Sundhedsstyrelsen
Danish Health and Medicines Authority

Danish Health and Medicines Authority

Laboratory and Inspection

Annual Report of activities concerning the OMCL-cooperation 2012

Chemical, Biological and Radiopharmaceutical Products

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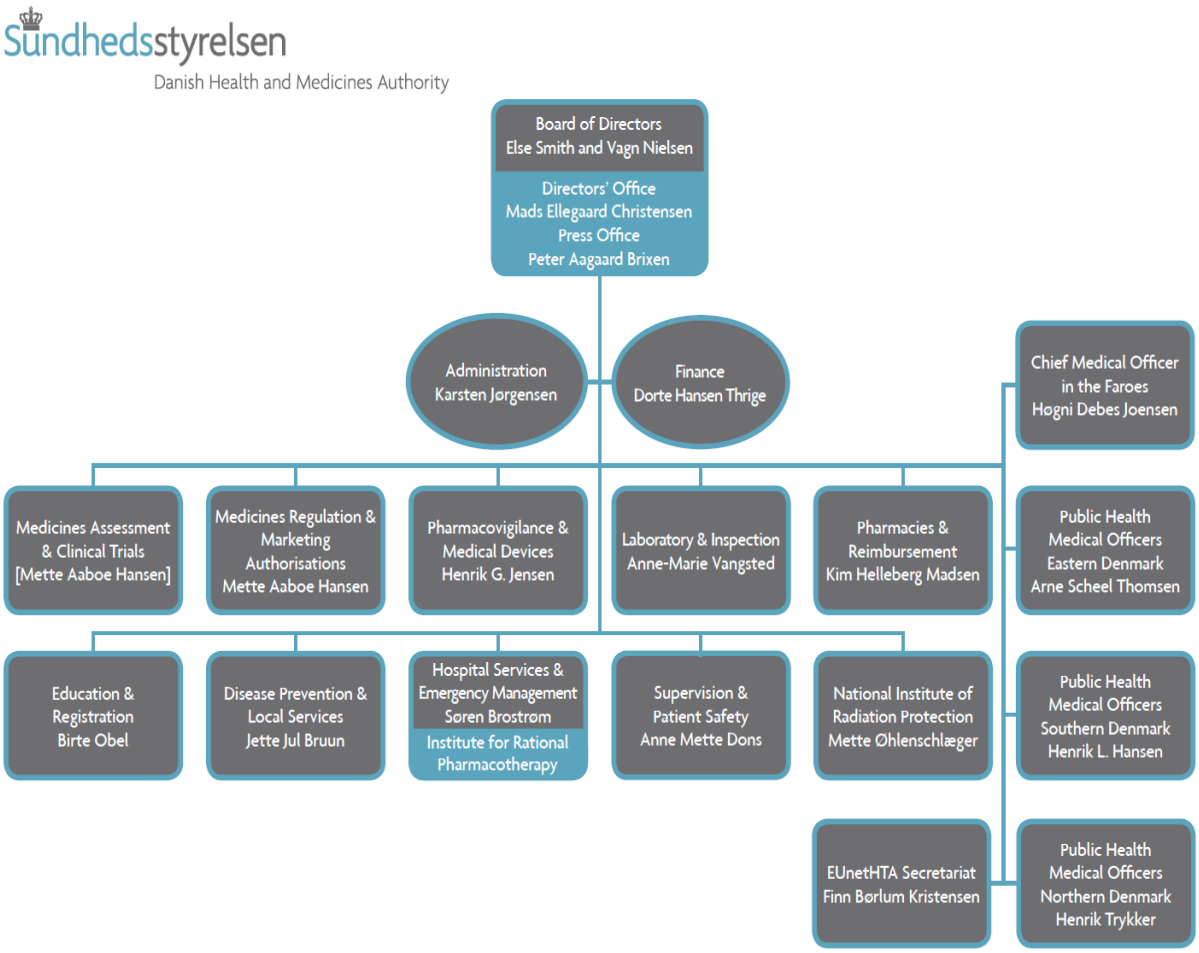
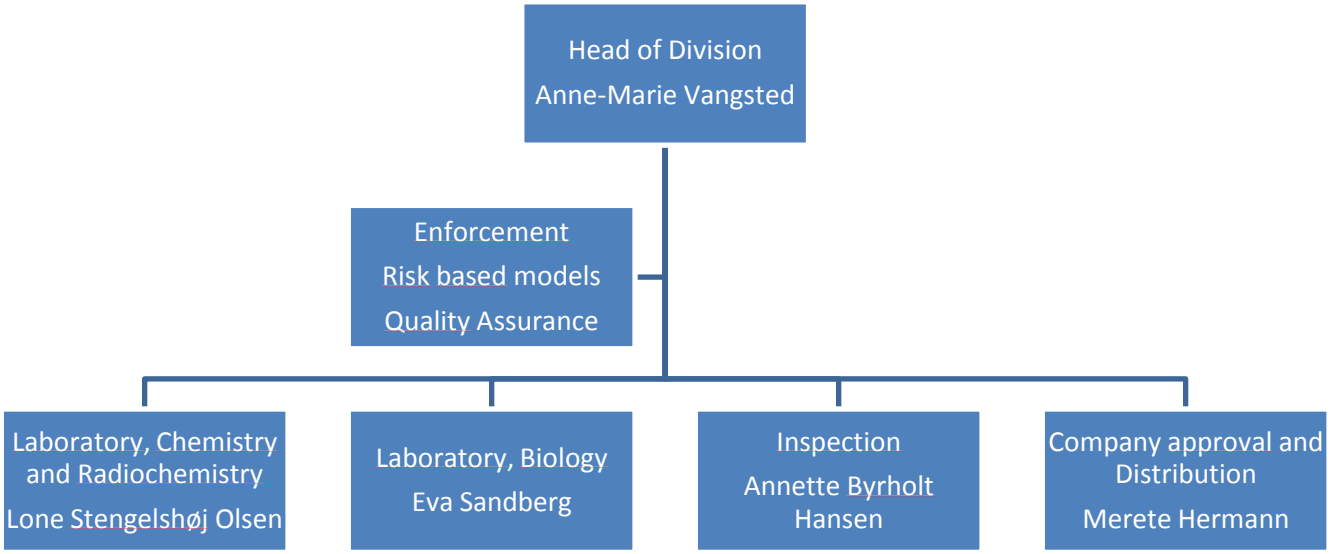
A.1. Organisation of the laboratory

A1.1 General structure.

Danish Health and Medicines Authority



Laboratory and Inspection



On 1 March 2012, the Danish Medicines Agency and the Danish National Board of Health merged, forming a new and larger organisation with around 700 employees, under the name of the Danish Health and Medicines Authority. 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 a total of 35 employees: 2 heads of department, 17 academic employees and 16 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 was expanded to include a flexible scope accreditation. The latest accreditation of the Laboratory was renewed in 2010.

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.

On 15-17 June 2010, the Laboratory was audited as part of the MJA programme and received the MJA attestation on 25 February 2011. The specified field of activity for the Laboratory was stated as: Testing of pharmaceutical products and API (biological, chemical and radiopharmaceutical), participation in the elaboration of standards and reference materials of Ph. Eur.

B.1 Activities related to the national market

B.1.1 Legal market

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 ingedient and impurities. The Laboratory performed supplementary tests where it was viewed to be relevant for the specific product or drug substance. These investigations reviewed the labelling, batch protocol and/or specification compliance, without the typical analysis performed in the Laboratory.

A total of 312 medicinal products and API were tested. A significant number of the products tested (44%) led to additional enquiries with the marketing authorisation holder's or manufacturer's concerning labelling, SOP´s, as well as specifications and stability issues.

Radiopharmaceuticals

The new organization has strengthened the collaborations between the Danish OMCL and the National Institute of Radiation Protection regarding sharing of knowledge and competences within the radioactive field.

The Danish OMCL participated in the radiopharmaceutical part of a Mutual Joint audit of the Hungarian OMCL. The stay in Hungary initiated a revisit to the Danish OMCL where several issues concerning analytical methods and instruments regarding calibration and qualification for radiopharmaceutical testing were discussed. Also, laboratory tests were performed. These interdisciplinary discussions are very much in line with the new monograph 2.2.66 Detection and measurement of radioactivity which is a product from the work in expert group 14 to which the Danish OMCL has contributed major.

In 2012, the analytical controls of different types of In-111 radio-pharmaceuticals were finalized. All products fulfilled the current specifications, however, the specifications needed to be updated for 4 out of 5 products.

Quality control of the labelling and packaging material of medicinal products

In 2012, the Danish Health and Medicines Agency in collaboration with EMA initiated a project controlling the labeling of parallel distributed medicinal products. The Danish OMCL selected 11 products and photographed inner and outer packaging material as well as the patient leaflets. The photos were sent to EMA for evaluation. The Danish OMCL received a report with the results and carried out the follow up discussions with the different MAHs. The outcome of these discussions is a change of the labeling of 7 out of the 11 evaluated products.

The Danish OMCL received a complaint regarding a misleading pictogram. We performed a spot check of 12 different non-prescription medications to see whether the pictograms could be misleading or had advertising characteristics. Only 3 out of 12 products were in compliance with the Danish legislation.

B.1.2 Illegal market

Illegal products and counterfeits

Illegal Products

The majority of the undeclared products suspected to contain APIs, which were analyzed in laboratory, were obtained from the custom services. Other products were received from healthcare workers and private citizens.

In total, 57 products were screened using HPLC and/or LC-MS:

- 15 out of 20 products screened for weight-loss compounds contained substances like sibutramine, BTS 54354, caffeine and/or phenolphthalein
- 4 out of 5 products screened for potency-enhancing compounds contained substances like sildenafil and tadalafil
- 30 out of 31 products screened for nicotine were positive
- 1 product screened for glucocorticoids contained dexamethason-acetat

We continued 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.) 5 products

Proficiency Testing Studies (PTS)

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

PTS 124 Bacteria endotoxins
PTS 129 Loss on drying
PTS131 UV-VIS
PTS 132 TLC

Collaborative studies (CRS/BRP)

CRS 1 Insulin glargine

OMCL Gene Therapy Working Group

We analyzed adeno-associated virus (AAV) by use of ELISA, SDS-PAGE and PCR, and plasmids were analyzed with Capillary Electrophoresis equipment.

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	Lars Husager
6B	Blood Products	Eva Sandberg
10 A	Organic chemistry	Birthe Moesgaard
10 C	Organic chemistry	Anne Kjølby
14	Radiopharmaceuticals	Inge Overby Jensen
15	Vaccines	Erik Østergaard
15 V	Vet. Vaccines	Peer Lyng Frandsen
CRP	Production and compounding of radiopharmaceutical preparations	Knud Ryhl Bjørnson
MAT	Monocyte activation test	Eva Sandberg
P4Bio	P4Bio	Eva Sandberg
ST	Standard Terms	Jacqueline Wissing

B. 3 Method related activities

Development of alternative methods to detect extraneous agents:

The Danish Medicines Agency continue to be active in the development of alternative methods for testing, in order to replace animal testing, and to fulfill the 3R-requirements (reduce, refine and replace). In this respect, the Danish OMCL has both developed real-time PCR assays for detection of viral nucleic acids, with the aim of screening vaccines for absence of extraneous agents (EA), and initiated collaboration with the National Institute for Health Data and Disease Control (SSI), in order to develop a DNA microarray protocol for detection of EA in veterinary vaccines.

Detection of extraneous agents in veterinary virus vaccines by real-time PCR.

Real-time PCR testing for EA has several advantages compared to the traditional methods like animal testing and testing in cell culture: real-time PCR assays are cheaper, faster (results within one day), and more ethical to perform compared to animal testing.

The development of new real-time PCR methods is an ongoing project at the Danish OMCL. The current focus of the project is on detection of EA in avian viral vaccines.

In 2011 collaboration between the Danish OMCL and the Poul Ehrlich Institute (PEI) was initiated. The objective of this collaboration is to share technical expertise and experience by the exchange of materials and methodologies. In addition the aim of the collaboration is to discuss minimum requirements, for example on the sensitivity and specificity of the PCR method. In the future these minimum requirements would allow Competent Authorities to assess and accept variation procedures dealing with PCR as an alternative EA testing method.

In one specific project in 2012 the sensitivity of conventional PCR method for detection of Infectious Bursal Disease virus (IBDV) used at PEI was compared to the real-time PCR method developed at the Danish OMCL. The sensitivity of the PCR methods was also compared to virus titration on cells performed at the Danish OMCL. IBDV vaccine samples and Marek's disease vaccine spiked with IBDV were send to PEI blinded.
The comparison of the two PCR methods for detection of IBDV showed that the real-time PCR method is around 10.000 times more sensitive than the conventional PCR method and 100 times more sensitive than virus titration on cells. Results from the real-time PCR performed on Marek's disease virus vaccine spiked with IBDV were inconclusive. Repetition of the study is planned for the future.

In 2012 development of a real-time PCR method for the detection of egg drop syndrome virus (EDSV) was initiated. This work will continue in 2013 and this method will be compared to PCR and EA test on cells in cooperation with PEI.

Microarray for detection of extraneous agents in veterinary vaccines

DNA microarray testing has emerged as a promising new technology for broad-spectrum virus detection, making it possible to test for the presence of thousands of viruses simultaneously.
Recently, microarray was used as a tool to identify adventitious virus in live-attenuated viral vaccines and a benign pig virus was identified in a rotavirus vaccine (Victoria JG, et al. (2010) J Virol 84: 6033-6040).

SSI has established a diagnostic platform for random amplification and subsequent microarray identification of viral pathogens in clinical samples. This platform will be the basis for the development of the microarray method to detect extraneous agents present in medicinal products.

B.4 Public relation activities

B.5 Future planning

B. 5.1 National

Future focus of the Laboratory

The laboratory at the Danish Health & Medicines Authority has planned to strengthen its expertise in the field of counterfeit medicines and illegal products. The laboratory therefore plans to invest in a new accurate-mass LC-MS, which will enable the identification of unknown compounds.

To further strengthen the existing and future laboratory services the Danish OMCL has planned to invest in an NMR system. The combination of analytical techniques by accurate-mass LC-MS and NMR will be a powerful tool in the identification of impurities and unknown compounds.