LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Danish Health and Medicines Authority / Danish Medicines Agency
Medicines Control and Inspection

Annual Report of activities concerning the

OMCL-cooperation 2015

Chemical, Biological and
Radiopharmaceutical Products

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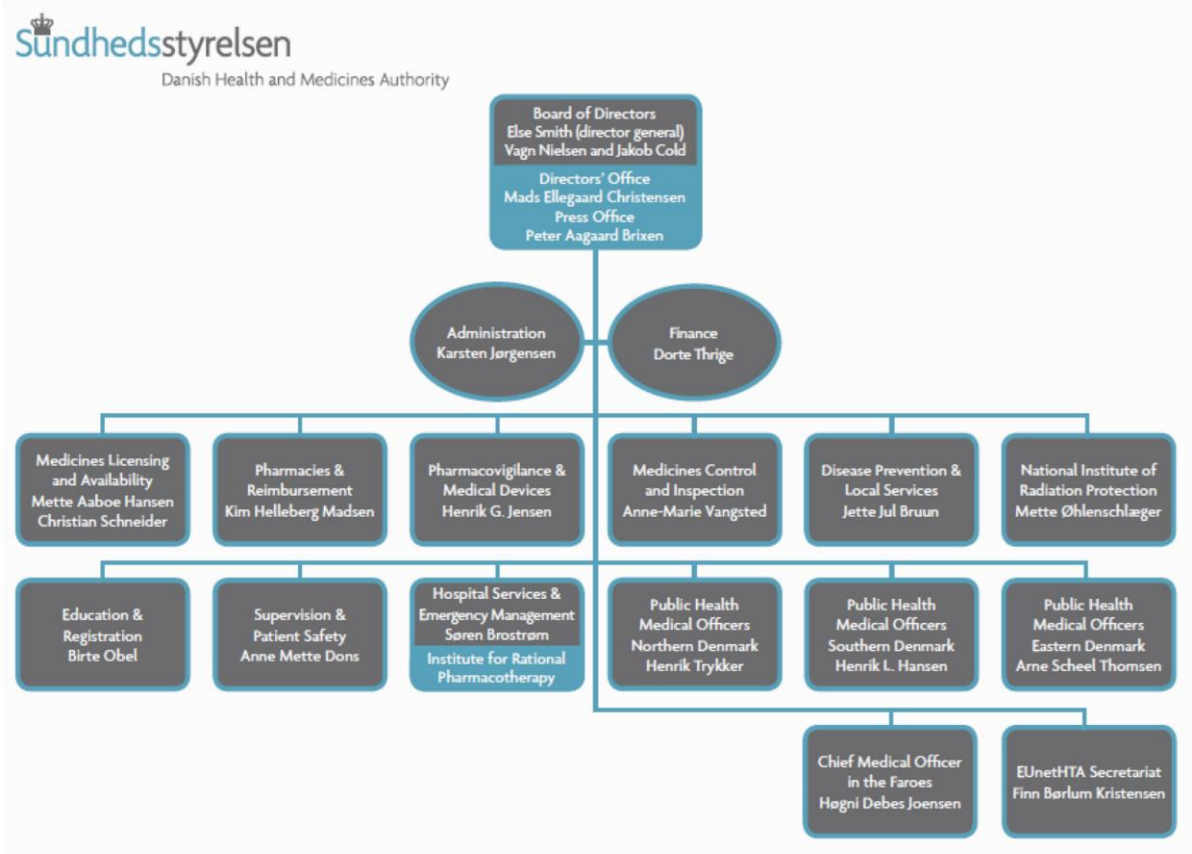
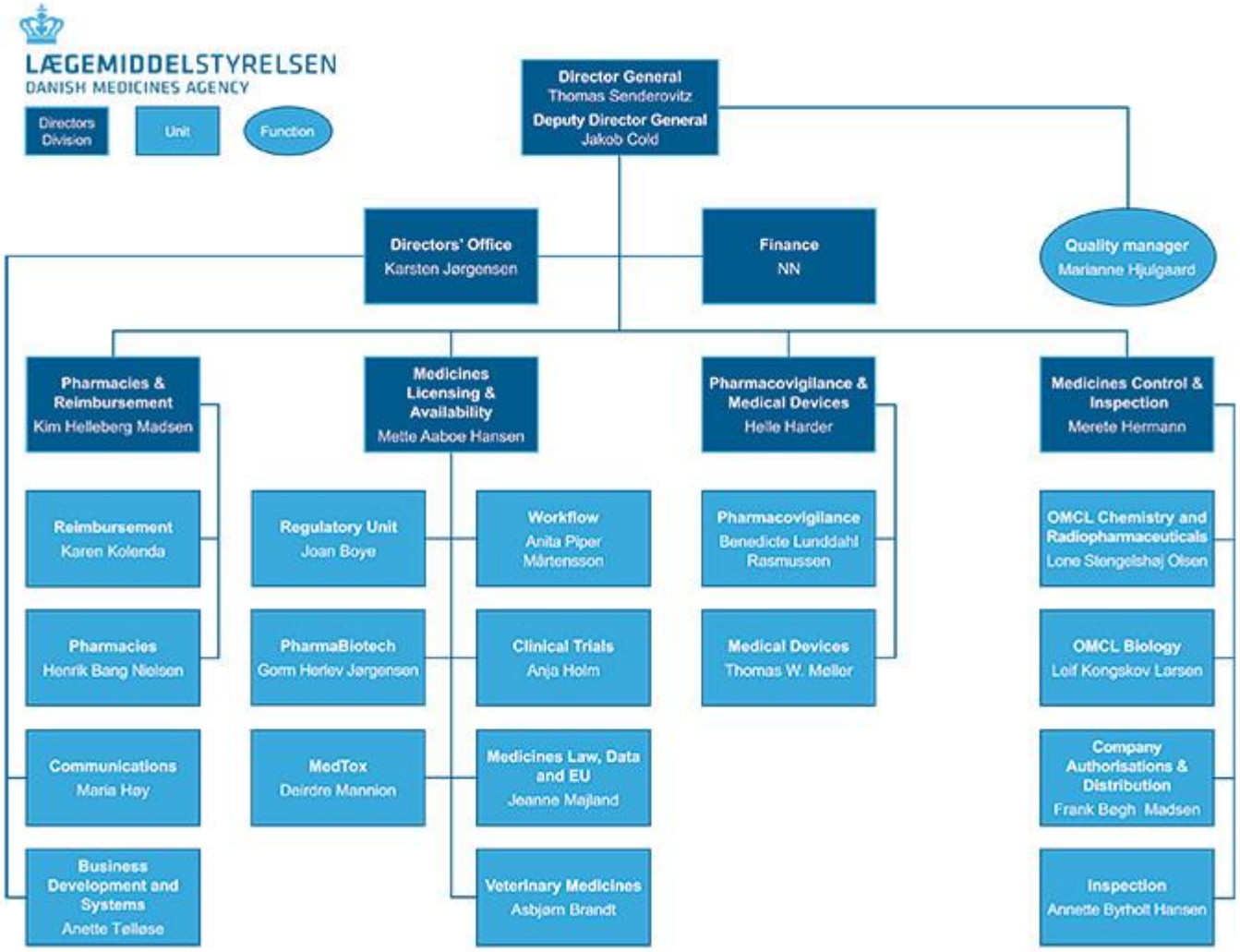
A.1. Organisation of the laboratory

A1.1 General structure.

Danish Health and Medicines Authority / Danish Medicines Agency



Several organizational changes happened in 2015. Most significantly, the Danish Medicines Agency, which in March 2012 merged with the National Board of Health became an independent agency again in late 2015.. The organization of the Danish Medicines Agency is illustrated below:



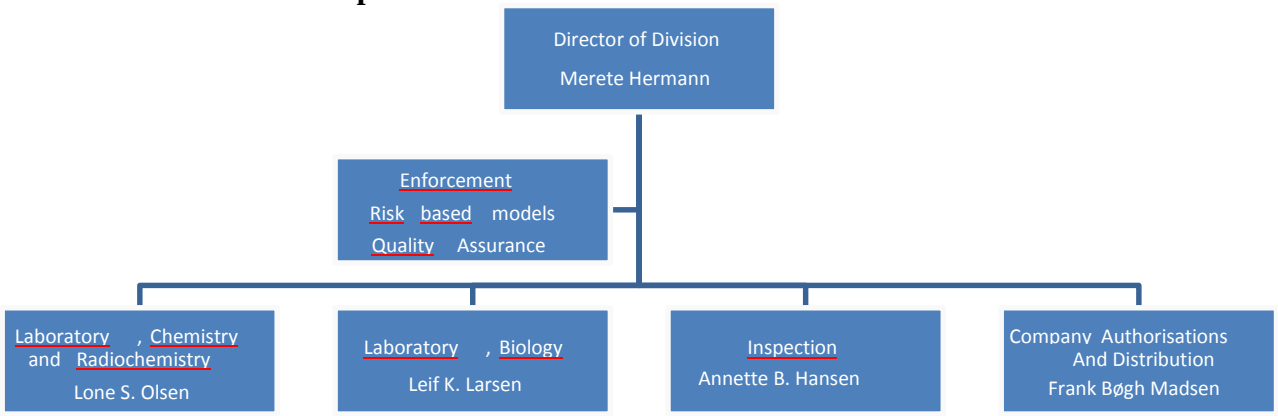
The Danish Medicines Agency has around 400 employees, and the five largest professional groups in our organisation are pharmacists, administrative assistants, physicians, lawyers and masters of social science.

The agency

- authorises and inspects pharmaceutical companies and licenses medicinal products on the Danish market
- monitors adverse reactions from medicinal products and authorises clinical trials
- monitors medical devices available in Denmark and supervises adverse incidents involving medical devices
- appoints proprietary pharmacists, organises the pharmacy structure and supervises pharmacies and retailers.

We perform most of our tasks in close collaboration with colleagues from regulatory authorities and organisations in the other EU countries.

Medicines Control and Inspection



The division "Medicines Control and Inspections" is responsible for the Danish Medicines Agency's regulatory duties with respect to laboratory testing and monitoring of medicinal products. The division handles complaints and reports about quality defects in medicinal products as well as any related withdrawals. The division supervises and is responsible for company authorisations for handling and manufacturing medicinal products and euphoriant substances.

The division also supervises:

- Clinical trials (GCP - Good Clinical Practice)
- Pharmacological and pharmacokinetic trials in animals (GLP - Good Laboratory Practice)
- Companies' monitoring of side effects (GVP - Good Vigilance Practice)

In addition to OMCL activities, the laboratory 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:

Heads of Unit	2
Scientists	15
Laboratory Technicians	11
Assistant/secretary	2
Trainees/students	1

Four scientists from the laboratory are working part time in the PharmaBiotech unit with assessment of the pharmaceutical quality of chemical and biological medicines.
Head of Unit Leif Kongskov Larsen has replaced Eva Sandberg and is now heading the biological laboratory.

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 surveillance 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.

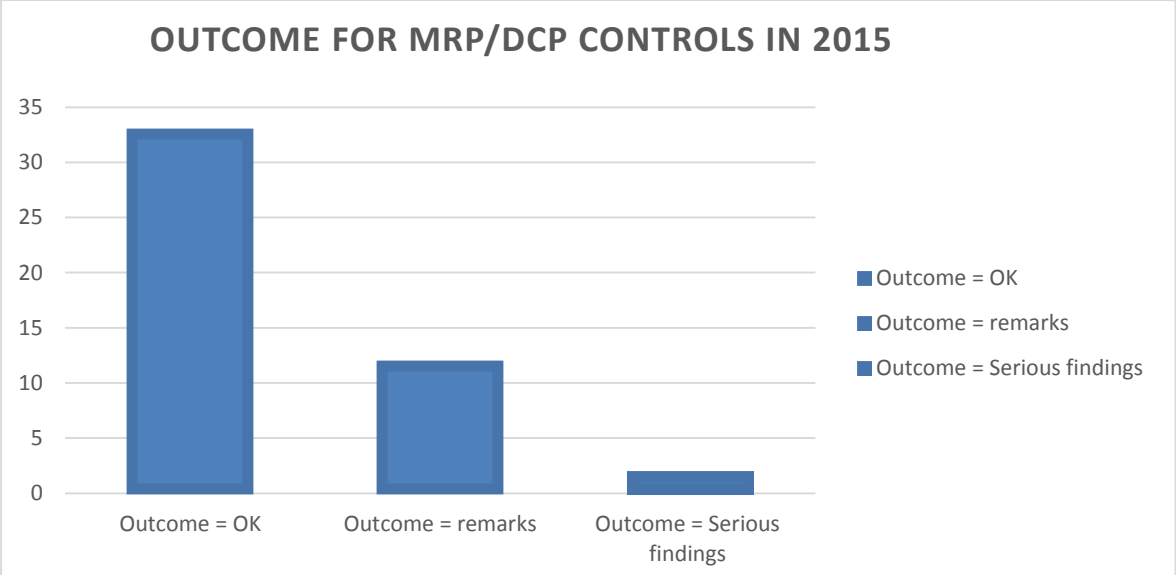
The Laboratory received the first MJA attestation on February 2011. The specified field of activity for the Laboratory is "Testing of pharmaceutical products and API (biological, chemical and radiopharmaceutical); Market surveillance testing and screening for illegal products. Elaboration of standards and reference materials to Ph.Eur.; Participation in PTS, CAP, BSP and MSS". An audit team successfully audited the Danish OMCL in June 2015 consisting of a Mutual Joint Audit (MJA) team and DANAK.

B.1 Activities related to the national market

B.1.1 Legal Supply Chain (authorised medicines)

The Laboratory carries out analyses on a range of nationally authorised medicinal products according to the authorised dossier of the marketing authorisation. In general, selected testing is performed, which typically includes appearance, identification of constituents, assay of active ingredient and impurities. In addition, the laboratory performs supplementary tests for specific products or drug substances. These investigations review the labeling, batch protocol and/or specification compliance, without the typical analysis performed in the laboratory.

A total of 279 medicinal products and API were tested. A significant number of the products tested (58 %) led to additional enquiries with the marketing authorisation holder or manufacturer concerning labelling, SOPs, as well as specifications and stability issues. In one particular case, the laboratory control resulted in a suspension of the marketing authorization of two strengths of a MRP product, as it was not possible to carry out a laboratory analysis of the drugs based on the available information for methods for identification (IR), assay (isocratic HPLC) and related (HPLC).



Some of the projects are highlighted below.

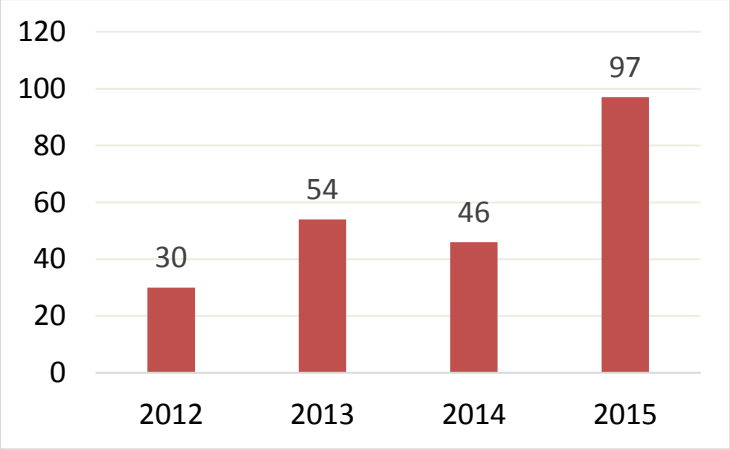
Test of APIs sampled by GMP inspector

The Laboratory took part in a collaborative project with the Inspection Unit of the Danish Medicines Agency. Three batches from three different active pharmaceutical ingredients (API) were sampled during GMP inspections in India. The APIs were atorvastatin calcium trihydrate, rosuvastatin calcium and orlistat. The samples were handed to the laboratory, where two of the APIs were analysed according to the relevant Ph.Eur. monographs. The third API, orlistat, was deemed not relevant as it was found not to be associated with any finished products on the Danish market, nor was there a valid Ph.Eur. monograph. The purpose of the project was both to strengthen the collaboration between the two units (Inspection and Laboratory) as well as to determine the quality of the sampled APIs.

The analysis results showed compliance with specification for the most part. For atorvastatin calcium trihydrate, an OOS result was found for an unspecified impurity. This was brought to the attention of the API manufacturer, who subsequently identified the impurity.
Overall, the project provided useful information concerning the collaboration between the units, and brought to light areas of improvement for future collaborative projects.

Increased numbers of complaints reported to the laboratory

The Laboratory receives complaints about medicinal products from patients, healthcare personnel, pharmacists, etc. When a complaint is received, the seriousness of the complaint is assessed and the next step decided.



In 2015, the Laboratory evaluated 97 different complaints which was twice as many as the year before. Many of the complaints were about the quality of the formulation (e.g. the tablets were difficult to swallow or divide) and issues regarding the labelling and packaging.

Child-resistant blister cards

The Laboratory received 32 complaints from 2011 to 2015 regarding child-resistant blister cards. The complaints described the following problems:

- The foil is hard to peel off, and/or is broken when trying
- You need to use tools like a pair of scissor or a knife.
- Quality issues when tablets are pushed through the foil, when the foil should be peeled off.

In general, there is uncertainty about the handling of these types of blister cards and instruction on how to open child-resistant blister cards is essential for the user-friendliness. In 2015, we examined 21 different blister cards. Only 4 out of 13 child resistant blister cards had been tested according to the ISO Standard EN ISO 14375:2004. In the future, the assessors will suggest the MAH to add an instruction on how to open the blister cards directly onto the blister card or at least give the instructions as a part of the PIL. The problem has also been discussed at a CMDH meeting.

Testing of radiopharmaceuticals in Denmark.

It is of special importance for the Laboratory to not only have a national accreditation, but also have an audit of our performances, because the Laboratory is now the only OMCL laboratory in Europe, which is able to perform analytical control on radiopharmaceuticals.

The use of radiopharmaceuticals in Denmark continues to rise. In particular, the use of cyclotron-produced isotopes for radiopharmaceuticals are becoming more prevalent and especially, Flour-18 isotope is widely used. Major centers (outside Denmark) have started to produce Tc-99m via cyclotron as a backup or replacement for Tc-99m produced from fission products. This has resulted in work in expert group 14 on a new monograph in the Pharmacopoeia for cyclotron produced Tc-99m. Our hope is that this new way of production will overcome a future shortage of Mo-99/Tc-99m.

In 2015, the radioactivity laboratory had focus on Tc-99m labelled radiopharmaceuticals. The projects were selected due to the following risk factors and is still ongoing:

- stability of a Tc-99m kit close to expiry date,
- new radiopharmaceuticals on the Danish market and
- problems with methods for quality control on Tc-99m kits in hospitals.

B.1.2 Legal Supply Chain (suspected samples)

The Danish Health and Medicines Authority did not carry out any analysis on counterfeit medicines during 2015.

B.1.3 Illegal Supply Chain.

The Laboratory continues to analyse products suspected of containing undeclared APIs. These samples are primarily obtained from customs services. In 2015, 29 such products were analysed, the majority by HPLC. Over the summer, the laboratory implemented a new LC-MS targeted screen. As a result, the samples analysed towards the end of the year were screened using this new LC-MS screen.

Four of the 6 products screened for potency-enhancing compounds were found to contain either sildenafil or tadalafil. 8 of the 23 products screened for weight-loss compounds were found to contain compounds associated with weight-loss such as sibutramine, synephrine and phenolphthalein (caffeine was also identified in 13 of the samples). Fluoxetine was identified in one weight-loss product, and 2-diphenylmethylpyrrolidine (stimulant psychoactive drug) in another weight-loss product.

B. 2 Activities related to the Network

The Danish OMCL has participated in the following activities:

CAP program

The Biological Laboratory participated in the following collaborative studies in the 2015 CAP program:
CAP2015/24 Myozyme
CAP2015/26 Nivestim
CAP2015/43 Synagis
CAP2015/29 Orencia

Other collaborative studies

The Biological Laboratory participated in the testing of the Etanercept monography, by testing BSP138

Proficiency Testing Studies (PTS)

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

PTS 156 - Loss on drying
PTS 157: Potentiometric Determination of pH
PTS158 - Infrared Absorption Spectrophotometry
PTS 159: Dissolution (Cefaclor)
PTS160: Liquid Chromatography, Assay (Melissa leaf dry extract)

The requirement for proficiency testing with in the field of radiopharmaceuticals has not been fulfilled this year.

Contribution to the European Pharmacopoeia

The Danish OMCL delegate to the Ph. Eur. Commission was Erik Wolthers.

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

No.	*Group*	*Danish OMCL-participant*
6	Biological Products	Eva Rauhe Bækdahl
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
P4Bio	P4Bio	Erik Østergaard

A substantial part of the Danish activities concerning development of pharmacopoeial monographs (e.g. “Pharmeuropa” evaluation) takes place in the three committees for chemistry, pharmacy and pharmacognosy.

The committees have participants primarily from industry and academia combined with assessors, regulators and laboratory experts from the Danish Medicines Agency. This composition of participants assures that both purely technical as well as legislative aspects of the monograph proposals are addressed.

Among specific items discussed can be mentioned:

Chemistry: Specific limits for impurities. Implementation of ICH Q3D for elemental impurities. Harmonisation of chromatographic methods with USP. Relation to "biological medicine" where test methods are becoming increasingly "chemical".

Pharmacy: Legislative and analytical aspects of Uniformity of Dosage Units. Use of water produced with reverse osmosis for parenterals. Co-processed excipients.

Pharmacognsy: Legislative and analytical aspects of the monograph for Extracts. Comparison of monographs for Traditional Chinese Medicine with the traditional European, especially with discussion of need for assay.

Common for all committees: Implication and handling of monographs and proposals for "Finished products". Deliberations over the question of participation in EDQM´s expert groups and working parties: How do we cope with increasingly limited resources while we wish to maintain our usual level of participation – with commenting and proposals but also with actual laboratory development?

B. 3 Method related activities

Development of alternative methods to detect extraneous agents

The Danish OMCL maintains 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.

Use of LC-MS in suspect samples

In 2015, the Laboratory developed a new LC-MS screening method for identifying undeclared APIs in suspect samples. The screen is a targeted screen in the first instance, with an in-house library currently containing around 30 compounds. The library is regularly updated with reference standards of interest. The LC-MS screen replaces three HPLC methods that were previously used to screen for potency-enhancing and weight-loss compounds. The new method enables us to analyse samples more efficiently, as well as screen for more compounds. It also enables the identification of unknown compounds, such as the fluoxetine and 2-diphenylmethyl pyrrolidine that were identified in two of the products analysed in 2015.

Capillary Electrophoresis
The Danish OMCL conducted analysis for deamidated forms on selected batches of Somatropin Solution for injection by capillary electrophoresis using a Beckman Coulter PA800 apparatus. All results were in accordance with the specified limits in Ph. Eur. 01/2016:2370 "Somatropin Solution for Injection". The experience was that while it is possible to conduct analysis on a complex sample with a minimum of sample preparation time the migration time of the analysis varied.

In relation to a biological CAP test the Danish OMCL attempted to transfer an imaged capillary isoelectric focusing (icIEF) method to a capillary isolectric focusing (cIEF) method. This was necessary in order to be able to run the method on the Beckman Coulter PA800 apparatus. However, there are many differences between the icIEF method and cIEF method and it was not possible to meet the acceptance criteria for the specific analysis. Therefore, no data could be reported. It should be noted, however, that with the cIEF method the electropherograms of the company reference and samples were comparable.

Ph. D project finalised
The aim of the ph. D. project "Accelerated drug-excipient compatibility studies including microwave heating and hyphenated analytical techniques" was to study drug-excipient compatibilities with the use of accelerated stability testing. A microwave oven was introduced as a predictive tool in order to save time during these investigations. Three model systems comprising the formation of covalent drug-excipient interaction products were selected for the evaluation. An additional criterion for the selected model systems was that they were representative for diverse drug formulations. The OMCL contributed to one of the publications:

Schou-Pedersen, A.M.V., Hansen, S.H., Moesgaard, B., Østergaard, J. Kinetics of the Esterification of Active Pharmaceutical Ingredients containing Carboxylic Acid Functionality in Polyethylene glycol: Formulation Implications. J. Pharm. Sci. 103 (8), 2424-2433. 2014.

Determination of freeze damage on HPV vaccines by use of flow cytometry
In our annual report from 2014, a project on parallel distributed HPV vaccines was mentioned. The focus of the control was on freeze damage of the vaccines during transportation. This project is ongoing, but in 2015, a publication was contributed by the Danish OMCL:
Østergaard, E., Frandsen, P.L., Sandberg, E. Determination of freeze damage on HPV vaccines by use of flow cytometry. Biologicals. 43(4), 266-73, 2015.

B.4. Public related activities

The Danish OMCL participated in a TV-programme "Kontant" about illegal medicines and its health risks.

B.5. Future planning

B.5.1 National

The Laboratory will update the library with reference standards of interest for the LC-MS screening method for identifying undeclared APIs in suspect samples.

Due to a major update of the act “Dansk Lægemiddelstandard” which regulates the terms for pharmaceutical preparations, a control project will be defined to see if the new terms have been fulfilled.

B.5.2 Network

In 2016, the Laboratory plans to participate in the following testing activities

- MSS 048 on tablets with authorised subdivision
- Biosimilar project testing Filgramstim/Nivestim

The Laboratory will also try to coordinate an API sampling for the API working group for testing with the Danish inspectors.