LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Annual OMCL Report 2021

Lægemiddelstyrelsen / Danish Medicines Agency
Axel Heides Gade 1
2300 København S
lmst.dk

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OUR MISSION

We create value for people, animals and society through efficient, safe, and available medicines and safe medical devices

Indholdsfortegnelse

Organisation of the Laboratory

General structure of the Danish Medicines Agency

The Danish Medicines Agency has around 630 employees, and the five largest professional groups in our organization are pharmacists, administrative assistants, physicians, lawyers and masters of science. We perform most of our tasks in close collaboration with colleagues from regulatory authorities and organizations in the other EU countries.

The Danish Medicines Agency

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

In 2016, The Danish Medicines Agency launched a new strategy for 2017-2021: Among Europe's best in class. In general, 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 (see next page). This strategy has been revised in 2022 and is available at our website.

The Division for Control and Security of Supply

The division "Control and Security of Supply" 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 authorizations for handling and manufacturing medicinal products.

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 introducing in 2020 an electronic system

“Klartboard” for planning activities in the laboratory. In addition to OMCL activities, the laboratory performs tasks in connection with the elaboration of monographs for Ph. Eur.

The Control Strategy for the agency

Medicines control is a task of the European and other international authorities. In order to fulfill our vision to become a driver of international collaborations, 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 have been putting efforts into establishing a mutual recognition procedure with the USA, and the Danish inspectorate achieved recognition in November 2018.

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.

Moreover, we carry out risk-based control adjusted to the individual situation. Risk models and the tools we use in the control of medicines must be dynamic in order to prevent them from becoming 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 and optimized accordingly.

At the OMCL, we have utilized the computational resources at DAC (Data Analytical Center) to establish an updated list of prioritized medicines selected for control. This selection has been based on many different parameters, such as time elapsed since last control, novelty, complaints from patients as well as medical professionals, and findings during previous controls.

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.

A separate Annual Report on OCABR activities is provided.

Personnel matters

The Biological and Chemistry & Radiochemistry Laboratories had 39 employees in 2021. The staff distribution according to role is presented in Figure 1.

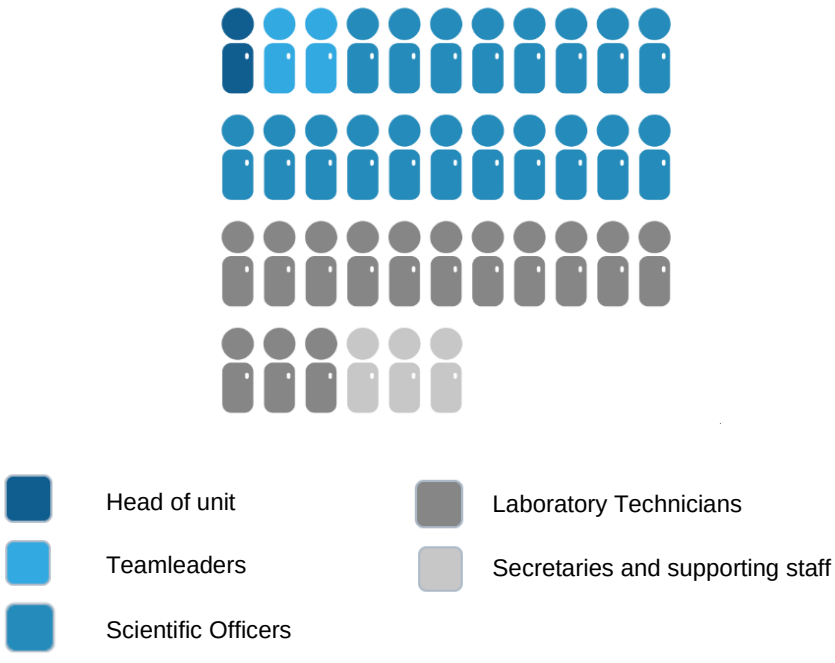

Figure 1. Staff distribution based on roles in 2021 at the Danish OMCL.

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 was renewed in March 2021.

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.

Our national accreditation body for the Laboratory is DANAK.

Types of testing:

- **Biological and biochemical**
- **Chemical testing**
- **Radiochemistry and radiation**

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, CRS and MSS”. The previous MJA (04/19) was successfully carried out in collaboration with DANAK.

Activities related to the National Market

Legal Supply Chain (Authorized Medicines)

The Laboratory carries out analyses on a range of medicinal products both according to the authorized dossier of the marketing authorization holder (MAH) as well as in-house (validated and non-validated) methods. In general, selected testing which typically includes appearance, physical tests such as uniformity of mass and hardness, assay of active ingredient(s) and impurities is performed. Furthermore, 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.

Sampling approach

With the introduction of DAC, the process of selecting medicines for control have been updated and utilizes powerful computational resources to include several parameters, such as time elapsed since last control, novelty, complaints from patients as well as medical professionals, and findings during previous controls. Liaising with DAC, has enabled the Danish OMCL to establish updated lists of prioritized medicines or groups of medicines for control.

A total of 435 finished products and APIs were controlled in 2021 respectively, see Figure 2. A significant number of the products tested (37%) led to additional enquiries with the marketing authorization holder or manufacturer concerning labelling, analysis methods, validation of analysis results as well as specifications and stability issues (see Figure 3).

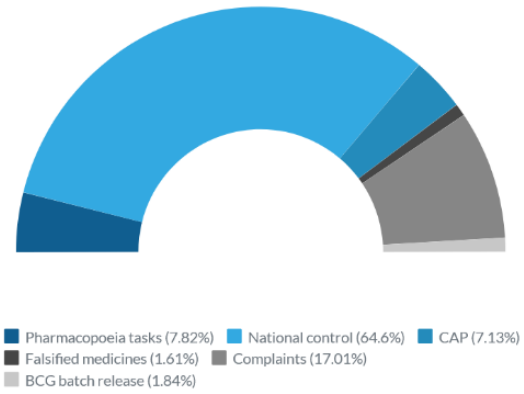

Figure 2. Cases handled by the Danish OMCL divided by the nature of the tasks for 2021.

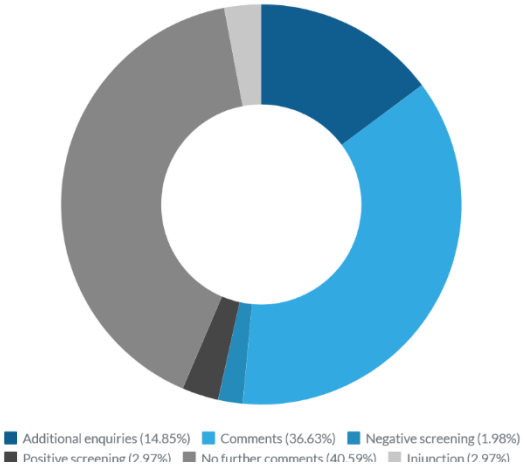

Figure 3. Case outcome for 2021

The Danish OMCL received 74 complaints of the pharmaceutical products from pharmacies, healthcare professionals and patients in 2021. Fourteen (14) samples were subsequently analysed in the laboratory. For the remaining complaints, labelling controls were performed.

Results, details/technical issues

See Appendix 1.

Legal Supply Chain (suspected samples)

The Danish Medicines Agency did not carry out any analysis on counterfeit medicines during 2021 (see Table 1).

Illegal Supply Chain

The Danish OMCL laboratory continues to analyse products suspected of containing undeclared APIs. The Danish Medicines Agency works closely with Danish customs to control medicine imports. Samples arriving at the OMCL are primarily analysed by liquid chromatography coupled to a high-resolution mass spectrometer (LC-HRMS).

The majority of the samples arriving at the laboratory can be divided into three types: slimming products, painkillers and medication used to treat erectile dysfunction. The products are usually in the form of either tablets or capsules. However, the OMCL also receives samples of powder.

In 2021, nine products were tested at the OMCL. Three products were screened for weight-loss compounds, one of which was found to contain sibutramine, two products were screened for potency-enhancing compounds, both of which were

found to contain sildenafil. Two products were screened for pain-relieving compounds and one product for melatonin. A cream product was screened for undeclared corticosteroids with the help of the Swedish OMCL.

The number of positive samples analysed by the Danish OMCL in 2021 is presented in Table 1.

Table 1. Total number of samples tested in the legal and illegal supply chain in 2021.

		2021
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	9
Total number of illegal samples identified (other than counterfeit samples)	c+d+e+f	5

Activities related to the Network

In this section, we report some of the highlights from the OMCL's activities related to the network in 2021.

Chemical Laboratory:

National Market Surveillance studies:

In 2021 the Danish OMCL performed market surveillance study on ADHD with the active ingredient Lisdexamfetamin. In 2022 we have continued the market surveillance study with ADHD medicines with methylphenidate as active ingredient.

Group 10A activity: Verification of the revised monography (related substances) of the Ph. Eur. Suxibuzone monograph (n. 1574) and testing of Suxibuzone from two different MAHs. A report with all the results has been sent to EDQM.

Stability test of the emergency storage of Oseltamivir phosphate in Denmark. We performed analysis on 10 random samples/batches and all samples complied with the specification limits.

Radioactivity laboratory

The radioactivity laboratory has been inspected and evaluated by the Danish national authorities for Radiation protection. The inspection was based on new legislation in Denmark which implement the European EURATOM directive. Our existing license for handling radioactivity had to be updated to the new requirements, which implied elaborating of a comprehensive report on safety assessment with a detailed description of the laboratories, personnel, training, permitted radionuclides and amounts, safety equipment and procedures, radioactive waste handling, calculations of radioactive doses to the personnel and the surroundings and dosimetry calculations for accidents and unwanted events

The accreditation body has often requested proficiency testing studies within the field of radiopharmaceutical and our laboratory participated 2020-2021 in a proficiency test exercise arranged by The National Physical Laboratory (NPL) in UK. The target for the NPL proficiency testing Exercise was testing of radioactivity concentration of selected radionuclides on environmental samples and not radiopharmaceuticals. We participated as a pilot test to evaluate, if these proficiency test exercises are valuable for our laboratory. The tested radionuclides were Co-60, Ba-133 and Eu-154. The result of the Proficiency test exercise was satisfying with z-scores of 1.0 or below and our conclusion is, that it is feasible to participate in NPL Proficiency test exercises in the future.

In 2021 the analytical control of radiopharmaceuticals has focused on control of Tc-99m labelled kits, both kits licensed according to the MRP/DCP procedure and some German licensed kits tested in cooperation with the German OMCL_LLBB. For the kits tested in cooperation with the German OMCL_LLBB the Danish OMCL has only performed the test methods where radioactivity was included.
In all the control projects we found insufficient information about disregard limit or quantification limit in the description of the radiochemical purity methods.

Further details of our control and the outcomes are available at EDQM and analytical control on radiopharmaceuticals licensed according to the MRP/DCP procedure are included in the MRP/DCP database in line with other pharmaceuticals.

The general monograph for radiopharmaceutical 0125 has undergone a major revision and update. Monograph 0125 is background for the monographs of finished products of radiopharmaceuticals.
All the meetings 2020-2021 has been on-line meetings, this has resulted in higher participation in the meetings, also from

countries outside Europe. But it is assumed that many of the discussions would be better when the physical meetings are back again.

Biological Laboratory

CAP testing

In 2021 the Danish OMCL have participated in CAP test on several biological products (EPO, Binocrit, Rekovelle, Tremfya and Crysvita). Some of the CAP tests were programed for 2020 but were finalized in 2021 due to delays caused by the COVID19 pandemic. The Danish OMCL preformed different tests on the samples including potency by cell assays, Capillary Electrophoreses SDS, and different HPLC methods. Results were reported to the EDQM.

Filgrastim Biosimilar testing

The Danish OMCL participated in the testing phase of the project on Filgrastim Biosimilar coordinated by EDQM CAP program. The aim was to do simultaneous testing of Filgrastim drug products using generic methods. The suggested approach for testing should not only demonstrate that quality criteria are met for single products but aims at confirming the comparability between biosimilars of one product group based on test results obtained in OMCLs. Six different Filgrastin biosimilars were sampled from the European market, 14 samples altogether, and were tested by several OMCLs. The Danish OMCL preformed seven different tests on the samples including potency by a cell proliferation assay, RP- and SE-HPLC and SDS page. Results were reported to the EDQM.

Gene Therapy Working Group

The Danish OMCL participated in the validation of a qPCR method for determination of the viral genome titres of AAV2-based gene therapy vector preparations in a collaborate study from the Gene Therapy Working Group under Biological Standardization Program coordinated by the EDQM. The aim was to assess the efficiency of the qPCR and the viral genome titres by different laboratories. Results were reported to the EDQM.

Publications:

GEONs API fingerprint project: Selection of analytical techniques for clustering of sildenafil citrate API samples
E. Deconinck *et al***.** Volume 239, 2022, 123123.
Through its Active Pharmaceutical Ingredient Working Group (API-WG) the General European Official Medicines Control Laboratory (OMCL) Network (GEON), co-ordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM), regularly organises market surveillance studies for specific APIs for conformity to their monograph in the European Pharmacopoeia. During the past years some studies were combined with a fingerprint study of the APIs. The idea is to obtain a fingerprint for each manufacturer of the API under investigation, allowing the OMCL network to identify future samples as well as to detect substandard and falsified APIs. This paper reports the results of the latest fingerprint study, organised on sildenafil citrate API samples. Seventy-nine samples from 14 different manufacturers were collected throughout the Network. Fingerprint data was collected through Mid-Infrared spectroscopy, Raman spectroscopy, liquid chromatography for related substances, gas chromatography for residual solvents, X-ray diffraction and Nuclear Magnetic Resonance (NMR) spectroscopy. Chemometrics applied to the collected data showed that all manufacturers could be discriminated based on the data of only three of these tests, i.e. gas chromatography for residual solvents, X-ray diffraction and proton NMR. Suspicious API samples for sildenafil citrate will therefore be analysed in the future with the selected techniques in order to link the sample to a manufacturer or demonstrate the absence of such link. If the sample cannot be attributed to one of the manufacturers, further analysis and research on provenance and identity will be required. Of course, if the suspected sample claims to originate from one of the manufacturers included in the study, analysis can be limited to the test distinguishing this manufacturer.

European fingerprint study on omeprazole drug substances using a multi analytical approach and chemometrics as a tool for the discrimination of manufacturing sources
H Rebiere *et al*. J. Pharm Biomed Anal. Vol. 208. 2022, 114444.
Like drug products, Active Pharmaceutical Ingredients (APIs) are subject to substandard and falsification issues, which represent a threat to patient health. In order to monitor the quality of drug substances and prevent the use of non-compliant APIs, Official Medicine Control Laboratories work together in a European network developing coordinated strategies and programmes. The API working group proposed a market surveillance study on omeprazole and omeprazole magnesium with the objectives of controlling the pharmaceutical quality of samples, checking compliance with the monographs of the European Pharmacopoeia, and collecting analytical fingerprints that could be further used to differentiate manufacturing sources for future authenticity investigations. The study described in this article reports the analysis carried out by 7 European laboratories on 28 samples from 11 manufacturers with 5 analytical techniques (related substances with HPLC, residual solvents with GC-MS, near infrared spectroscopy, proton nuclear magnetic resonance spectroscopy and X-ray powder diffractometry). The large amount of resulting analytical data were centralized and treated with two chemometric methods: Principal Component Analysis and Hierarchical Clustering Analysis. Data were analyzed separately and in combination (data fusion), allowing us to conclude that NMR and XRPD were suitable to differentiate samples originating from 9 out of

11 manufacturers. Analytical fingerprints associated with chemometrics were demonstrated to be a valuable methodology to discriminate manufacturers of omeprazole and omeprazole magnesium APIs and detect future substandard and falsified APIs.

Key Issues in 2021

Control of ADHD medicines

A large control campaign controlling ADHD medicines have been initiated

Counterfeit products

Continue the work on analysing falsified medicines and suspicious unknown products.

Method related activities

In this section, we report some of the highlights from the OMCL's method related activities in 2021.

Control of ADHD medicines

In 2021, a large national control project regarding all medicines containing methylphenidate or lisdexamfetamine, used to treat ADHD was initialed by the Danish OMCL. The both of these compounds are listed as controlled substances and requires specific export/import certificates, and the process of acquiring materials for analysis is therefore lengthy. Due to the complexity of the analyses as well as the prolonged acquisition process, the project will continue in 2022.

Nitrosamines

In 2021 the Danish OMCL continued to work on developing a method to test for nitrosamines. The work has moved from GC-MS to LC-MS (QTOF), where the focus has been on assessing the sensitivity of the equipment and the potential need for investing in new equipment, such as a triple quadrupole LC-MS. The assessment is expected to conclude in 2022.

GAP analysis on vaccines

The Danish OMCL made a GAP analysis on the ability to test vaccines. For the analysis that are part of the official control authority batch release (OCABR), we seek a collaboration with the OMCL performing the OCABR. The Danish OMCL will focus on test for impurities, test for endotoxins and pyrogens by the LAL and MAT test, respectively, and test for sub-visual particles. The project is ongoing.

Future Planning

1 National

A focus for the future is to finalise a strategy for the analytical control of samples suspected to belong to the illegal supply chain.

2 Network

In the future, one of the main priorities for the Danish OMCL is to develop a LC-MS based method to identify and quantify nitrosamines present in very low concentration in medicines. The laboratory has in close collaboration with the instrument vendor Waters developed a testing strategy that will be tested and, if successful, implemented in 2022.

Moreover, the Danish OMCL is in the midst of developing an optimised quantitative/semi-quantitative GC-MS method for the analysis of residual solvents in finished products and API's. The aim is for the method to be optimised, validated and tested by the end of 2022.
Another future aim for the Danish OMCL is to develop a sample preparation method for cremes, with subsequent analysis using LC-MS' for identification and quantification.

After the successes with MSS058 and MSSFP004 on sildenafil APIs and finished products, the Danish OMCL also plans to participate in future MSSs such as the coming MSS059 and MSSFP005 concerning tadalafil APIs and finished products respectively.