Danish Medicines Agency

Medicines Control Division

Annual report 2010 of the Danish Medicines Agency's laboratory control activities

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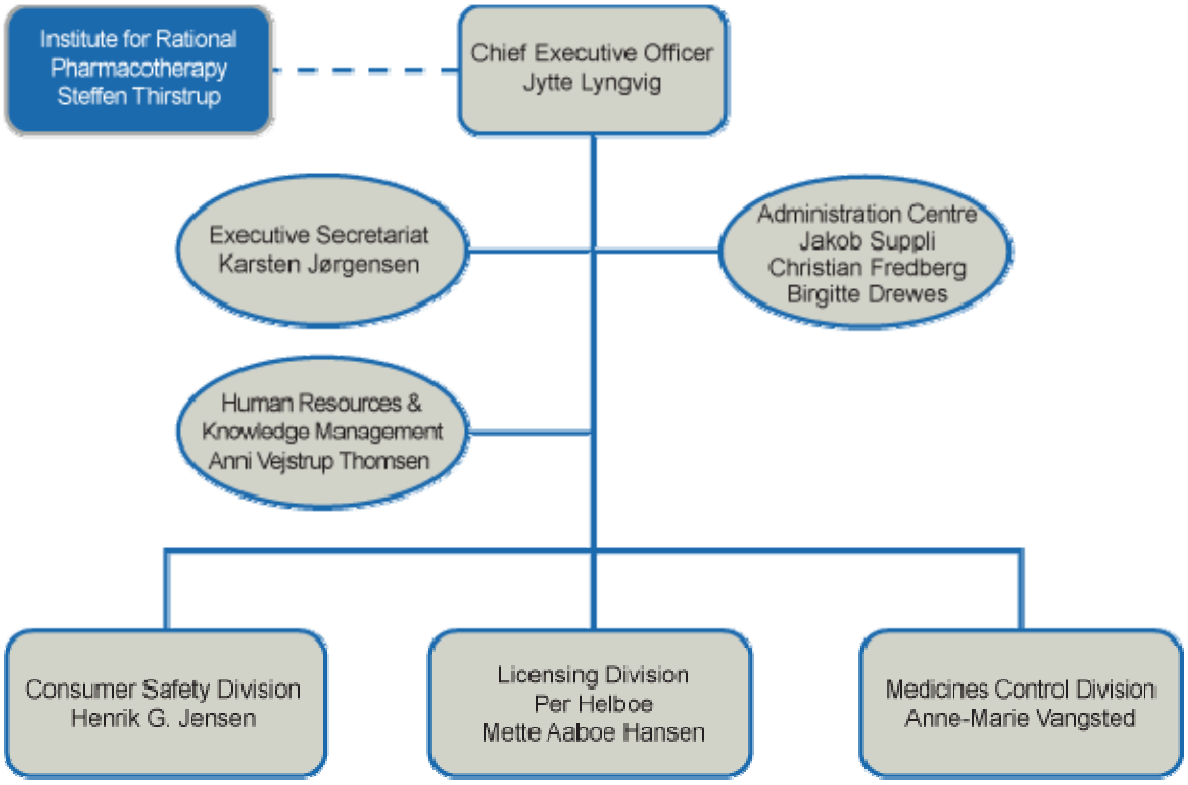
A.1. The Laboratory's organisational placement in the Danish Medicines Agency

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

Danish Medicines Agency



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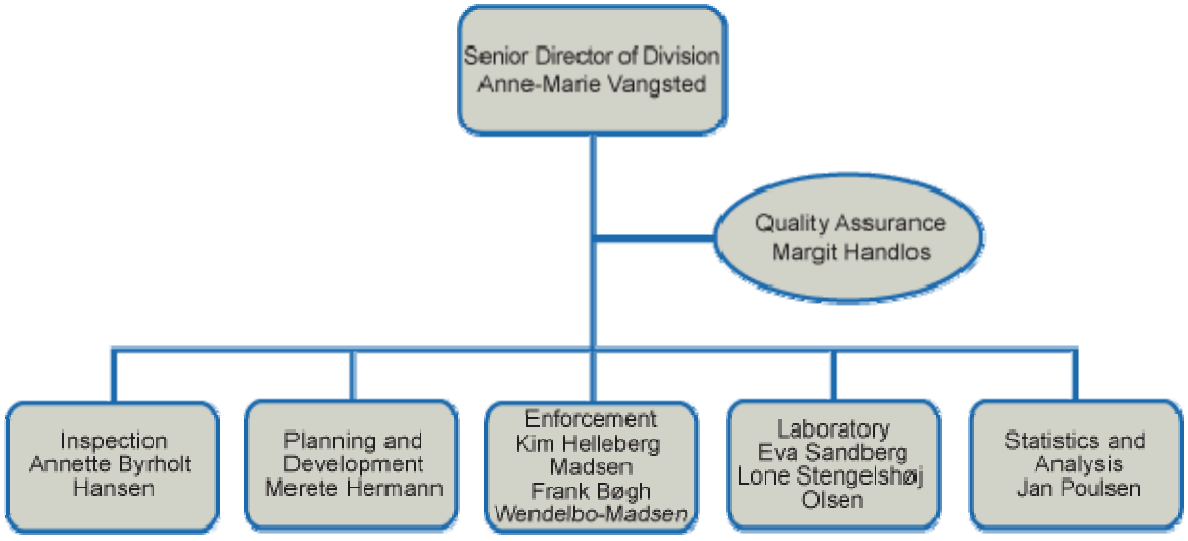

The medical authorities in Europe cooperate in a network called the Official Medicines Control Laboratories (OMCL). This report has been prepared to inform the network of the activities of the Danish OMCL.

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 40 employees: 2 heads of department, 18 academic employees and 20 technical employees.

A. 2 Quality Assurance System
Since 1995, the Laboratory has been accredited according to ISO 17025. In 2006, the accreditation was expanded to include a flexible scope accreditation. The accreditation was renewed in 2010.

The scope of the accreditation is testing of pharmaceutical products and active ingredients and is attached to a specific list of methods mainly from Ph. Eur. and a list of techniques approved by the accreditation body.

Test types:
- Biological, biochemical testing
- Chemical testing, Analytical chemical testing
- Microbiological testing
- Radiochemistry, radiation

Our accreditation body is DANAK.

On 15-17 June 2010, the Laboratory was audited as part of the Mutual Joint Audit (MJA) programme and received the MJA attestation on 25 February 2011. Field of activity: 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 (SOPs) called QualiWare. The equipment module will be fully implemented in 2011.

B.1.1 Legal market
In the Laboratory, we perform tests on nationally authorised medicinal products pursuant to the dossier of the marketing authorisation. In general, we only perform selected tests, which normally include: appearance, identification and assay and tests for impurities. The Laboratory has also performed other tests if we have considered it relevant for the specific product or drug substance.

These checks could involve labelling, batch protocol or specification compliance without analysis performed in the Laboratory.

A total of 545 products were tested in 2010.

The tests resulted in the withdrawal of only two products from the market due to incorrect labelling, but a high share of the tests (73 %) caused us to discuss matters concerning labelling, SOPs as well as specifications and stability issues with the manufacturer.

Radiopharmaceuticals
Projects on testing radiopharmaceuticals containing In-111 and I-131 radionuclides are in progress. The equipment has been calibrated with traceable radionuclide standards from the National Physical Laboratory (NPL). I-131 Sodium Iodide capsules have been tested. The capsule project showed difficulties with transferring a computer method described in the company documentation to the Laboratory. In the capsule project, tests for another OMCL were also performed.

Quality control of the labelling and packaging material of medicinal products
In 2010, the Danish Medicines Agency processed several cases concerning problems with the labelling and packaging material of medicinal products. A variety of problems were identified, including mix-ups between drug names and/or packaging design that look alike and poor legibility of package leaflets. In 2010, we continued to receive complaints regarding repackaging of parallel imported products.

Problems with labelling and packaging material are reported by patients and healthcare professionals to the Danish Patient Safety Database, which is a national reporting system that registers adverse incidents occurring at hospitals. In 2010, the Danish Medicines Agency screened approx. 2,400 reports on adverse incidents that had been reported by hospitals to the Danish Patient Safety Database. 17 of these reports resulted in control cases regarding labelling and packaging material or the quality of the medicinal product.

In 2010, the Danish Medicines Agency also received several complaints regarding the user-friendliness of packaging material, in particular from patients with rheumatism in their hands who experience difficulties handling and opening medicine containers and blister cards.

It should be easy for patients to have access to the latest version of a package leaflet. To this end, the Danish Medicines Agency has developed a web-portal for package leaflets. It is mandatory for marketing authorisation holders to upload package leaflets (Danish: indlægsseddel) to the portal on www.indlaegsseddel.dk. In 2010, we have checked whether the companies have conformed with this requirement. We checked the leaflets of 233 products from 115 companies. We remain to check the package leaflets of 265 products from primarily large companies in 2011.

We generally attempt to build up “work sharing” with other OMCLs.
When selecting products for control, emphasis is put on: Risk-based control and conducting of control of new products which have been marketed within the past few years.

B.1.2 Illegal market

Illegal products and counterfeits

The Danish Medicines Agency maintained focus on illegal products and counterfeits in 2010. A new area of interest this year was electronic cigarettes (or e-cigarettes). In Denmark, e-cigarettes containing nicotine are considered a medicinal product. This means that they must be approved with a marketing authorisation before they may be sold legally on the Danish market. At present, there are no nicotine-containing e-cigarettes with a marketing authorisation in Denmark.

In 2010, a total of 122 samples of illegal products or counterfeits were analysed and screened for either potency-enhancing compounds, weight-loss compounds or nicotine, depending on the sample in question. The majority of these products were seized by custom officers or in police raids.

Of the 122 samples, 64 e-cigarettes were screened for nicotine using a modified Ph. Eur. HPLC method to identify nicotine as well as estimate a semi-quantitative level of nicotine present. A total of 63 samples were found to contain nicotine.

The results showed that online sale of illegal medicines and healthcare products may pose a serious risk to the health of consumers. The products may contain active pharmaceutical ingredients in varying quantities, quality and composition, with no guarantee of their safety and effect.

B. 2 Activities within the OMCL network

The Danish OMCL has participated in the following activities:

Testing of Centrally Authorised Products (CAP)

We have tested a total of 11 batches of three different products that had been sampled in different EU member states.

Proficiency Testing Studies (PTS)

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

PTS107 - Assay by liquid chromatography (LAB/K)
PTS107 - Assay by liquid chromatography (LAB/B)
PTS108 - Dissolution testing
PTS111 - Semi-micro determination of water
PTS112 - Gas chromatography
PTS113 - Potentiometric Determination of pH
PTSRAD002 - Radiochemical purity by planar chromatography

Collaborative studies (CRS/BRP)

Heparin Low-Molecular- Mass (Anti-FXa and Anti-FIIa)
Heparin HPLC
IgG BSP 99 (Fc function)
FVIIa Ph. Eur. monograph (peptid mapping, glucan mapping, SDS-PAGE, HPLC)

Contribution to the European Pharmacopoeia
The Danish OMCL delegates to the Ph. Eur Commission were Erik Wolthers and Eva Sandberg. In 2010, the following staff members participated in Groups of Experts:

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 Bjørnsson
MAT	Monocyte activation test	Eva Sandberg
P4Bio	P4Bio	Eva Sandberg
ST	Standard Terms	Jacqueline Wissing

B. 3 Method-related activities

Development of flow cytometry based potency assay for freeze-dried BCG vaccine
The purpose of the BCG vaccine project was to develop a new method for determination of vaccine potency. The traditional method, involving culturing and count of colony forming units, takes five weeks to complete. The new method that we were trying to develop was based on viability determination using flow cytometry, which should be possible to complete within one day. The project ended in 2010 as we could not find correlation between the two potency tests.

Detection of extraneous agents in veterinary virus vaccines by real-time PCR
The veterinary virus vaccine project involves the development of real-time PCR assays for detection of viral contents, in particular for the purpose of screening the vaccines for the presence of extraneous agents.
Real-time PCR testing for extraneous agents has several advantages over the traditional methods: Assays are very fast to perform (results within one day), and animal testing is avoided, which makes it more ethically justifiable and much cheaper compared to traditional tests. In 2010, the work on development of new real-time PCR methods was continued. The project's current focus is detection of extraneous agents in avian viral vaccines.

Cell therapy products:
The purpose is to obtain knowledge concerning the biology of stem cells, including experience with stem cell relevant assays. Transplantation with autologous stem cells, in some cases differentiated into a more specialised cell type, belongs to future therapeutic possibilities. In order to obtain a sufficient amount of cells, several weeks of in vitro culturing is often necessary before the cells can be reinjected into the patient. During the culturing process, the cells may reach a stage of senescence, where they are no longer mitotic. For this reason, it is necessary to try to establish

limits for the degree of culturing/senescence, within which the cells can still be used for transplantation. The expression of specific cell surface markers helps to describe the composition of the stem cell population with regards to e.g. senescent cells. We are in the process of establishing a method for determining the expression of such cell surface markers. At the same time, we wish to describe the senescence process, based on which we can then establish limits for the amount of senescent cells in the material to be used for transplantation. In 2010, we made small cell banks at various passage levels in order to use standardised cell material for analysing cells with respect to differentiation and senescence markers.

B.4 Future planning

B. 4.1 National

Risk-based planning and performance of control

During 2007-2008, the Danish Medicines Agency successfully completed three pilot projects on the topic of risk management. The three fields chosen as pilot projects were: 'risk model for the ranking of MRP products', 'risk-based focus on illegal distribution on the internet' and 'risk-based focus on clinical trials'. The project 'risk model for the ranking of MRP products' was initiated in collaboration between several OMCL laboratories.

Since 2008, the Danish Medicines Agency has worked with the implementation 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 prioritisation and coordination of the Danish Medicines Agency's control activities. The risk-based model will ensure continuous systematic identification and assessment of risks related to medicinal products and other healthcare products and will enable us to measure and follow up on initiated control activities. The implementation of the risk management model will continue in 2011.

Fingerprint

The need for regulatory control of the pharmaceutical market may change from actual product checks to the need for verifying the authenticity (origin) of medicines and active pharmaceutical ingredients. Raw material identification, for example, is a critical step in the quality control process, which has tremendous impact on customer safety. We will continue to work nationally and internationally in the fight against counterfeit medicines and will advise and collaborate with the pharmaceutical industry and manufacturers of other healthcare products to combat fraud in the production and distribution chain.

Unlicensed pharmaceutical preparations

In Denmark, we have a production of unlicensed pharmaceutical preparations prepared by pharmacies mainly for named individuals, but also for stock holding. The Danish Medicines Agency plans to perform compliance checks of labelling, batch testing frequency and determination of shelf life for several pharmacy-prepared medicinal products.