Sundhedsstyrelsen
Danish Health and Medicines Authority

Danish Health and Medicines Authority

Medicines Control and Inspection

Annual Report of activities concerning the

OMCL-cooperation 2014

Chemical, Biological and Radiopharmaceutical Products

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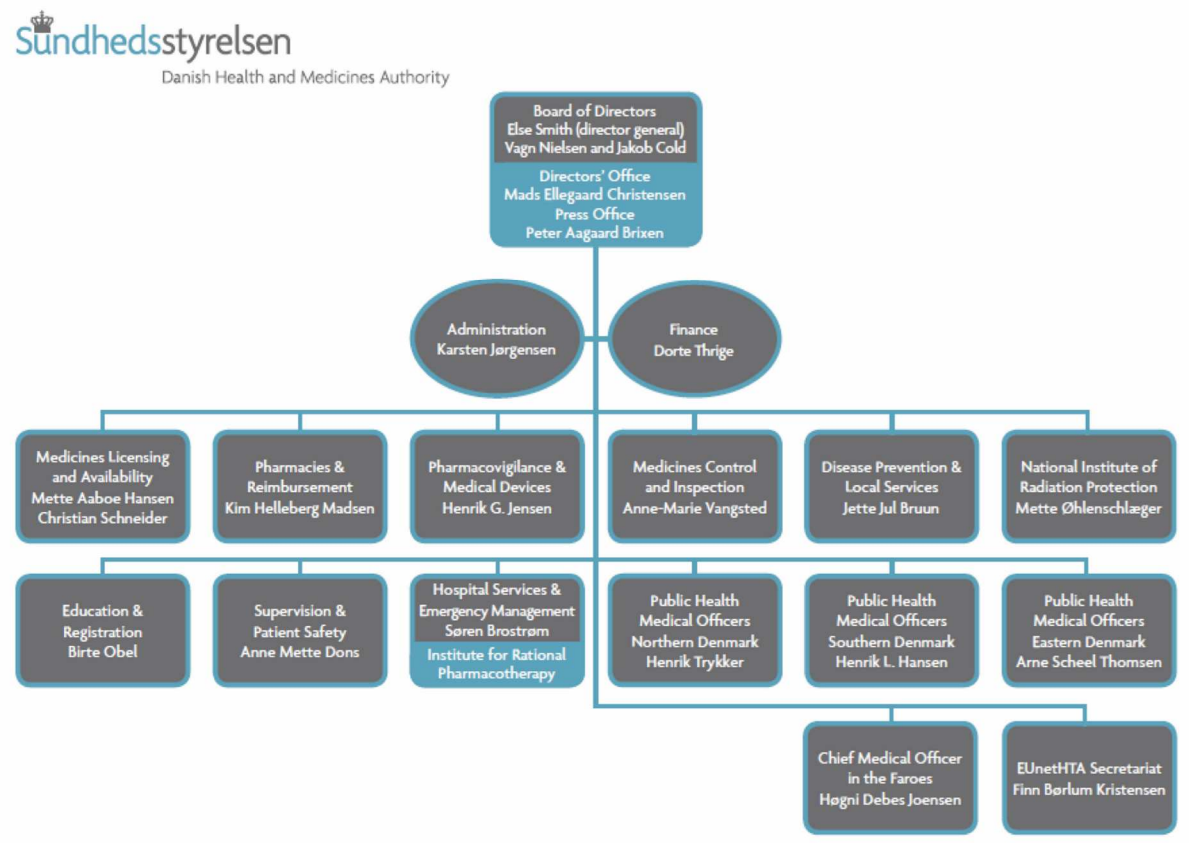
A.1. Organisation of the laboratory

A1.1 General structure.

Danish Health and Medicines Authority



On September 2014, Vagn Nielsen resigned from the position as Director. Anne-Marie Vangsted was in a period acting head of another division than Medicines Control and Inspections and Merete Hermann was appointed head of division in her place. Later on, in February 2015 Anne-Marie Vangsted was appointed as Director for the DHMA's supervision. Eva Sandberg resigned from her position as head of the biological department 31. December 2014.

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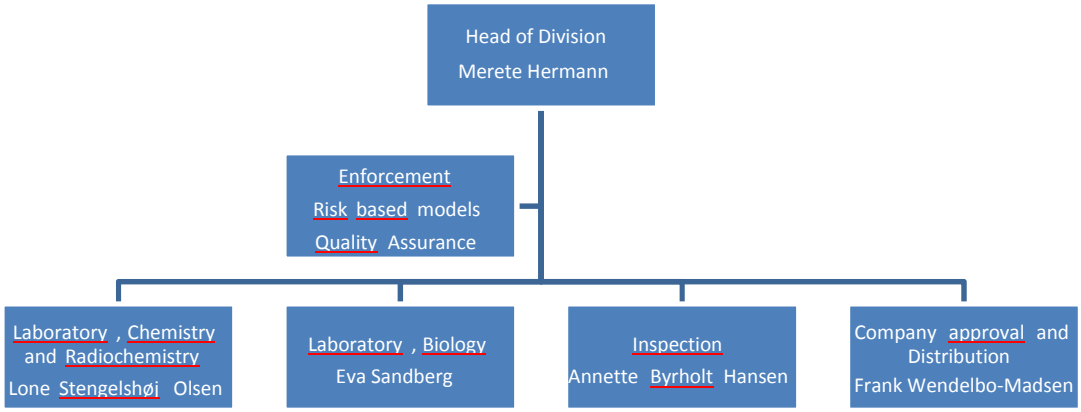
Medicines Control and Inspection



In addition to OMCL activities, the laboratory also 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: 2 heads of department, 14 academic employees and 15 technical employees.

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 inspection programme. In 2006, the accreditation included a flexible scope accreditation. The latest accreditation of the Laboratory was 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 MJA attestation on February 2011. The specified field of activity for the Laboratory is "Testing of pharmaceutical products and API (biological, chemical and radiopharmaceutical), participation in the elaboration of standards and reference materials of Ph. Eur". The Danish OMCL will be audited by a joint audit team in June 2015 consisting of a MJA audit team and DANAK.

The Danish Health and Medicines authority was subject of a BEMA in May 2014. The conclusion from the audit team was, "the agency shows a high level of maturity and is dedicated to continuous improvement, which is managed across all functions relevant to medicines regulation both at national as well as European level".

B.1 Activities related to the national market

B.1.1 Legal Supply Chain (authorised medicines)

In the laboratory, we perform analyses on a range of nationally authorised medicinal products pursuant to the authorised dossier of the marketing authorisation. In general, we perform selected tests, which typically include: appearance, identification of constituents, assay of active ingredient and impurities. Also, the laboratory performed supplementary tests for the specific products or drug substance. These investigations reviewed the labeling, batch protocol and/or specification compliance, without the typical analysis performed in the laboratory.

A total of 253 medicinal products and API were tested. A significant number of the products tested (49 %) led to additional enquiries with the marketing authorisation holder's or manufacturer's concerning labeling, SOP´s, as well as specifications and stability issues.

Control of off-label used medicines

In spring 2014, the Laboratory contributed to the Danish Ministry of Health´s evaluation of medicines used for inducing labor. The prostaglandin misoprostol is currently used off-label to mature the uterus to promote natural birth. The following medicines containing misoprostol were analyzed for dose variation (Uniformity of Content) by HPLC:

- capsules from a hospital pharmacy (pharmaceutical preparation),
- capsules for a clinical trial made at another hospital pharmacy,
- Angusta tablets from the company Azanta Denmark A/S (medicine from India on compassionate use permit),
- Cytotec tablets manufactured by Pfizer (medicine for treating gastric ulcers)

All analyzed batches complied with the dose variation requirements in the European Pharmacopoeia (Ph.Eur). We examined the disintegration time for the capsules

prepared at hospital pharmacies and for the Angusta tablets. All the tested batches complied with Ph.Eur.

The Laboratory has subsequently made a number of recommendations for clarifications and additions to the existing rules for pharmacy preparations of medicines in Denmark. The results project was presented at the annual meeting of control laboratories in Europe in Interlagen Switzerland, May 2015.

The Danish OMCL participated in the MSS Heparin.
After the GMP inspection carried out by the Irish, Danish and French inspectorates in November 2012 on heparin production in China, a Multi Surveillance Study (MSS) were initiated. In the MSS study heparin and low molecular weight heparin products were tested. We tested products from Ireland and France using NMR, SAX-HPLC and other related substances. None of the products tested deviated from standards.

The status for testing of radiopharmaceuticals.
We still see an increasing use of radiopharmaceutical medicines, especially regarding the use of so-called PET (Positron Emission Tomography) radiopharmaceuticals. PET radiopharmaceuticals are a powerful tool and of great value both for early diagnosis of cancer, but also for surveillance of any effect of cancer treatments. Furthermore, new radiopharmaceuticals are regularly licensed, typically according to the MRP/DCP or CAP procedure. We have also seen new marketing authorisation holders entering the market during the last years.

In 2014, the Danish OMCL participated in and gave a presentation at the European Pharmacopoeia Training session on Radiopharmaceutical preparations held by EDQM.

Concerning our analytical control in 2014, we have finally completed the project regarding control of the different types of Technetium Sestamibi kits for radiopharmaceutical preparations, used for myocardial perfusion scintigraphy and scintimammography among others. Another project regarding analytical control of Technetium Mertiatide kits for radiopharmaceutical preparation, used for renal scintigraphy, was also completed.

Other OMCL´s participated in these projects by sending batch for analysis or by receiving the test report on the Danish batch. For all MRP/DCP products the outcome of our control are included in the OMLC MRP/DCP database, but further to this a comprehensive testing plan, status and results are published on the EDQM extranet for each year in a folder named ‘Radiopharmaceuticals’. These reports also include results for control of national licensed radiopharmaceuticals, which in most cases could be considered very similar with the national product licensed in other European

countries. This assumption is based on the historically European coordinated licensed process on radiopharmaceuticals performed in the nineties, a process that could be compared to the current MRP/DCP procedure.

B.1.2 Legal Supply Chain (suspected samples)

The Danish Health and Medicines Authority did not carry out any analysis on counterfeit medicines during 2014.

B.1.3 Illegal Supply Chain.

A total of 50 products with suspected undeclared APIs were analysed in the laboratory. The majority of these products were obtained from customs services. Some products were also received from healthcare personnel. Of the 50 products screened using HPLC:

- 16 of the 28 products screened for weight-loss compounds were found to contain substances such as sibutramine, caffeine and phenolphthalein.
- 5 of the 12 products screened for potency-enhancing compounds were found to contain substances such as sildenafil.
- 8 out of 10 products screened for nicotine tested positive.

We also continue to collaborate with other OMCLs regarding testing of counterfeits and illegal products, in particular the Swedish OMCL, who has assisted us on a number of occasions in identifying and quantifying unknown compounds using both LC-MS and NMR.

B. 2 Activities related to the Network

The Danish OMCL has participated in the following activities:

Testing of Centrally Authorised Products (CAP)

Benefix
Metalyse

Proficiency Testing Studies (PTS)

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

PTS142 **Head Space GC**
PTS147 **Potentiometric Titration** (2.2.20)
PTS149 **Dissolution Test** (2.9.3, immediate release tablets, basket apparatus, UV determination)
PTS150 **Liquid Chromatography, Assay** (2.2.29, RP-C8, UV detection)

The requirement for proficiency testing with in the field of radiopharmaceuticals is always a challenge, but in relation with the analytical control of Technetium Mertiatide, we performed relevant inter-laboratory comparison with the laboratory at ARPANSA in Australia.

Collaborative studies (CRS/BRP)

Hepatitis A vaccine (inactivated, non-adsorbed) BSP 116

Contribution to the European Pharmacopoeia

The Danish OMCL delegates to the Ph. Eur. Commission were Erik Wolthers and Eva Sandberg.

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

No.	*Group*	*Danish OMCL-participant*
6	Biological Products	Eva Sandberg
6B	Blood Products	Eva Sandberg
10A	Organic chemistry	Birthe Moesgaard
10C	Organic chemistry	Anne Kjølby
14	Radiopharmaceuticals	Inge Overby Jensen
15	Vaccines	Erik Østergaard
15 V	Vet. Vaccines	Peer Lyng Frandsen
MAT	Monocyte activation test	Eva Sandberg
P4Bio	P4Bio	Eva Sandberg

B. 3 Method related activities

Development of alternative methods to detect extraneous agents (EA):

The Danish OMCL maintain the 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, refine 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 Danish OMCL has an 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. 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.