LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Danish Health and Medicines Authority / Danish Medicines Agency
Medicines Control and Inspection

Annual Report of activities concerning the

OMCL-cooperation 2016

Chemical, Biological and
Radiopharmaceutical Products

This document is for National Control Authority use only

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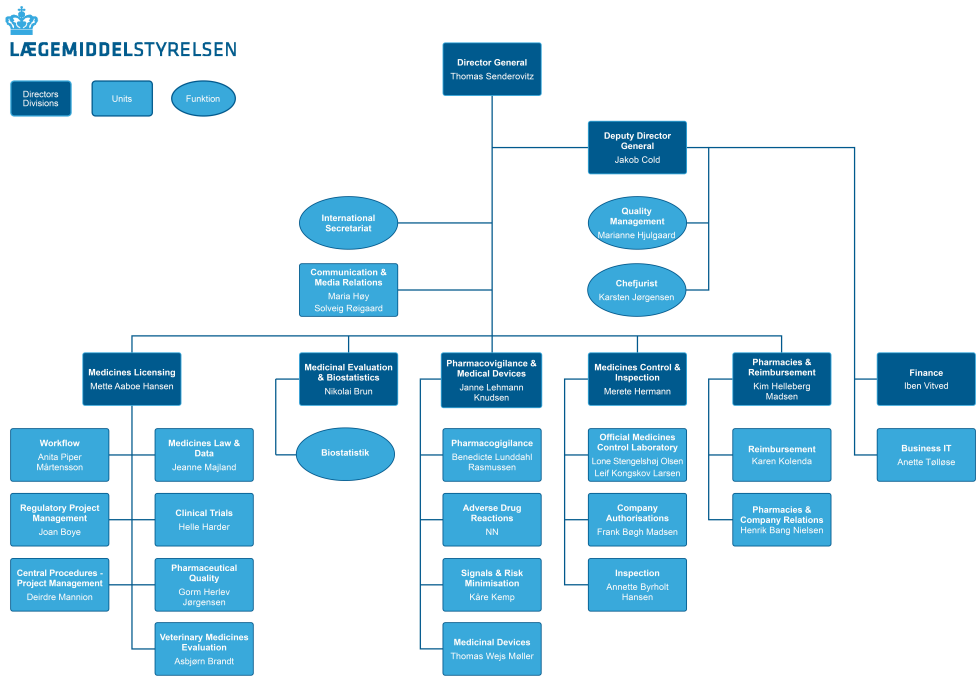
A.1. Organisation of the laboratory

A1.1 General structure.

Danish Medicines Agency



The Danish Medicines Agency has around 400 employees, and the five largest professional groups in our organisation are pharmacists, administrative assistants, physicians, lawyers and masters of social science.

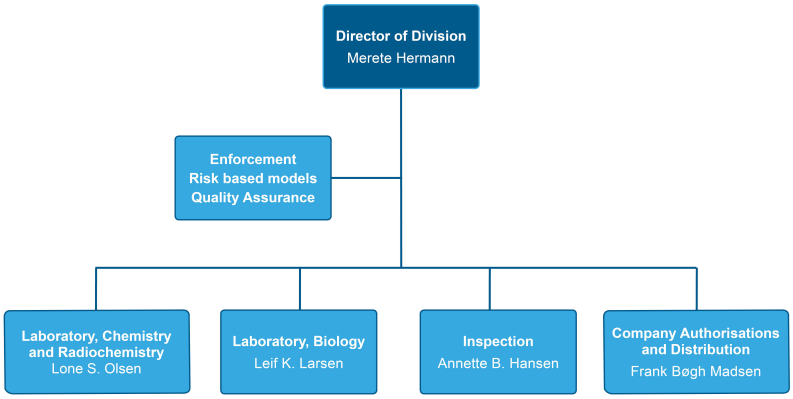
The Danish Medicines Agency

- authorises and inspects pharmaceutical companies and licenses medicinal products on the Danish market
- monitors adverse reactions from medicinal products and authorises clinical trials
- monitors medical devices available in Denmark and supervises adverse incidents involving medical devices
- appoints proprietary pharmacists, organises the pharmacy structure and supervises pharmacies and retailers.

We perform most of our tasks in close collaboration with colleagues from regulatory authorities and organisations 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 withdrawals. The division supervises and is responsible for company authorisations for handling and manufacturing medicinal products and psychoactive substances.

The Control Strategy

Medicines control forms part of the European and other international communities. 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 are putting efforts into establishing a mutual recognition procedure with the USA.

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

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

The Biological and Chemistry & Radiochemistry Laboratories has 31 employees:

Heads of Unit	2
Scientists	15
Laboratory Technicians	11
Assistant/secretary	2
Trainees/students	1

Four scientists from the laboratory has beenworking part time in the PharmaBiotech unit with assessment of the pharmaceutical quality of radiopharmaceuticals, chemical and biological medicines.

A. 2 Quality Management System

Since 1995, the Laboratory has been accreditated 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 latest renewed in April 2014.

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 authorised 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 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”. An audit team successfully audited the Danish OMCL in June 2015 consisting of a Mutual Joint Audit (MJA) team and DANAK.

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 266 medicinal products and API were tested. A significant number of the products tested (70 %) led to additional enquiries with the marketing authorisation holder or manufacturer concerning labelling, SOPs, as well as specifications and stability issues.

Some of the projects are highlighted below:

HPV-containing vaccines were analyzed with the "Shake test" method recommended by WHO, to reveal whether the vaccines had been damaged due to freezing during storage and transportation. No vaccines were identified as damaged using this method.

Testing of radiopharmaceuticals in Denmark.

We still see an increase in use of radiopharmaceuticals in Denmark, especially regarding positron emitting radionuclides, such as F-18 and Ga-68. The first Ga-68 kit for radiopharmaceutical preparation was marketed in Denmark in 2016.

In 2016 our analytical control of Radiopharmaceuticals has focused on

- selected follow-up controls
- compliance with the current monograph for the finished product in the European Pharmacopeia
- control of ROTOP products in collaboration with the German OMCL_BBB.

The outcome of one of the tests resulted among others in a request for revision of the European monograph on 'Technetium (Tc-99m) mebrofenin injection'. Now, the work is ongoing in the Group 14 'Radioactive compounds'.

For another product, a variation is in process now with regard to discussion of methods and with focus on compliance with the current monograph for the finished product.

As always, further details regarding our control and the outcomes are available on the EDQM extranet in the folder named Radiopharmaceuticals. Any MRP/DCP control will also be included in the MRP/DCP database in line with other Pharmaceuticals.

In the collaboration with the German OMCL_BBB regarding testing of selected ROTOP products the control of the individual products was shared between the OMCLs, in other words the Danish OMCL has only performed the methods including radioactivity. In the past year, we also got the opportunity to welcome and to introduce a German colleague from OMCL_BBB to our work with testing of Radiopharmaceuticals in relation with a visit to our laboratory in 2016.

Further to this, the laboratory has an ongoing cooperation with the National Institute of Radiation Protection, under the Danish Health Authority. The focus for cooperation is knowledge sharing of equipment for radioactive measurements. Comparisons of test results will give us an extra quality control of our method performance. It will also fulfill the requirement for proficiency testing for selected methods on our accredited method list which always is a challenge in the field

B.1.2 Legal Supply Chain (suspected samples)

The Danish Health and Medicines Authority did not carry out any analysis on counterfeit medicines during 2016.

B.1.3 Illegal Supply Chain.

The laboratory continues to analyse products suspected of containing undeclared APIs. These samples are primarily obtained from customs services. In 2016, 34 such products were analysed using LC-MS. 14 products were screened for potency-enhancing compounds, 10 of which were found to contain sildenafil or a related analogue. One product was found to contain allopurinol. 20 products were screened for weight-loss compounds, 5 of which were found to contain compounds associated with weight-loss such as sibutramine, synephrine and phenolphthalein. The results were reported in the KnowX database.

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	34
Total number of illegal samples identified (other than counterfeit samples)	c+d+e+f	27

B. 2 Activities related to the Network

In 2016, the Danish OMCL participated in the following testing activities

- MSS 048 on tablets with authorised subdivision

  36 samples from the Danish market were tested for subdivision according to the Ph.Eur. monograph 0478 *subdivision of tablets*. The results for 2 out of 36 samples were out of specification. For some of the samples, a special technique was required to divide the tablet into halves or quarters. If such techniques were described in the patient leaflet, these techniques were used for the tests. Some of the samples (mainly uncoated tablets) crumbled more or less under subdivision. As the results are presented in mg, and not as percentage of the mean mass of a whole tablet, one could argue that the results from subdivision only shows if the tablet is divided into two equal parts, but not whether these parts are actually 50 % of the whole tablet.

- Biosimilar project testing Filgrastim/Nivestim

  The Danish OMCL has been part of a feasibility study of biosimilar Filgrastim drug products initiated by expert group 6 and EDQM. We conducted Potency Cell-based assay and Quantity of G-CSF, HMW species by SE-HPLC, and impurities with molecular masses differing from that of filgrastim by SDS-PAGE. The results are outlined in document PA/PH/CAP (16) 143.

CAP program

The Biological Laboratory participated in the following collaborative studies in the 2016 CAP program:
CAP2016/05 Avastin
CAP2016/19 Fasturtec

Other collaborative studies

The Biological laboratory participated in the collaborative Study CS515 Tetanus Immunoglobulin

Proficiency Testing Studies (PTS)

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

PTS163: Low-molecular-mass heparins chromogenic assay
PTS 165 - Volumetric Titration (visual and potentiometric end-point)
PTS 166: Loss on Drying (Ph. Eur. 2.2.32, method d, antibiotic sample)
PTS167 - Semi-micro Determination of Water (Ph. Eur. 2.5.12, antibiotic sample)
PTS 168: Liquid Chromatography, Assay (Ph. Eur. 2.2.29, RP-C18, UV detection)
PTS169: UV-Vis Spectrophotometry (Ph. Eur. 2.2.25)
PTS172: Anti-D antibodies in human immunoglobulin

The requirement for proficiency testing within the field of radiopharmaceuticals has not been fulfilled this year.

Contribution to the European Pharmacopoeia

The Danish OMCL delegates to the Ph. Eur. Commission was Erik Wolthers and Lone Stengelshøj Olsen.

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

No.	*Group*	*Danish OMCL-participant*
6	Biological Products	Eva Rauhe Bækdahl
10A	Organic chemistry	Birthe Moesgaard
14	Radiopharmaceuticals	Inge Overby Jensen

15	Vaccines	Erik Østergaard
15 V	Vet. Vaccines	Peer Lyng Frandsen
P4Bio	P4Bio	Leif Kongskov Larsen

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 three committees for 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.

Highligths "Chemistry": Continued difficult discussion about the interpretation of the ICH Q3D guideline for elemental impurities. Harmonisation of chromatographic methods with USP. Handling of new monographs for "Finished Products", where the first has been included in the European Pharmacopoeia and a dozen others are a long way through the pipeline.

A special situation where legislation and chemical analysis have to define a new relationship has arisen regarding the handling of impurities in antibiotics produced by fermentation. Most of those substances are known as safe drugs through many years, but continued improvements in sensitivity and selectivity in chemical methods are demonstrating a large number of "new" impurities – which we need to decide how to deal with.

Highlights "*Pharmacy":* The group receives direct input from EDQM´s expert group for Pharmaceutical Dosage forms, where a very big workload has been taken up in aligning the historically different and sometimes contradictory definitions and terms. Legislative and analytical aspects of Uniformity of Dosage Units. Co-processed excipients have presented an unexpected challenge, because lack of stringent definitions seems to us to represent a risk for ill defined legislation. We have taken this discussion on to EMA´s Quality Working Party.

Highlights *Pharmacognsy:* Legislative and analytical aspects of the monograph for Extracts. Interesting proposal for alternatives to the *assay* determination in traditional Chinese medicine. Some parties see the cost/benefit relation as it is now as completely untenable.

The expected opening of a trial period of legal medicinal use of some cannabis products has given discussion of available European monographs for such products.

Work has begun on the creation of a committee for dealing with Biologicals and biologically derived medicinal substances. Such substances take a key role in developing therapies and offer new and different challenges compared to the "classic" chemical substances because they represent a much higher degree of complexity.

Highlights from the Danish contribution in the different expert groups:

In Group 10A: We have handled two requests for revision of the monograph for carbidopa – redetermination/confirmation of the correction factors for two impurities. We have also developed and validaded a new analytical (HPLC) method for the test for related substances to be implemented in the monograph for chlorpropamide. Examination of the possibility to replace the existing assay method (titration by use of color indicator) by a new assay method (potentiometric titration) in the monograph for chlorpropamide - i.e. development and validation of a potentiometric titration method. Finally, we have contributed with information concerning the production of medicinal products to the Danish market in relation to planning of the future work with the European pharmacopoeia monographs.

The Group 14 has finished the monograph for Sodium pertechnetate (Tc-99m) (accelerator-produced) injection. The monograph cover a new production method for Sodium pertechnetate (Tc-99m) injection, which can be important in case of a future shortage of Mo-99/Tc-99m. A new monograph on the work program is a Ga-68 labelled ligand, which is able to bind PSMA (Prostate specific membrane antigene), the preparation is used for diagnosis of prostate cancer.
The group has also started work on a document regarding special validation issues for radioactive tests and methods, in order to have a more harmonized view on the requirements for validation.

B. 3 Method related activities

Development of alternative methods to detect extraneous agents

Although not many activities have been performed in 2016, the Danish OMCL is still part of the project group to work on development of alternative methods for extraneous agents (EA) testing of veterinary vaccines. The goal is to be able replace animal testing and to meet the 3R-requirements (reduce, re-fine and replace). To achieve this, the Danish OMCL has developed real-time PCR assays for detection of extraneous viral DNA in veterinary vaccines. Furthermore, the results of the ongoing collaboration with the National Institute for Health Data and Disease Control (SSI), in order to develop a microarray protocol for screening of extraneous viral DNA in veterinary vaccines have been submitted for publication in a scientific paper.
The Danish OMCL furthermore continues the collaboration with the Paul Ehrlich Institute (PEI) to compare PCR methods and cell-based assays for the detection of extraneous agents in veterinary vaccines.

B.4. Public related activities

No activities to be reported this year.

B.5. Future planning

B.5.1 National

The Laboratory will continue to update the library with reference standards of interest for the LC-MS screening method for identifying undeclared APIs in suspect samples. The focus for 2017 will be NSAID.

Due to a major update of the act “Dansk Lægemiddelstandard” which regulates the terms for pharmaceutical preparations, a control project will be defined in 2017 to see if the new terms have been fulfilled.

B.5.2 Network

The Laboratory will coordinate an API sampling for the API working group for testing with the Danish inspectors. The Laboratory will also contribute to the testing of the API.