIs. These samples are primarily obtained from customs services. In 2018, 23 such products were analyzed using LC-MS. Four products were screened for potency-enhancing compounds, two of which were found to contain sildenafil and one product both sildenafil and tadalafil. 17 products were screened for weight-loss compounds, 14 of which were found to contain compounds associated with weight-loss such as sibutramine and phenolphthalein (bisacodyl and hydroxyzine were also found). Two products were screened for pain-relief compounds and found to contain tramadol.

In 2018, the laboratory collaborated with The Danish Veterinary and Food Administration in a project to screen for undeclared weight-loss and potency-enhancing compounds in dietary supplements. The products were sampled by the Danish Veterinary and Food Administration and the analysis was

carried out by the Danish Medicines Agency. In total, seven products were analyzed. None of the products were found to contain weight-loss or potency-enhancing compounds.

Total number of suspected counterfeit samples	a	0
Total number of confirmed counterfeit cases of licensed medicines in the legal supply chain	b	0
Total number of suspected illegal samples tested	g	30
Total number of illegal samples identified (other than counterfeit samples)	c+d+e+f	c+3084

B. 2 Activities related to the Network

In 2018, certain types of nitrosamines (N nitrosodiethylamine (NDEA) and N-nitrosodimethylamine (NDMA)) were detected in a number of active substances used in the treatment of hypertension and in related medicines. Nitrosamines are known as possible carcinogens for humans: only very low amounts are acceptable according to current regulatory requirements (ICH M7 "cohort of concern"). Their detection requires highly sensitive analytical methods.
The EDQM coordinated the activities of the Official Medicines Control Laboratories (OMCLs) Network in Europe to ensure that methods were available to control these impurities and the Danish OMCL participated in this work.

CAP program

The Danish OMCL participated in the following collaborative studies in the 2018 CAP program:

- CAP2018/18 Imrestor 5,5 mg/ml, solution for injection
- CAP2018/21 Kadcyla 100 mg, Powder for concentrate for solution for infusion
- CAP2018/33 Plegridy 125 µg, Solution for injection
- CAP2018/40 Repatha 140 mg, solution for injection

Other collaborative studies

The biological group participated in the collaborative Study BSP144 Phase 3, Assesment of methods for determination of glycan composition of erytropoitin. The work has improved our experience with analysis of N-glycans in biological medicines by HPAEC-PAD.

Proficiency Testing Studies (PTS)

For the purpose of quality assurance, the following PTS-samples were analyzed:

PTS 187: Volumetric titration (visual and potentiometric end-point)
PTS 188: Liquid chromatography, assay (Ph. Eur. 2.2.29, RP-C18, UV detection, tablets)
PTS 189: UV-Vis spectrophotometry (Ph. Eur. 2.2.25)

The requirement for proficiency testing within the field of radiopharmaceuticals has not been fulfilled this year in the traditional PTS program from EDQM. However, as mentioned in the section

regarding *testing of radiopharmaceuticals*, the cooperation with the National Institute of Radiation Protection, under the Danish Health Authority verify the calibration of selected equipment and gives an added quality control of the method performance in the laboratory.

Contribution to the European Pharmacopoeia

The Danish OMCL delegates to the Ph. Eur. Commission were Anders Uhrenholt Vestergaard, Birthe Moesgaard and Lone Stengelshøj Olsen.

Members of our staff participating in the Groups of Experts were:

No.	*Group*	*Danish OMCL-participant*
6	Biological Products	vacant
10A	Organic chemistry	Birthe Moesgaard
14	Radiopharmaceuticals	Inge Overby Jensen
15	Vaccines	Erik Østergaard
15 V	Vet. Vaccines	Peer Lyng Frandsen
P4Bio	P4Bio	vacant

The Danish OMCL is an active participant in the work of European Pharmacopeia and values the progress of the 3R principles. A substantial part of the Danish activities concerning development of pharmacopoeial monographs (e.g. “Pharmeuropa” evaluation) takes place in the 4 committees for biology, chemistry, pharmacy and pharmacognosy.

The committees have participants primarily from industry and academia combined with assessors, regulators and laboratory experts from the Danish Medicines Agency. This composition of participants assures that both purely technical as well as legislative aspects of the monograph proposals are addressed. The committees made comments of all four editions of PharmEuropa that were in hearing during 2018.

The Danish Medicines Agency has been working on an official Monograph "Cannabisblomst" (Cannabis flos) with reference to Ph. Eur. tests (e.g. Pesticides, Aflatoxines, Heavy Metals, Microbial Contamination) and to Ph. Eur. General Monographs. Manufacturers and suppliers are expected to comply with the requirements of the new DK monograph if they want to sell their cannabis products to the Danish market. According to the publication, the Danish Cannabis Monograph is based on the Dutch OMC (Dutch Office for Medicinal Cannabis) monograph and the (non-public) EDQM-working-document (PA/PH/Exp. 13B/T (16) 38, August 2016).

B. 3 Method related activities

Nothing new to report.

B.4. Public related activities

See our participation in the Danish TV 2 Station 2's program “the illegal road to beauty”
https://www.facebook.com/laegemiddel/videos/353623095121733/

B.5. Future planning

B.5.1 National

The focus for 2018/2019 will be on gaining competencies for the analysis of biological medicinal products with mass spectrometry. In addition, the OMCL will continue to update the library with reference standards of interest for the LC-MS screening method for identifying undeclared APIs in suspect samples. We will also use the LC-MS technology as part of authenticity testing. In the beginning of 2018, the Danish OMCL has invested in a new GC-MS to support the authenticity testing of legal medicinal products. A screening method for identifying residual solvents will be implemented and used in 2019.

B.5.2 Network

The Laboratory will participate in the heparin testing and future API testing.