LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Danish Medicines Agency
Medicines Control and Inspection

Annual Report of activities concerning the

OMCL-cooperation 2017

Chemical, Biological and
Radiopharmaceutical Products

This document is for National Control Authority use only

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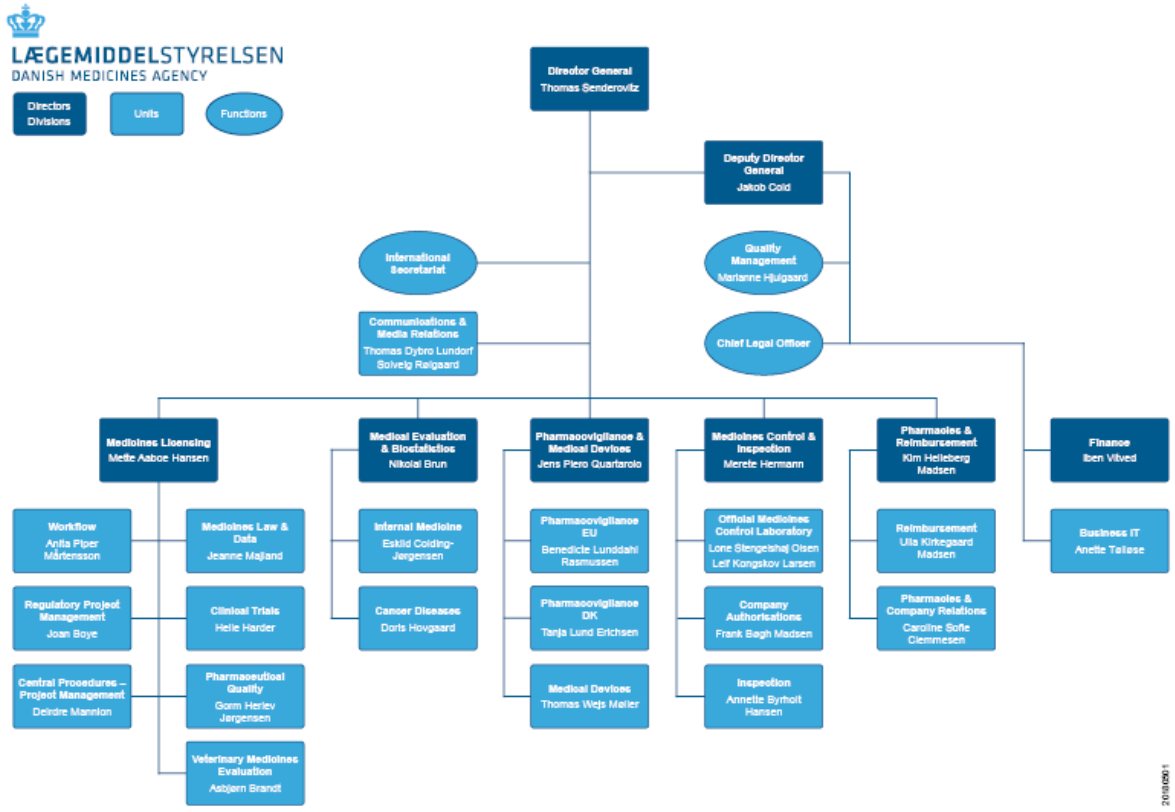
A.1. Organisation of the laboratory

A1.1 General structure

Danish Medicines Agency



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.

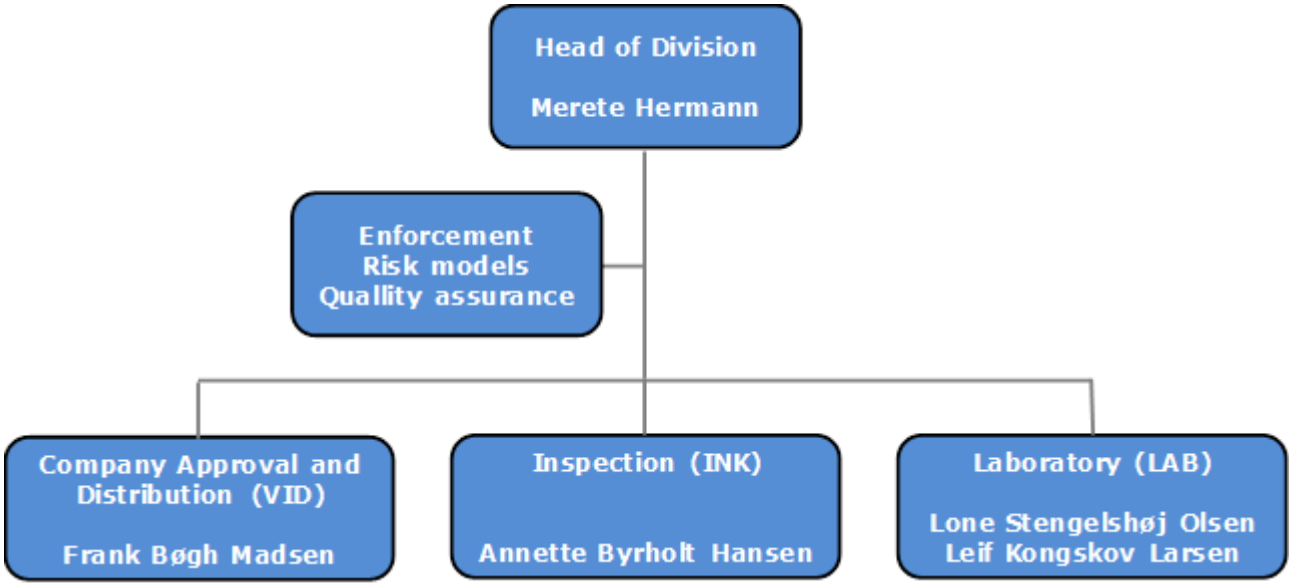
The Danish Medicines Agency

- 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. In 2016, The Danish Medicines Agency launched a new

strategy for 2017-2021: Among Europe's best in class! The strategy emphasizes our commitment to both public health and growth in Denmark and describes a number of focus areas built on the five points of our vision.

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 recalls. The division supervises and is responsible for company authorisations for handling and manufacturing medicinal products and psychoactive substances.

The Control Strategy

Medicines control is a task of the European and other international authorities. We want to increase our efforts in the international arena and make use of recognition across borders to make medicines control more efficient. This means that we are putting efforts into establishing a mutual recognition procedure with the USA.

We are seeking dialogue and offering guidance in our control, but we also act decisively when patient safety is at risk. We put a high priority on securing the quality of legal medicinal products, but we also want to warn citizens against illegal and falsified medicinal products. We want to increase our focus on illegal distribution, particularly illegal online sale of medicines.

We carry out risk-based control adjusted to the individual situation. Risk models and the tools we use in the control must not be static, because that would make them predictable. Consequently, we plan to revise and expand our risk models and toolbox. The OMCL has been working extensively

with a model for scoring risk parameters based on available data and the model will be evaluated in 2018/2019 and optimized accordingly.

The complexity and the number of control points mean that we cannot check each control point every time. Thus, the use of communication to promote learning and improve compliance with rules is very important. We want to increase communication about our expectations and learning points before, during and after our control.

The Lean transformation was launched in the Danish Medicines Agency in 2017. The Lean transformation is driven by an ambitious goal of optimizing operation and internal processes of the Agency. By the end of 2017, the OMCL is working along with most of the Agency with:

- Setting standards - Delivering right quality at the right time and reducing costs.
- More efficient processes - to work with fewer stations and shifts to reduce throughput times in the projects.
- Workflows - to create dedicated time for case management and to reduce distractions.
- Increase customer satisfaction by being specific about our needs so that customers deliver the right materials the first time in order to get the results from our control faster.
- Visualization by the use of project board management - to create overview, prioritization, productivity, progress and quality improvements, etc.

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 36 employees:

Heads of Unit	2
Scientists	17
Laboratory Technicians	13
Assistant/secretary	2
Trainees/students	2

A. 2 Quality Management System

Since 1995, the Laboratory has been accredited 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 accreditation of the Laboratory will be renewed in February 2018.

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 authorized 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 radio-pharmaceutical); 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 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 265 medicinal products and APIs were tested. A significant number of the products tested (52 %) led to additional enquiries with the marketing authorisation holder or manufacturer concerning labelling, SOPs, as well as specifications and stability issues.

Some of the projects are highlighted below:

Screening for pyrogens in injectables using the Monocyte-Activation Test (MAT) in combination with the Test for Bacterial Endotoxins (BET).

The Monocyt-Activation Test (MAT) is primarily intended to be used as a replacement test for the rabbit pyrogen test. Only very few injectables are registered with this test so far as part of the specification but the Danish OMCL used the test in combination with the test for Bacterial Endotoxins (BET) to screen 15 injectables for the content of pyrogens and endotoxins. Several injectables contained substances which neither were pyrogenic nor endotoxins but showed high activity in the

MAT due to the active ingredients of the injectables. No injectables were withdrawn from the market due to excess content of endotoxins or pyrogens.

Authenticity Testing

Authenticity testing was a focus for the laboratory in 2017, when 15 kg of pregabalin API was stopped by customs disguised as Stevia powder. 1 million empty capsules with markings similar to that of Lyrica 300 mg capsules were also stopped. The incident resulted in a control project in the laboratory, where the product Lyrica 300 mg capsules was sampled from the legal market, with a focus on parallel-distributed products.

In total, 19 packages were examined, and the following tests were carried out: appearance, uniformity of mass, ID by IR, assay by HPLC and related substances by HPLC. Identification was also determined using Raman, and selected samples were screened for identification of pregabalin by LC-MS.

The results showed compliance with the specifications. Furthermore, the parallel distributed packages were deemed to be authentic. A labelling control was also carried out, using EMAs European Public Assessment Report (EPAR) for Lyrica capsules 300 mg as a reference. There were no comments regarding the labelling.

Testing of radiopharmaceuticals in Denmark.
In 2017, our analytical control of radiopharmaceuticals focused on

- CAP testing of Quadramet
- selected follow-up controls and stability testing
- compliance with the current monograph for the finished product in the European Pharmacopeia
- control of ROTOP products in collaboration with the German OMCL_BBB.

The CAP product Quadramet is a solution for injection containing the active substances samarium (Sm-153) lexidronam pentasodium. It is used to relieve bone pain in patients with bone metastases. Quadramet is delivered frozen in dry ice and has a shelf-life on 4 days, but should be used within 6 hours of thawing. Testing this type of product is always a big challenge. It includes many different practical issues to handle and a presentation will be given at the up-coming OMCL meeting regarding testing of Quadramet among others.

For another product, compliance with the specification and methods in the current monograph for the finished product has been ensured by approval of variation application.

As always, further details regarding our control and the outcomes are available on the EDQM extranet in the folder named Radiopharmaceuticals. Any MRP/DCP control will also be included in the MRP/DCP database in line with other Pharmaceuticals.

The collaboration with the German OMCL_BBB regarding testing of selected ROTOP products continued in 2017. The control of the individual products was still shared between the OMCLs, in other words the Danish OMCL has only performed the methods including radioactivity.
Further to this, a collaboration with the Brazilian Authority ANVISA regarding assessment, GMP inspection and quality control of Radiopharmaceuticals has taken place, resulting in a visit from our Brazilian colleagues to our laboratory with focus on testing of Radiopharmaceuticals.

In 2017, the laboratory continued the cooperation with the National Institute of Radiation Protection, under the Danish Health Authority. The focus was the testing of Sm-153 and Tc-99m preparations and their radionuclidic impurities in order to verify the calibration of selected equipment. The comparison of the test results gives an extra quality control of the method performance in the laboratory. It also fulfills the requirement for proficiency testing for selected methods on our accredited method list, which is always a challenge in the field.

B.1.2 Legal Supply Chain (suspected samples)

The Danish Health and Medicines Authority did not carry out any analysis on counterfeit medicines during 2017.

In 2017, the laboratory collaborated with The Danish Veterinary and Food Administration in a project to screen for undeclared pain-relieving compounds (primarily NSAIDS) in legal dietary supplements. The products were sampled by the Danish Veterinary and Food Administration and the analysis was carried out by the Danish Medicines Agency, In total, 16 products were analysed. None of the products were found to contain undeclared pain-relieving compounds.

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 2017, 13 such products were analysed using LC-MS. 6 products were screened for potency-enhancing compounds, 4 of which were found to contain sildenafil. One product was also found to contain oxytetracycline. 5 products were screened for weight-loss compounds, 3 of which were found to contain compounds associated with weight-loss such as sibutramine. One unknown sample packaged as Stevia powder was also analysed and found to contain pregabalin. Another sample was screened for pain-relieving compounds.

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

Total number of suspected counterfeit samples	a	0
Total number of confirmed counterfeit cases of licensed medicines in the legal supply chain	b	0

Total number of suspected illegal samples tested	g	29
Total number of illegal samples identified (other than counterfeit samples)	c+d+e+f	0

B. 2 Activities related to the Network

In 2017, the Danish OMCL participated in the following testing activities related to the OMCL network

- SUP008
- A collaboration with the German OMCL_BBB regarding testing of selected ROTOP products

API working group

The Danish OMCL is an active member of the API Working group and participated last year in the atypical Market Surveillance Study (MSS) of Omeprazole API. The MSS was a part of the API Fingerprint project (MSSFP003) in which the APIs Omeprazole, Omeprazole Magnesium and Omeprazole Sodium were analysed. The ultimate aim of the API Working Group is to develop expertise in fingerprinting for APIs at risk of being falsified by employing techniques and methodologies that could be used for the investigation of real cases of falsification of APIs. The MSS of Omeprazole API was carried out by 10 OMCLs where seven OMCL were involved in testing.

The Danish OMCL was one of two OMCLs performing HPLC testing for Related Substances. 28 samples were tested and results were reported to EDQM for the investigation of fingerprint.
One of the OMCL strategic goals is a strong collaboration with other departments of the Danish Medicines Agency as Medicines Licensing (Pharmaceutical Quality) and Inspectorate. The collaboration with the Inspectorate resulted in the sampling of 6 Omeprazole API samples performed during the inspections at the production sites. All these samples were included in the MSS and contributed to a more complete picture of the Omeprazole API on the European market. The results of the MSS will be discussed at the next API Working Group meeting in June 2018. Some propositions of the next MSS is already in pipeline.

CAP program

The Danish OMCL participated in the following collaborative studies in the 2017 CAP program:

- CAP2017/08 Enbrel, 25 mg, Solution for injection Etanercept
- CAP2017/09 Enbrel, 25 mg, Powder and solvent for solution for injection Etanercept
- CAP2017/13 Gazyvaro, 1000mg, Concentrate for solution for infusion
- CAP2017/29 Quadramet, 1,3 GBq/mL, Solution for injection

Other collaborative studies

The biological group participated in the collaborative Study BSP153, Prekallikrein Activator in Albumin BRP.

Proficiency Testing Studies (PTS)

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

PTS 172: Anti-D Antibodies in Human Immunoglobulin
PTS 173: Prekallikrein Activator in Human Albumin
PTS 176: Osmolality (Ph. Eur. 2.2.35)
PTS 177: Liquid Chromatography, Assay (Ph. Eur. 2.2.29, RP-C18, UV detection)
PTS 178: Dissolution (Ph. Eur. 2.9.3, immediate release tablets, paddle apparatus, spectrophotometric determination)
PTS 179: Thin Layer Chromatography (Ph. Eur. 2.2.27)
PTS 182: Human coagulation factor VIII potency assay

The requirement for proficiency testing within the field of radiopharmaceuticals has not been fulfilled this year in the traditional PTS program from EDQM. However, as mentioned in the section regarding *testing of radiopharmaceuticals*, the cooperation with the National Institute of Radiation Protection, under the Danish Health Authority verify the calibration of selected equipment and gives an added quality control of the method performance in the laboratory.

Contribution to the European Pharmacopoeia

The Danish OMCL delegates to the Ph. Eur. Commission were Erik Wolthers, Anders Uhrenholt Vestergaard and Lone Stengelshøj Olsen.

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

No.	*Group*	*Danish OMCL-participant*
6	Biological Products	vacant
10A	Organic chemistry	Birthe Moesgaard
14	Radiopharmaceuticals	Inge Overby Jensen
15	Vaccines	Erik Østergaard
15 V	Vet. Vaccines	Peer Lyng Frandsen
P4Bio	P4Bio	Leif Kongskov Larsen

The Danish OMCL is an active participant in the work of European Pharmacopeia and values the progress of the 3R principles. A substantial part of the Danish activities concerning development of pharmacopoeial monographs (e.g. “Pharmeuropa” evaluation) takes place in the 4 committees for biology, 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. The committees made comments of all four editions of PharmEuropa that were in hearing during 2017. In total, 176 monographs were reviewed and discussed in one or more of the 4

expert committees. The Danish comments were sent to EDQM on 77 of these monographs, 12% were related to Pharmacy, 16% to Biology, 21% to Pharmacognosy, and 52% related to Chemistry. Also, several topics have been discussed during 2017, primarily on co-processed excipients, finished product monographs, and the development of a national monograph for cannabis flower for medicinal use. The first two were due to PharmEuropa hearings, whereas the last topic is due to the political willingness to partake a trial period with medicinal cannabis.

In 2017, the Danish OMCL participated in the testing of new proposals to PharmEuropa, one monograph was tested from PharmEuropa 29.3.

Highlights from the Danish contribution in the different expert groups:

Group 10A: Regarding the monograph for Fluoxetine hydrochloride, we have validated a new HPLC method for assay and test of related substances, which we have developed. Additionally, we have also tested the suitability of Karl Fischer water determination in the present monograph when doubling the sample amount.

Group 14: In the field of radiopharmaceutical and nuclear medicin a lot of work is going on these years within treatment of cancer with Theranostics. Theranostics is a combination of diagnosis of the cancer with a substance labelled with a radionuclide and a following treatment of the cancer with the substance labelled with a radionuclide used for targeted therapeutic purpose (for example a beta-emitting radionuclide). This development is reflected in the Expert group 14, where work is going on with substances with radionuclides for diagnostic use (for example Ga-68-PSMA) and precursors for radiolabelling (for example Y-90 for radiolabelling). In addition, a new monograph for Ga-68 for radiolabelling (produced by accelerator) is under development.
In a sub-group of group 14 a document concerning validation of radiopharmaceutical methods is under elaboration. When finished, the document will be merged with the style guide to a new guide for elaboration of monographs on radiopharmaceutical preparations.

B. 3 Method related activities

Development of alternative methods to detect extraneous agents

The absence of extraneous agents (EA) in the raw material used for production and in finished products is one of the principal safety elements related to all medicinal products of biological origin, such as live-attenuated vaccines. The aim of this study was to investigate the applicability of the Lawrence Livermore Microbial detection array version 2 (LLMDAv2) combined with whole genome amplification and sequencing for screening for viral EAs in live-attenuated vaccines and specific pathogen-free (SPF) eggs. We detected positive microarray signals for avian endogenous retrovirus EAV-HP and several viruses belonging to the Alpha-retrovirus genus in all analyzed vaccines and SPF eggs. We used a microarray probe mapping approach to evaluate the presence of intact retroviral genomes, which in addition to PCR analysis revealed that several of the positive microarray signals were most likely due to cross hybridization with the EAV-HPΔpol and ALV-E ev1, ev3 and ev6 loci sequences originating from the chicken genome. Sequencing of the vaccines on a MiSeq instrument verified the microarray findings and showed similar cross hybridization. Our results suggest that genomic microarrays and sequencing of avian attenuated vaccines may be applied in tests for EA. Results published in *Biologicals* Vol. 51 (2018) p. 37-45.

Improved method for measuring ethylene oxide

Ethylene oxide gas (EO) is widely used for sterilization of medical devices and for pharmaceutical packaging materials, which does not tolerate thermal sterilization methods. The gas penetrates into the plastic and leave small amounts of EO. In the European Pharmacopeia and in ISO standards, limit values for content are defined based on different methods and principles. However, for the determination of EO in disposable syringes, the method in the Pharmacopeia is troublesome and needed revision. The Danish Medicines Agency's laboratory has in collaboration with Professor Vagn Handlos and The French authorities developed a revised method for EO determination. The Allergy clinic at the Gentofte Hospital have had patients in the clinic who are allergic to EO, and the clinic has monitored the patient's histamine release in the blood, when they have been exposed to EO-sterilized equipment. The new method were used to determine EO in utensils, such as the Allergy Clinic patients have been in contact with. Preliminary data for this work show a correlation between high EO content in the utensils and increased histamine release.

B.4. Public related activities

The Danish OMCL has participated in two different television broadcasts informing the public about the danger of buying and using unknown products from the internet, which may be illegal or falsified.

See our participation in the Danish TV 2 Station 2's program “the illegal road to beauty”
https://www.facebook.com/laegemiddel/videos/353623095121733/

B.5. Future planning

B.5.1 National

The focus for 2018 will be on gaining competencies for the analysis of biological medicinal products with mass spectrometry. In addition, the OMCL will continue to update the library with reference standards of interest for the LC-MS screening method for identifying undeclared APIs in suspect samples. We will also use the LC-MS technology as part of authenticity testing. In the beginning of 2018, the Danish OMCL has invested in a new GC-MS to support the authenticity testing of legal medicinal products. A screening method for identifying residuel solvents will be implemented.

Due to a major update of the act “Dansk Lægemiddelstandard” which regulates the terms for pharmaceutical preparations, a control project has been defined in 2017 to see if the new terms have been fulfilled. This project will continue in 2018.

Lastly, a kick off to a future collaboration with the Chinese Authority, National Institutes for Food and Drug Control (NIFDC) began in 2017 and interchange of information and visits will take place in 2018. Participating in an inter-laboratory comparison or proficiency-testing program is a well recognized parameter used to assure the quality of the test results by monitoring proficiency and performance and documenting the competencies. It supplements the quality system and is a demand in ISO 17075. The comparison evaluates parameters like analytical competences, testing routine, calibration of the equipment, and the need for corrective actions and improvements.

However, for the radiopharmaceutical tests it is a challenge to find a suitable scheme in which to participate in. As a first step in establishing such a project, a mapping of the types of equipment

used and testing methods used as standard methods, if any, as well as the types of radionuclides and finished products tested by the Danish OMCL and NIFDC to determine the common denominator. These preparations would take place by a face to face meeting in China to design the inter-laboratory comparison test.

B.5.2 Network

The Laboratory will participate in the heparin testing and future API testing.