Danish Medicines Agency

Medicines Control Division

Annual Report 2011 of the Danish Medicines Agency´s laboratory control activities.

Danish Medicines Agency
Medicines Control Division
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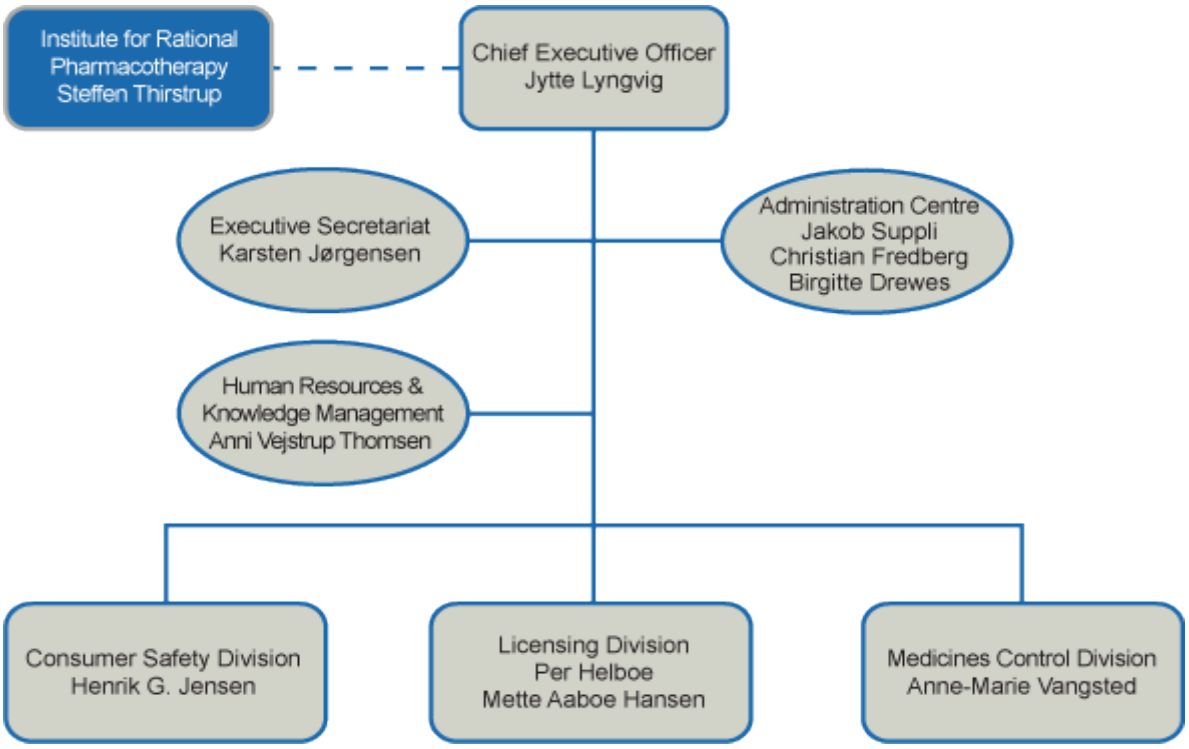
A.1. The Laboratory´s organisational placement in the Danish Medicines Agency

A1.1 Organisation chart of the Danish Medicines Agency and the Medicines Control Division

Danish Medicines Agency



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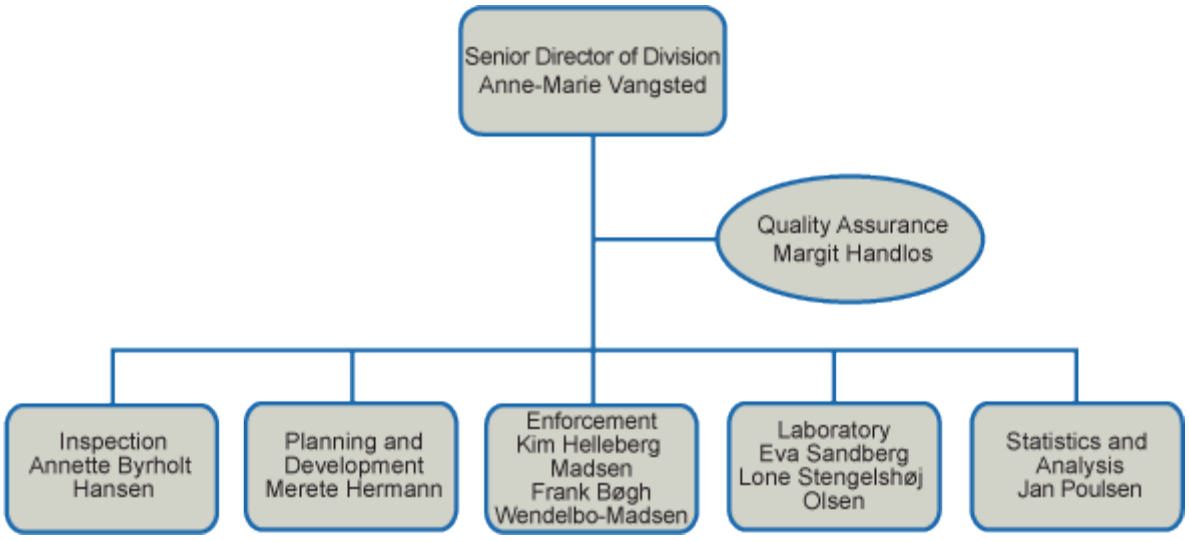

On 1 March 2012, the Danish Medicines Agency and the Danish National Board of Health merged, forming a new and larger organisation with around 700 employees, under the name the Danish Health and Medicines Authority. The new organisational structure is planned to be presented in the next annual report for 2012.

The medicinal authorities in Europe cooperate in a network called the Official Medicines Control Laboratories (OMCL). This report has been prepared to inform the network of the activities of the Danish OMCL.

European laboratory cooperation in OMCL
The purpose of OMCL is to exchange knowledge and experience and to promote the elaboration of new common standards within the area of laboratory control of medicinal products.
In addition to the laboratory control activities, the Laboratory also performs tasks in connection with the elaboration of monographs for the European Pharmacopoeia (Ph. Eur.)

A. 1.2 Staff
The Laboratory has a total of 37 employees: 2 heads of department, 18 academic employees and 17 technical employees.

A. 2 Quality Assurance 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,
- Microbiological,
- 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.

In 2010, we implemented a new electronic quality assurance system for our Standard Operating Procedures (SOP´s) called QualiWare. The equipment module was fully implemented in 2011.

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 ingredients and impurities. However, this year we have increased our focus on pharmaceutical formulations like different forms of tablets 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 461 medicinal products were tested which resulted in the withdrawal of 24 products from the market, due to incorrect labelling and package leaflets. A significant number of the products tested (61%) 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 use of radiopharmaceutical products is still increasing and new radiopharmaceuticals are regularly introduced to the market. There is an ongoing and increasing need for the early and accurate diagnosis of diseases, for cancer treatments, as well as surveillance on the effect of cancer treatments. To meet these therapeutic needs the use of radiopharmaceuticals is an important factor and a strong tool to achieve patient benefits.

In 2011, we continued the analytical control of different Sestamibi products, which are used for the diagnosis of ischaemic heart disease, myocardial infarction and malignancy in patients suspected of breast cancer. The analytical control includes the original product Cardiolite, which is marketed according to national procedure, as well as four generic products marketed according to MRP/DCP procedures. In 2011, we finished the control for one of the generic products named Stamicis. Two OMCLs participated by sending one batch each for control and other OMCLs requested the test report. The results are included in the MRP-database.

We also performed analytical control of different types of In-111 radiopharmaceuticals, in total four of the five products planned for 2011. We also received one batch for control by another OMCL and others have requested a copy of the test reports. At the present time the technical assessments and correspondences with the companies are still ongoing.

Quality control of the labelling and packaging material of medicinal products

In 2011, the Danish Medicines Agency processed several cases concerning specific problems with the labelling and packaging material of medicinal products. Repackaging of parallel imported products is still a major issue, which has resulted in several patient and pharmacy complaints. We also received several complaints regarding the parallel importers' repackaging from the brand leader companies/the original MA-holder.

Other incidents of labelling and packaging material problems are also reported through the Danish Patient Safety Database (www.dpsd.dk), which is a national reporting system that registers the occurrence of adverse events in the entire health care sector. Up until September 2010 the database only recorded incidents from the hospitals. Since then, and the expansion of the health care sector into this system, the number of reports has risen from 35.000 in 2010 to approximately 50.000 in 2011. For 2012 the expected number of reports is 100.000. The Danish Medicines Agency has screened approximately 4000 reports on the medicinal adverse events reported to the Danish Patient Safety Database. From these, 32 reports resulted in control cases regarding the investigation of labelling and packaging material.

In 2011, we finished our control of the database www.indlaegsseddel.dk, which is a web-portal for Danish package leaflets. It is a statutory requirement for the Market Authorisation Holder to upload package leaflets in the database. There are approximately 5,300 different medicines (including different strengths of the same medicine) on the Danish market, and for all of these, we have checked the extent to which:

- a package leaflet is available on indlaegsseddel.dk
- the package leaflet is easy to read (legibility)
- the package leaflet has a revision date.

About 8 % (431) had significant deficiencies in relation to the statutory requirements, which have been rectified in the period 2011.

Antidepressants SSRI (selective serotonin reuptake inhibitors)

In 2011 we performed a specific compliance check to verify if the warnings related to the medicines use, for the treatment of depression (SSRI), had been updated with respect to information related to pregnancy and breast-feeding. 26 of these products were examined and in 21 cases the package leaflet, in the package or/and on the website www.indlaegsseddel.dk, had not been updated. In this investigation 11 companies were reported to the police for non-compliance with the legislation and 17 of these products were recalled from the market.

Prevention of Medication Errors

The Danish Medicines Agency has a duty and responsibility to act on potentially problematic issues and highlight any challenges related to the use of certain medicines in specific situations. Consequently in autumn 2008 we established a working group under the 'Prevention of Medication Errors' network to prepare proposals for defining and listing high-risk medicines. The Danish OMCL participated in this work programme.

The purpose of the work programme was to identify those medicines posing a special risk to patients based on preventable adverse drug events (pADEs). Incorrect use of these particular medicines may have health consequences for the individual patient and potentially result in additional costs for society. Both reporting systems and scientific studies indicate that these specific medi-

cines are involved in adverse events resulting in acute hospitalisation, prolongation of existing hospitalisations or other serious events.

The working group finalised their work in 2011 with the report ”Medicines most frequently involved in serious adverse drug events”. This has resulted in two lists of medicinal products most frequently involved in serious adverse drug events, listed by active substance and medicine group, respectively. The report and the two lists can be found at www. laegemiddelstyrelsen.dk/highalertmedicines.

B.1.2 Illegal market

Illegal products and counterfeits

Illegal Products

There was a continued focus on illegal products at the Danish Medicines Agency throughout 2011, and a total of 88 products were analysed in the Laboratory. The majority of these products were obtained from the custom services, and others products were received from healthcare workers and private citizens.

The 88 products were screened for following compounds/active ingredients:

- 42 for weight-loss compounds
- 24 for potency-enhancing compounds
- 18 for nicotine
- 4 for glucocorticoids.

The samples were analysed using HPLC and/or LC-MS. We also continue to collaborate with other OMCLs, 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.

Weight-loss compounds

Of the 42 samples analysed, 36 were found to contain a weight-loss compound. Examples include sibutramine, caffeine and phenolphthalein.

Potency-enhancing compounds

Of the 24 samples analysed, 16 were found to contain potency-enhancing compounds. Examples include sildenafil and the sildenafil analogue hydroxythiohomosildenafil.

Nicotine

Of the 18 samples analysed, all except one were found to contain nicotine.

Glucocorticoids

Of the four samples analysed, three were found to contain glucocorticoids (betamethasone).

B. 2 Activities within the Network

The Danish OMCL has participated in the following activities:

Testing of Centrally Authorised Products (CAP)

We have tested a total of 25 batches of 5 different products that have been sampled in different EU member states.

Proficiency Testing Studies (PTS)

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

PTS 120 LC-MS
PTS121. Micro Water Determination
PTS 122 Volumetric titration
PTS 124 Endotoxiner

Collaborative studies (CRS/BRP)

BSP107. Hepatitis A Vaccines: new in vitro assay.
BSP108. Collaborative Study for the Establishment of Replacement batches of Somatropin CRS.
BSP090. Establishment of Recombinant Major Allergens Bet v 1 and Phl p 5a as European Pharmacopoeia BRP's and Validation of ELISA Methods for their Measurement

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:

Nr	*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 methododologies. 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 the sensitivity of conventional PCR method for detection of Marek's disease (MDV) used at PEI was compared to the real-time PCR method developed at the Danish OMCL. MDV DNA and vaccine samples were received blinded from PEI. Direct PCR-test on vaccine preparation, without purification of DNA, was shown to be possible. However the sensitivity is around 100 times lower when samples are not extracted for DNA**.**

The comparison of the two PCR methods for detection of Marek's disease showed that the real-time PCR method is around 10 times more sensitive than the conventional PCR method. In addition with real-time PCR we were able to estimate the relative MDV concentration in the samples.

In 2011 egg drop syndrome virus (EDSV) strains was received from the Hungarian OMCL. Development of a real-time PCR method for detection of EDSV has been initiated in 2011.

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).

Statens Serum Institut 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.

Cell therapy products.
During recent years stem cells have been used, for example, for therapy of chronic coronary artery disease. The cells used have either been undifferentiated cells or differentiated to endothelial progenitor cells. The literature is not very consistent with respect to the characterization of culture media used to differentiate stem cells to endothelial progenitor cells: Serum concentration, cell density, growth factors etc. have been reported to influence the differentiation of stem cells. In order to reproduce some of the experiments from the literature we have cultured stem cells under different conditions. We have found that expression of cell surface marker to a high degree varies with the culture conditions, however the effect of VEGF (Vascular endothelial growth factor) which is supposed to trigger the differentiation of stem cells, stimulates under the conditions used only weakly the differentiation of stem cells to endothelial progenitor cells.

Pre-formulation studies on possible interaction between the API and the excipients.
In 2011, a Ph.D-study has been initiated. Pre-formulation studies on possible interaction between the API and the excipients should be performed as part of a drug development process in order to determine if unwanted impurities have arisen from this interaction. If new impurities appear at a concentration level in the range from 0,1-1 % of the parent drug substance (dependent on the daily dose), they have to be identified according to ICH. Traditionally, such interaction studies have consisted of performing accelerated stability testing, which is very time consuming. This Ph. D-project will investigate the possibility to use micro waves to provide rapid chemical reactions and compare with the results obtained in normal stability studies. Advanced analytical techniques will be used to detect the possible impurities, e.g. HPLC-SPE-NMR, LC-MS, and NIR. This specialised study is expected to be completed in 2014

B.4 Future planning

B. 4.1 National

Risk-based planning and conducting of controls
During 2007-2008 the Danish Medicines Agency successfully completed three pilot projects on the topic of risk management. The three fields chosen to be pilot projects were: ‘ranking of MRP products’, ‘risk-based focus on illegal internet drug distribution’ and ‘risk-based focus on clinical trials’. The pilot project focusing on the ranking of MRP-products was initiated as collaboration between several OMCL laboratories.

Since 2008 the Danish Medicines Agency has worked with the framework of a general risk management model, based on experience from the three pilot projects. The implementation of a general risk management model will improve the prioritization and coordination in the control activities at the Danish Medicines Agency. The risk-based model will ensure an ongoing systematic identification and assessment of risks relative to medicinal products and other healthcare products and enable us to measure and follow up on the initiated control activities. The work with implementing the risk management model will continue into 2012 and beyond.

Fingerprint
The priorities for regulatory control of the pharmaceutical market may shift from actual product checks (i.e. analysis of final products on the market) to the focus on the verification of authenticity (origin) of medicines and active pharmaceutical ingredients. Raw material identification, for example, is a critical step in the quality control process that has tremendous impact on customer safety. We will continue to work nationally and internationally in the campaign against counterfeit medicines and advise and collaborate with the pharmaceutical industry and manufacturers of other health products against fraud in the production and distribution chain.

Unlicensed pharmaceutical preparations
In Denmark, we have a production of unlicensed pharmaceutical preparations prepared by pharmacies on a named patient basis, as well as those held in stock. The Danish Medicines Agency have performed controls on labelling, batch testing frequency and the determination of shelf life for several pharmacy prepared medicinal products. The project eliminated many points where the legislation can be improved because the rules were not clear This work is still ongoing

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 is presently equipped with several new HPLCs as well as a triple-quadrupole mass spectrometer. These analytical instruments continue to be used for the target screening of such samples. This targeted screen approach, however, has its limitations as the samples often contain unknown compounds, which may not be detected in this way. The laboratory therefore plans to replace its triple-quadrupole LC-MS with 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 Medicines Agency 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.