Sundhedsstyrelsen
Danish Health and Medicines Authority

Danish Health and Medicines Authority

Medicines Control and Inspection

Annual Report of activities concerning the OMCL-cooperation 2013

Chemical, Biological and Radiopharmaceutical Products

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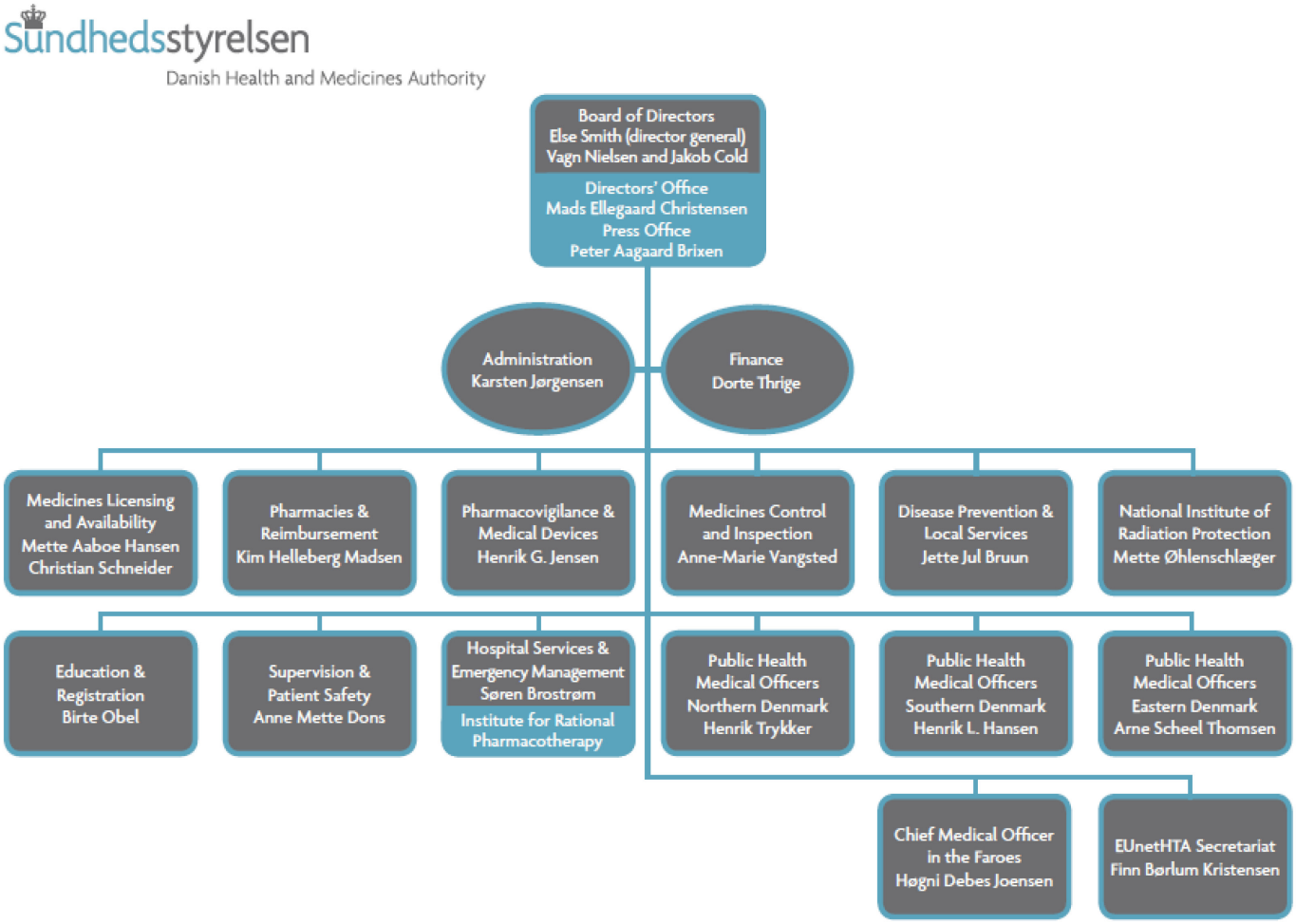
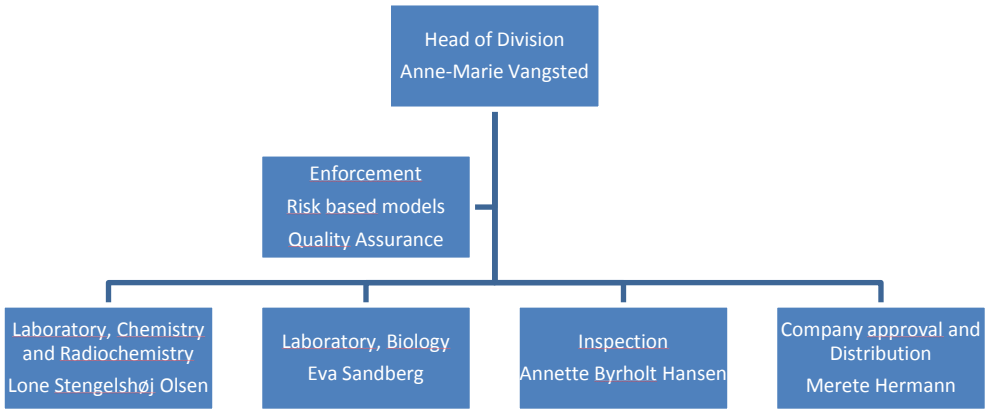
A.1. Organisation of the laboratory

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 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 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 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. The Laboratory performed supplementary tests where it was viewed to be relevant for the specific product 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 251 medicinal products and API were tested. A significant number of the products tested (25%) led to additional enquiries with the marketing authorisation holder's or manufacturer's concerning labeling, SOP´s, as well as specifications and stability issues.

An*alysis of medicine used in a clinical study in collaboration with the GCP inspectors*

During a clinical phase 4 study involving tablets containing the active ingredients oxycodone in combination with naloxone, the company responsible for the study (sponsor) received several complaints from patients. The complaints concerned mix-ups with tablets in the blister pockets. In one case two patients discovered that there were two pink tablets in the blister package instead of the expected one pink tablet (20/10mg) and one yellow tablet (40/20mg).

A GCP (good clinical practice) inspector from Danish Health and Medicines Authority was informed about the complaints and followed up by investigating the blister packages from one of the patients. The inspector suspected the worst case scenario that the tablets which were supposed to contain oxycodone, a narcotic substance in combination with naloxone had been replaced with a placebo.

The laboratory was contacted by the GCP inspector. Since there was doubt as to the content and the strength of certain tablets, the inspectors wanted the content of the tablets to be identified.

By using Raman, IR spectroscopy and HPLC analysis the Danish OMCL identified the content of the tablets as oxycodone and naloxone in the strength 20/10mg which is half the amount of what the tablets should have contained.

It was concluded that a packaging mistake was the cause to the mix up of tablets in this clinical study.

Orodispersable tablets contra lyophilisate tablets

The Danish OMCL has received several complaints on orodispersible and lyophilisate tablets where the patients experienced varying effects, when using tablets from different suppliers. In Danish pharmacies the patient is given the cheapest medicinal product on the market at a given time. Therefore if a patient uses longtime medication they can receive the same products from different suppliers, providing the products has the same active ingredient and formulation type.

The Laboratory´s investigation showed that tablets had different pharmaceutical properties such as different disintegration times. The Danish standard term did not differentiate between orodispersible and lyophilisate tablets. When analyzing the products due to the European Pharmacopeia it was not obvious which disintegration testing method to use. The results of the investigation were that the two formulation types now have individual Danish standard terms. It is still possible to interchangeable between these products at the pharmacies. There have been no changes to the limit for disintegration in the European Pharmacopeia. The difference in the experience of the two types of formulation is that the lyophilisate tablets immediately dissolve when it is in contact with the saliva in the mouth while the orodispersible tablet dissolves within 3 min.

During this project we analyzed several tablets of both formulation types, and nearly all of them followed the limits to disintegration in the European Pharmacopeia. A couple of parallel imported lyophilisate tablets showed OOS results,

probably due to perforation of the blisters during the repacking/ relabeling procedure.

Olanzapine project:

In relation to the commencement of a new monograph for olanzapine January 2012, the laboratory initiated September 2012 a project in order to test if the quality of samples of olanzapine batches used in the production of medicines released for the Danish marked after January 2012 were within the specifications in the monograph. It was controlled if the documentations for the products at the Danish marked were updated in accordance with the monograph. Finally, it was tested if the marketing authorization holders (MAH's) were able to within a reasonable timescale to provide the documentation for traceability from the batches of the raw material (olanzapine) to those of the finished products and reverse. This is of major importance in cases of withdrawals of a medicine product from the marked.

Six MRP/DCP approved medicines products with Denmark as reference country were chosen for the project. The project was announced at the OMCL MRP/DCP database in order to receive test samples from other OMCL countries. However, no olanzapine samples were received from other OMCL countries for the testing. Only three batches of the 6 medicines products in the project had been released for the Danish marked later than January 2012. Of these three, two of the samples were tested to be within the specifications while one sample was out of specification with respect to the level of unspecified impurities. In general, the documentation was not updated in relation to the new monograph. It was, in general, a slowly and troublesome process for the MAH's to provide the documentation for traceability between batches of olanzapine and the finished product batches released for the Danish marked. One of the MAH's gave up providing the relevant documentation. Hence this case was handed over to the German authority who has promised to include the item in their next GMP-inspection of the MAH in 2014.

B.1.2 Legal Supply Chain (suspected samples)

Counterfeits

The Danish Health and Medicines Authority did not carry out any analysis on counterfeit medicines during 2013.

B.1.3 Illegal Supply Chain

A total of 54 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 54 products screened using HPLC:

- 34 of the 38 products screened for weight-loss compounds were found to contain substances such as sibutramine, caffeine and phenolphthalein.
- 10 of the 13 products screened for potency-enhancing compounds were found to contain substances such as sildenafil.
- 3 out of 3 products screened for nicotine tested positive.

Seven of the above samples were part of a collaborative project with the Danish Veterinary and Food Administration. Collaboration with the Danish Veterinary and Food Administration is important as many of these products fall under different laws depending on the outcome of any analysis. In this project, the products were selected and sampled by the Danish Veterinary and Food Administration and subsequently analysed by the Danish Health and Medicines Authority. Of the seven products analysed in the laboratory, 2 were found to contain undeclared potency-enhancing compounds.

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) 3 products

Proficiency Testing Studies (PTS)

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

PTS 133 Dissolution
PTS 139 pH
PTS 140 Water: Semi-micro determination
PTS 141 Liquid chromatography- related substances

Collaborative studies (CRS/BRP)

Human coagulation factor VIIa (rDNA) concentrated solution CRS 1
Interferon beta-1a CRS 3

OMCL Gene Therapy Working Group

In 2013 the Danish OMCL continued participating in the OMCL Gene Therapy Working Group. Recombinant virus and plasmids were characterized by ELISA, SDS-PAGE, Capillary Electrophoresis and PCR.

Heparin PCR project

Heparin is extracted porcine intestines and because of the risk of transmitting transmissible spongiform encephalopathies (TSE) it is not acceptable to produce Heparin that originate from ruminant tissues. The Danish OMCL participated in an OMCL study with the goal to test heparin samples collected at a GMP inspection for the presence of ruminant DNA in porcine derived heparin. For this purpose the Danish OMCL used a real time PCR analysis developed at LEO Pharma. The heparin samples were of three types: Three heparin crude sodium samples, six raw heparin sodium samples and one anion-exchange resin sample. The real time PCR analysis showed that whereas the crude and raw heparin sodium samples were negative for ruminant DNA, the resin heparin sample was positive for ruminant DNA. The results were reported to the Irish Medicinal Board that coordinated the OMCL study.

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
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 Poul Ehrlich Institute (PEI) to compare PCR methods for detection of viral DNA. In one project the sensitivity of PCR and virus titration on cells for detection of Egg Drop Syndrome virus was compared. Results both from PEI and the Danish OMCL showed that PCR was superior with regard to sensitivity to detect Egg drop Syndrome virus.

NMR:

Cooperation between the Danish OMCL and the University of Copenhagen (Faculty of Health and Medical Sciences) was established in preparation for a pharmaceutical student to perform the laboratory work for his master thesis "Analysis of coffee based slimming products, suspected to contain illegally added active pharmaceuticals ingredients, using a nuclear magnetic resonance spectroscopy-based multivariate approach". The aim of the project was to investigate the potential of applying nuclear magnetic resonance (NMR) spectroscopy based methods for screening and identification of illegally added substances to coffee based dietary supplements claimed to have a slimming effect. At the Danish OMCL we currently perform the screening of these products by a HPLC method with PDA detection. According to the nature of HPLC methods we are limited by a predefined "window" where we can screene for a selected limited number of active substances. The advantage of NMR spectroscopy is that this method is not limited by "windows". This would make it possible for us to detect/identify substances which have been added and which are outside the "windows" in the HPLC methods.

B.5 Future planning

B. 5.1 National

New LC-MS

In 2013 the Danish Health and Medicines Authority invested in a new accurate-mass LC-MS. We received the instrument in December, a QTOF from Waters (Synapt G2 Si HDMS). We have high expectations for the instrument and, in the first instance, intend to use the LC-MS in our work with illegal medicines, screening for both known and unknown compounds. The LC-MS will also play a part in the analysis of other products in the laboratory such as finished products and APIs.

New Capillary Electrophoresis Apparatus

In 2014 the Danish OMCL has purchased a new Beckman PA800plus capillary electrophoresis apparatus. The new apparatus will be used for national control of medicine and to contribute to the development of capillary electrophoresis methods to the European Pharmacopeia.