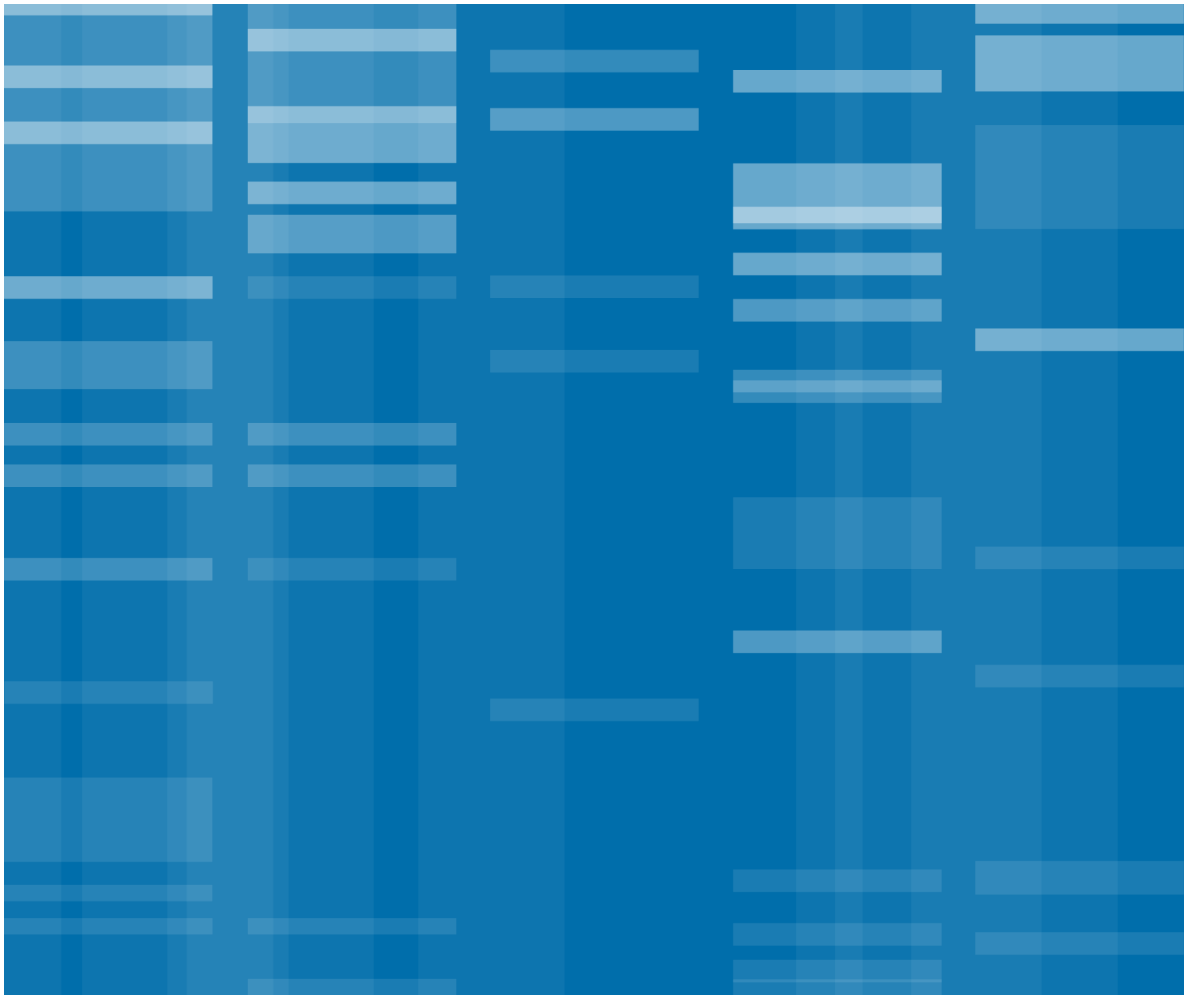
LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Danish Medicines Agency

Annual OMCL Report 2022 and 2023



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1 Organisation of the Laboratory

1.1 General structure of the Danish Medicines Agency

The Danish Medicines Agency has around 650 employees, and the four largest professional groups in our organisation are pharmacists, administrative assistants, doctors, lawyers and masters of social science (organizational chart next page, Figure 2). 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

- authorises and inspects pharmaceutical companies and licenses medicinal products in the Danish market
- monitors adverse reactions from medicinal products
- authorises clinical trials
- decides which medicines are eligible for reimbursement
- 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.

In 2022, The Danish Medicines Agency launched a revised strategy for 2022-2026. Our mission, vision and four strategic benchmarks are described in figure 1.

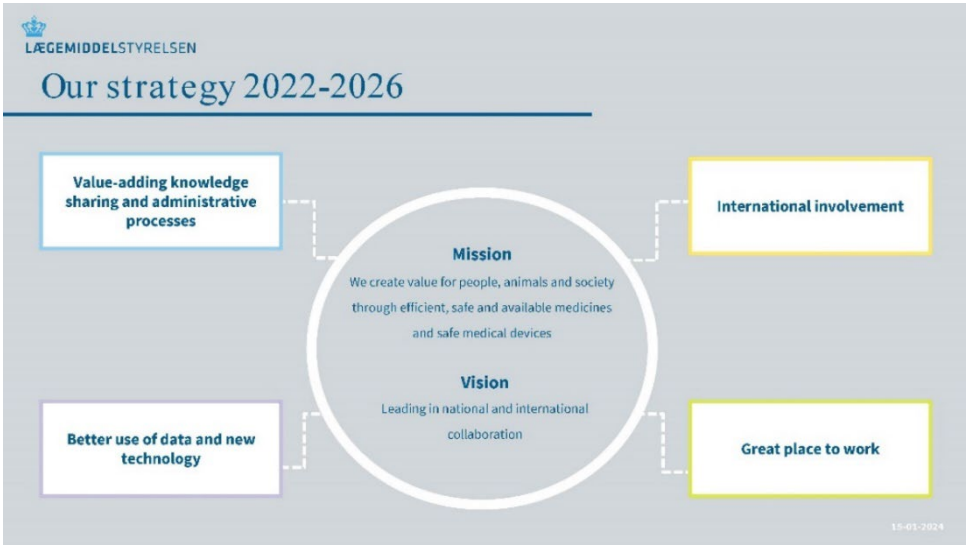


Figure 1
Mission vision and four strategic benchmarks for the Danish Medicines Agency.
Source: LMSneT: Praesentation-LMST-UK

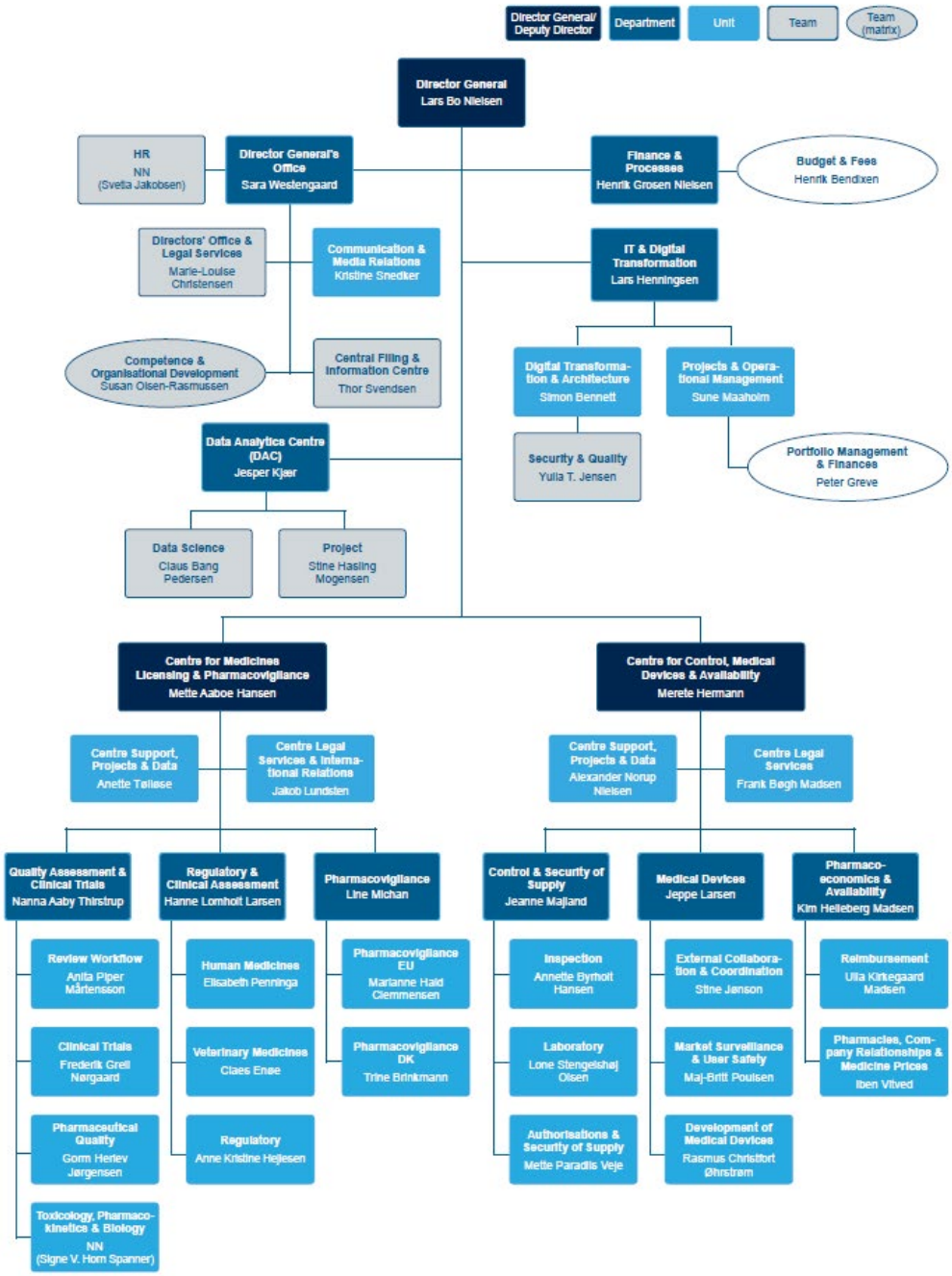


Figure 2
Organizational chart of the Danish Medicines Agency
Source: https://laegemiddelstyrelsen.dk/en/about/

1.1.1 Department for Control and Security of supply

The department “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 department handles complaints and reports about

quality defects in medicinal products as well as any related recalls. The department supervises and is responsible for company authorizations for handling and manufacturing medicinal products. Also, the Danish inspectorate is located in this department of the Danish Medicines Agency.

In addition to OMCL activities, the laboratory performs tasks in connection with the elaboration, testing and perform verification of monographs for Ph. Eur.

The complexity and the number of control points mean that we cannot check each control point every time. For selection of new projects for medicinal products and active substances for testing, the Danish OMCL has developed a risk-based model based on OMCL documents and inputs from other countries. Consequently, we have worked extensively to revise our risk model together with our computational resources at DAC (Data Analytical Center). We are now utilizing a risk model database which has define many different risk parameters based on available electronic data sources. These parameters are such as time elapsed since last control, consumption, complaints from patients as well as medical professionals, and findings during previous controls and inspections. We have ranked the different risk parameter, and therefore the risk model database gives us an automatic risk scoring. Moreover, we carry out risk-based control adjusted to the individual situation. Therefore, from this risk model database, we extract different projects depending on our scope for example elderly products, formulation as vaginal products. The result is an updated list of prioritized medicines selected for control of products for the next three years.

Meanwhile we have an agreement with the Data Analytic Center on upgrade the data sources on a regular basis. Furthermore, the risk models must be dynamic in order to prevent them from becoming predictable, therefore we intend to evaluate and optimize the risk model in 2024 so we can have a new list of prioritized medicines in 2025.

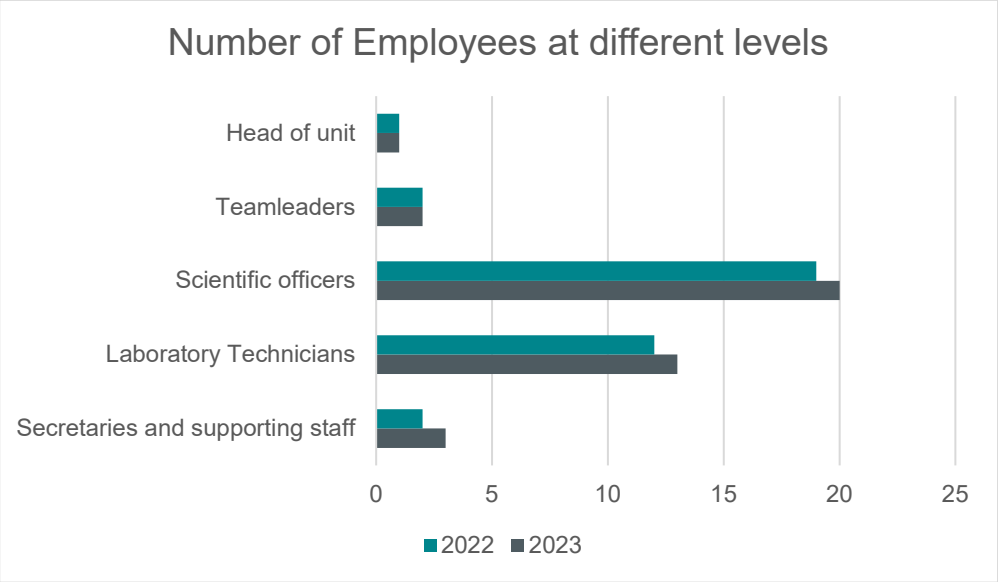
Thus, the use of communication to promote learning and improve compliance with rules is very important. We want to increase communication about our expectations and learning points before, during and after our control.

A separate Annual Report on OCABR activities is provided.

1.2 Personnel matters

The Danish OMCL Laboratory is divided in tree teams: Chemical and Radiopharmaceutical Laboratory, Biological Laboratory and General Regulatory Tasks. In total, the Laboratory had 36 employees in 2022 and 39 employees in 2023. The staff distribution according to role is presented in Table 1.

TABLE 1
STAFF DISTRIBUTION BASED ON ROLES IN 2022 AND 2023 AT THE DANISH OMCL



1.3 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 May 2023.

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 most recent MJA in 2023 was successfully carried out as a joint audit with DANAK.

Work has been ongoing with focus on evaluation of measurement uncertainty, data security and computerised systems.

1.4 Internal collaboration

The GXP-inspectors, quality assessors and OMCL are located in the same organization and geographical location. GXP inspectors and OMCL are organized in the same department and building. The quality assessors, GMP/GDP inspectors and OMCL staff have access to the same databases and all data are available to enable quality assessors to make decisions on the acceptability of manufacturers nominated on applications for marketing authorisations as well as post-marketing control. The inspectors are obliged to update the common database after inspections including the inspection result as a score, and for GMP inspections, the information about issued GMP certificate. The quality assessors and OMCL staff have access to the same database. Information on conducted lab controls on specific medicinal products are shown in the same database via a link to the ECM-system. Marketing authorisations are included and linked to data on company authorisations and inspections.

Competence teams – a number of multidisciplinary teams have been set up across the Agency, which cover topics including grey zone products with blood, cells and tissues, pharmacovigilance, parallel imports and radiopharmaceuticals. All members contribute with relevant subject for discussion during the meetings and risks can be identified and handled accordingly.

Triggered inspections can be requested by assessor/OMCLs and other stakeholders. Academic employees from OMCL, Licensing, Clinical trials and others, have a standing invitation to participate in all types of inspections, and are sometimes requested formally because of special circumstances. Inspectors can sample during inspections and bring samples to the OMCL for testing. If decided before the inspection details on the sampling are agreed in advance.

Hand over meetings between inspectors and OMCL staff/quality assessors are planned when needed (to make the understanding between inspectors and assessors better). A yearly meeting before finalizing the OMCL activity is usually planned.

The collaboration between quality assessors, inspectors and OMCL, is formalized and the advantage of being under the same roof is of huge importance; the inspector can go to the assessors/OMCL and discus any issue with the chemists, as well as the opposite way. Inspectors are asked questions and informed about trigger for inspection through a mail-account.

Also located in the department is the unit "Authorisations and Security of Supply" who handles complaints and reports about quality defects in medicinal products as well as any related recalls. When any systematic defects are detected they can inform the OMCL or the Inspectors to trigger a test or inspection.

Business Object reports are defined for systematic data extract, e.g. variations, life cycle reports, and a dash board is available for the risk-based control programme in the OMCL.

2 Activities related to the national market

2.1 Legal supply Chain (Authorised 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. Where possible these investigations review the labeling, batch protocol, certificate of analysis (CoA) and/or specification compliance, without the typical analysis performed in the laboratory.

2.1.1 Sampling approach

As mentioned in 1.1.1 the introduction of the risk-based model in collaboration with 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.

For every case one or various tests were conducted on the finished product, API or illegal substance. Thereby, the case number does not reflect the amount of single analyses conducted in the Laboratory. The workload for each case has increased as the analyses get more complex and we conduct more tests per case than previous years. The Danish OMCL's workload is described by our number of controls, this was 463 in 2022 and 362 in 2023. The yearly target figure for number of controls is more than 350.

A total number of 183 finished products were called in for control in 2022 and 162 in 2023. The distribution and number of the types of cases are shown in figure 3.

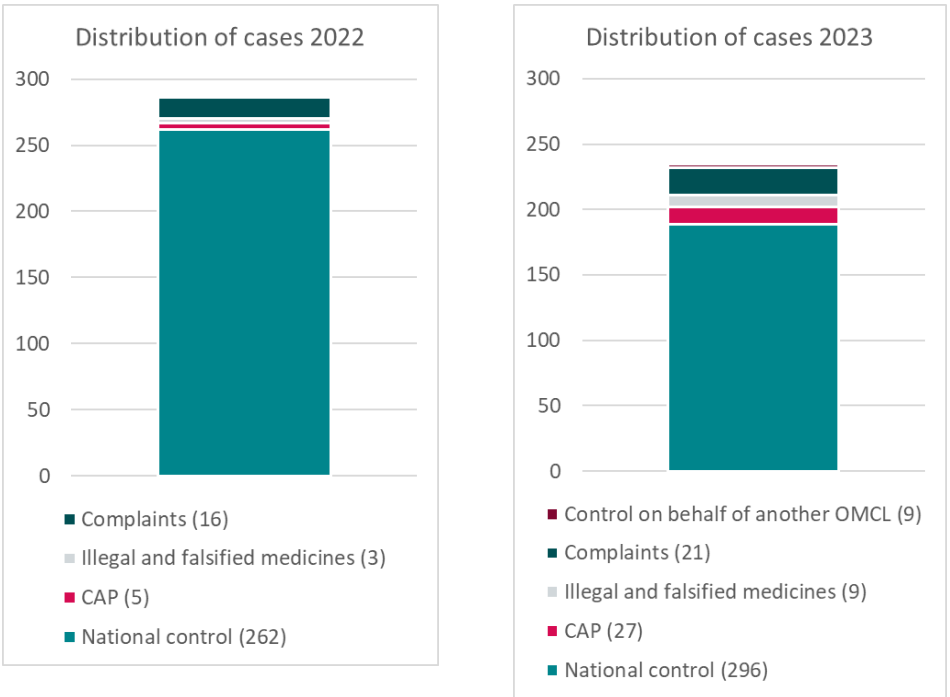


Figure 3
Data from: SAB BI report "Sagsstyringsrapport og kvartalsstatistik – laboratoriekontrol", "Figur, pr år"
Data extracted 11th January 2024.

Complaints are complaints of pharmaceutical products from pharmacies, healthcare professionals and patients.

The outcome distribution of the laboratory control for each case is shown in figure 4. As mentioned each case may cover more than one test. In this figure the worst outcome of the tests performed in each case is reported.

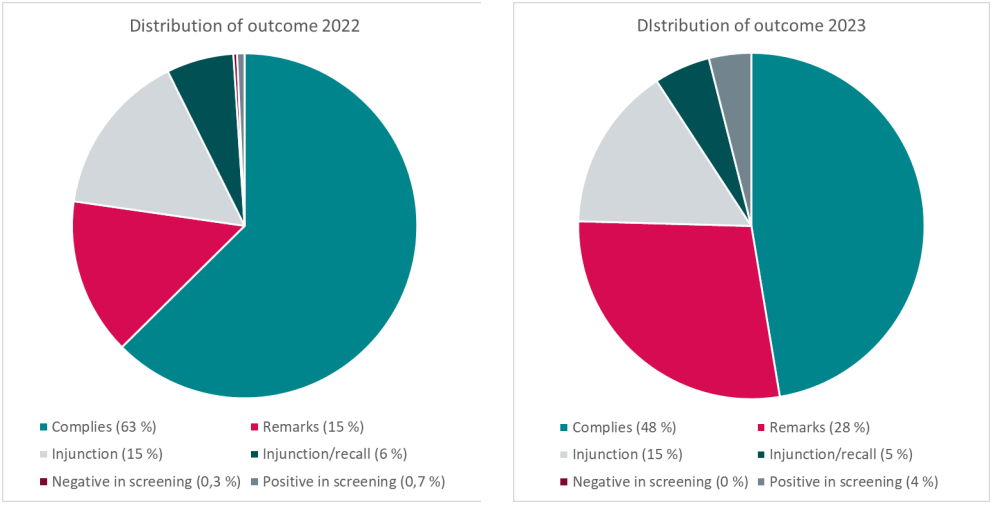


Figure 4
Data from: SAB BI report "Sagsstyringsrapport og kvartalsstatistik – laboratoriekontrol", "Liste inkl. sagsudfald"
Data extracted 11th January 2024.

Of the cases with "remarks", "injunction" and "injunction/recall" 65 % were due to labelling, 30 % due to the documentation for the product and 5 % resulted from the laboratory analysis for the year 2022. In 2023 the distribution was 69 % labeling issues, 27 % documentation issues and 4 % issues with the laboratory control.

2.1.2 Results, details/technical issues

For a list of the finished products analysed by the Danish OMCL see "*2022 OMCL Annual Report Annex 1"* or "*2023 OMCL Annual Report Annex 1*". These annexes will not be published on the website. The findings have been discussed with and are corrected by the MAH.

2.2 Legal Supply Chain (medical devices)

The control of medical devices on the Danish marked is not in the scope of the Danish OMCL. The market surveillance and user safety are managed by the department for Medical Devices within the Danish Medicines Agency.

2.2.1 Sampling approach

Healthcare professionals, manufacturers, distributors and importers of medical devices have a duty to report it to the Danish Medicines Agency if a device results in an accident or incident regardless of whether the cause is a device malfunction or misuse. Citizens can also submit reports.

2.2.2 Results, details/technical issues

No testing of medical devises was performed by the Danish OMCL in 2022 and 2023.

2.3 Legal Supply Chain (suspected samples)

The Danish Medicines Agency did not carry out any analysis on counterfeit medicines during 2022 nor in 2023 (see Table 2).

2.4 Illegal Supply Chain

The Danish OMCL laboratory continues to analyse products suspected of containing undeclared APIs. However, the number of products received at the laboratory has fallen considerably in the last few years. Samples arriving at the OMCL from customs via our DKMA enforcement team are primarily analysed by liquid chromatography coupled to a high-resolution mass spectrometer (LC-HRMS). The products are usually in the form of either tablets or capsules. However, the OMCL also receives samples of powder.

In 2022, only three products were tested at the OMCL. Two products were screened for potency-enhancing compounds and were both found to contain tadalafil, while the third product was screened for weight-loss compounds, and was found to contain caffeine, synephrine and yohimbine.

In 2023, nine products were tested at the OMCL. Two products were screened for pain-relief compounds and were found to contain tramadol and pregabalin respectively, one product was screened for weight-loss compounds (sibutramine was identified), and the remaining six products were found to contain melanotan II.

The number of samples analysed by the Danish OMCL in 2022 and 2023 is presented in Table 2.

TABLE 2
TOTAL NUMBER OF SAMPLES TESTED IN THE LEGAL AND ILLEGAL SUPPLY CHAIN IN 2022 AND 2023

		2022	2023
Total number of suspected counterfeit samples	a	0	0
Total number of confirmed counterfeit cases of licensed medicines in the legal supply chain	b	0	0
Total number of suspected illegal samples tested	g	3	9
Total number of illegal samples identified (other than counterfeit samples)	c+d+e+f	2	9

Case outcome applicable for c, d, e and f is available in "*2022 OMCL Annual Report Annex 1"* or "*2023 OMCL Annual Report Annex 1*". These annexes will not be published.

3 Activities related to the Network

In this section, we report some of the highlights from the OMCL's activities related to the network in 2022 and 2023.

Proficiency Testing Studies

For the purpose of quality assurance, the Danish OMCL have analysed the following PTS-samples in 2022: PTS216, PTS218, PTS219, PTS224, PTS226.

In 2023 the following PTS-samples were analysed: PTS233, PTS234, PTS229, PTS235, PTS236, PTS237, PTS238, PTS239, PTS 244. Also, the BSP for EPO BSP159 and BSP167 – Collaborative Study for the Establishment of the Prekallikrein Activator (PKA) in albumin BRP replacement batches, were performed. Furthermore, a PTS for Subvisible particles (Ph. Eur. 2,9,19) from another provider were performed to test new equipment.

A few of the PTS's were analysed by all tree laboratory teams (Chemical, Radiopharmaceutical and Biology).

3.1 Chemical and Radiopharmaceutical Laboratory:

Cannabis Flower monograph

As part of the standardization, we tested the Cannabis Flower Ph. Eur. monograph (PA/PH/Exp. 13B/T (20) 4 ANP in Q1 of 2023 before it was launched in PharmEuropa.

We required samples with different levels of THC and CBD to covering all from a Danish manufacturer. The tests performed were Foreign matter, Loss on drying, Total CBN and Assay.

The result of the testing were several comments to the draft monograph for example to the system suitability limit for the total CBN which were changed afterwards. The monograph has been published at the EDQM webside and will be part of the Ph. Eur. in 2024.

All samples complied with the requirements in the draft monograph.

Medicinal products prepared in pharmacies

The Danish Medicines Agency has worked with the regulation of unlicensed pharmaceutical preparation of medicines for a long period.

In 2016, a regulation suggestion was found in the Resolution CM/Res (2016)1- on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. This was implemented in the Danish legislation in 2016 in adaptation of national regulation for medicines BEK. No. 454 19/05/2016 (DLS) (version at the time).

An interdisciplinary project between the assessors, the inspection and the OMCL was set up to verify how well this legislation was followed. A list of bulk-produced unlicensed pharmaceutical preparation of medicine products was been obtained from all regions of hospital pharmacies in Denmark. Selected preparations were chosen using a risk basis approach, of which full documentation was requested to verify the adaptation of DLS. In addition, already ongoing control cases on unlicensed pharmaceutical preparation of medicine products in the laboratory were included for the project assessment also from private pharmacies. Presentation of the results from this project were given at the annual OMCL meeting in 2023.

Collaboration project with INK, API sampling

In 2022, members of the laboratory joined the inspectors (INK) on inspections, as experts. One of this collaboration projects with the INK was at a national API product and QC site.

4 API's were selected to be sampled during the inspection, and analyzed as a laboratory control. The API's were selected based on various criteria. Of the selected API's, three were sampled and analyzed, and one only documentation control was performed.

For the three API's analyzed, a total of 13 individual analysis across 9 different analysis techniques were performed.

Of the most significant findings, one of the API's were tested following a BP monograph. It was identified that the Assay method in the monograph was not possible for the LAB to perform, and that MAH were using an in-house method as Assay. This in-house method was not part of the dossier, and MAH were requested to submit relevant documentation for such in-house Assay method. Furthermore, a significant error in the BP monograph were identified and BP contacted. Regarding the API were only documentation was performed, it was identified that the documentation was insufficient, but MAH could not promise to update it, as the future of the API had to be evaluated.

All laboratory and documentation findings were shared with INK and included in INK's risk assessment for the next inspection at the MAH's API product and QC site.

National Market Surveillance studies

Nicotine products

In 2020/21 a project where started in collaboration with the Swedish OMCL evaluating the Nicotine products on the Danish and Swedish marked. In 2021 the control of the documentation where finalized on 7 products.

In 2023 Analytical control was performed for 3 of them, whereas 1 of them where from Sweden. The analytical control included HPLC Assay of the active ingredient, as well as related substances and other ingredients. All results conformed to the specification limits. The outcome of the controls showed mainly difference in some of the related impurities, COA versus the analytical method SOP.

ADHD medicines containing methylphenidate

Based on our risk-based model the Danish OMCL performed in 2021 a market surveillance study on ADHD with the active ingredient Lisdexamfetamin. In 2022 and 2023 we continued the market surveillance study further on with testing ADHD medicines containing the active pharmaceutical ingredient methylphenidate. We tested 19 medicinal products from 7 different manufacturers. The outcome of the controls showed, that it is important in the analysis method, clearly to be written which specific detector is used in quantitative analysis. Furthermore, we had several comments to the documentation, which afterwards were updated.

Vaginal and rectal preparations

In 2023, a national control project regarding rectal and vaginal preparations was initiated by the Danish OMCL. The project was formulated on the basis of a risk assessment of the pharmaceutical products available on the Danish market with a focus on various parameters that may have an impact on patient/quality assurance. The overall purpose of the project was to test for disintegration of vaginal and rectal preparations (suppositories and pessaries), and thus get our new disintegration equipment tested and maintain test experience of our technicians in the Laboratory.

Eye preparations

7 products were chosen for the project, most of them registered between 1957 and 2000. Control of the documentation was performed for all 7 products. Analytical control was performed for 5 of them, chosen based on the documentation control.

The analytical control included HPLC Assay of the active ingredient for all 5 products analyzed, as well as related substances and other ingredients for some of them. All results conformed to the specification limits.

The main findings in the control of documentation was: Traceability problems between specifications, CoA's, method descriptions and validation reports. Missing traceability to a primary reference standard on the certificate of a working standard from MAH. Incorrect calculation formulas in method descriptions. Incorrect correction factors for specified impurities, resulting in reconsideration of the specification limits for the impurities. Insufficient validation of analytical methods.

The outcome of the control was that 5 of the products will have their dossier updated according to the findings in our control, while 2 of the products were taken off the marked by MAH as a consequence of low sale.

Participation in MSS studies MSS059, MSSFP005 and MSS060

In 2022 the DKMA have participated in three Market Surveillance Studies (MSS studies), which were initiated by the API working group and coordinated by the EDQM.

DKMA participated in the MSS059 Tadalafil API and tablets, where we analyzed 24 finished products and 15 APIs for assay, related substances and dissolution (only finished products). All products were collected directly from the MAH and were products on the DK market.

For the MSSFP005 the DKMA performed GC-MS hyphenated headspace analysis on 46 APIs collected in the MSS059 Tadalafil API and tablets collected from the European market. The scope for DKMA were to analyze for 10 known residual solvents on the GC-HS-MS. Other agencies were coordinated to perform other techniques such as NMR, LC-MS, HPLC and others. All data were collected and chemometric analysis on all data were performed. The API working group are working on an article that hopefully will be released in coming year.

In the MSS060 Olanzapine API and tablets, we required 15 finished products and 10 corresponding APIs from the MAH on the DK market. We analyzed the finished products for appearance, identification, mass variation, assay, content uniformity and dissolution. For the APIs they were analyzed for water content (semi-micro determination, (Ph. Eur. 2.5.12), assay and related substances. We reported the results to EDQM.

Testing of radiopharmaceuticals 2022-2023

The Danish OMCL has performed analytical control of selected radiopharmaceuticals. The analytical control was initiated by different channels as, complaint from a hospital, requests from another OMCL and our in-house testing plan with focus on radiopharmaceuticals, which have not been tested before. The control included medicinal products with the formulation *kits for radiopharmaceutical preparation* with focus on determination of radiochemical purity after radioactive labelling with the radionuclide Technetium-99m.

The complaint was related to the method non-filterable radioactivity stated in European Pharmacopoeia in the finished product monograph on Technetium (Tc-99m) macrosalb injection.

Another product was tested in accordance to a coming update of a method in the finished product monograph on Technetium (Tc-99m) oxidronate injection.

The details and outcomes of the control on radiopharmaceuticals, for example the control on the finished product Tektrotyd, are available in the MRP/DCP database at EDQM.

As the Danish OMCL is the only laboratory with facilities and competences in testing of radiopharmaceuticals within the network of Official Medicines Control Laboratories (OMCL), all control performed on radiopharmaceuticals independent on licensing procedure are exchanged within the network in the specific folder ‘Document Upload’ in the MRP/DCP database.

3.2 Biological Laboratory

CAP testing

The Danish OMCL participated in 8 collaborative studies in the 2022 and 2023 CAP program. One of these studies were continued from the 2021 CAP program.

Further 2 studies will continue from 2023 in 2024. 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

Participation in MSS studies

In 2022 the DKMA have participated in a Market Surveillance Study (MSS study) initiated by the National Institute of Pharmacy and Nutrition in Hungary (Hungarian OMCL) and coordinated by the EDQM.

Since 2017, the Hungarian OMCL had received numerous quality complaints regarding problems with the breaking of glass ampoules. The main problem was the formation of micro and semi-micro glass particles when opening the ampoules.

Prior to the MSS study, the Hungarian OMCL had launched a national market surveillance study to investigate the actual frequency of this quality defect (contamination of solutions with glass particles after opening the glass container of the ampoule). In at least 20% of the opened ampoules, particles were detected in the injectable solution. In order to get an overview of the overall market situation in the EU with regard to this type of quality defect, the Hungarian OMCL proposed to organize an MSS within the OMCL network (GEON).

DKMA participated in the 'MSS61 Breaking of Glass Ampoules', where we analyzed 120 glass ampoules for quality defects before and after breaking of the ampoule. In addition, 3 analyses of the content of each ampoule were performed: (1) Visible Particles (Ph.Eur. 2.9.20), (2) Extractable Volume (Ph.Eur. 2.9.17), and (3) Subvisible Particles (Ph.Eur. 2.9.19). All ampoules were collected directly from MAH and were products on the DK market. The results were reported to EDQM.

Gene Therapy Working Group

DKMA hosted the 13th meeting in the OMCL Gene therapy working group in nov-dec 2023.

3.3 General Regulatory Tasks

National Market Surveillance study on anti-tampering devices.

The Danish Medicines Agency's laboratory has completed the Project on control of anti-tampering devices. Of the 191 tested packages, 19 (10%) had an anti-tampering device that did not function properly, thereby it was possible to access the medicine without any visible marks on the packaging. Particularly packages made of glossy or coated cardboard, it was easy to remove the anti-tampering device when designed as a label/wafer/tape with or without perforation. The general conclusion is that the Danish market is doing well in regard to the quality of anti-tampering devices on marketed pharmaceutical packages.

CAP sampling and label check

For centrally authorised products CAP sampling and label check were performed for packages on the Danish marked.

In 2022, 6 products were sampled. No generic or parallel-distributed products were sampled in 2022 because no products with sufficient expiry date could be found or due to supply difficulties.

Non-compliance with labelling requirements were detected for 2 products. The non-compliances detected were of minor importance.

In 2023, 15 products were sampled. Of the 15 products sampled in 2023, 4 were parallel distributed. No generic products were sampled in 2023.

Non-compliance with labelling requirements were detected on 3 products. The non-compliances detected for the 2 products were of minor importance. The last non-compliance detected lead to a recall assessment.

Danish Pharmacopoeia

In 2022 the Danish pharmacopeia (Danske Lægemiddelstandarder, DLS) got an exhaustive revision. This work was a corporation with inspectors, assessors and the OMCL facilitated by our jurists and the Danish Pharmacopeia secretary. The result was implemented in Danish law in 2023.

Contribution to the European Pharmacopoeia (Ph. Eur.)

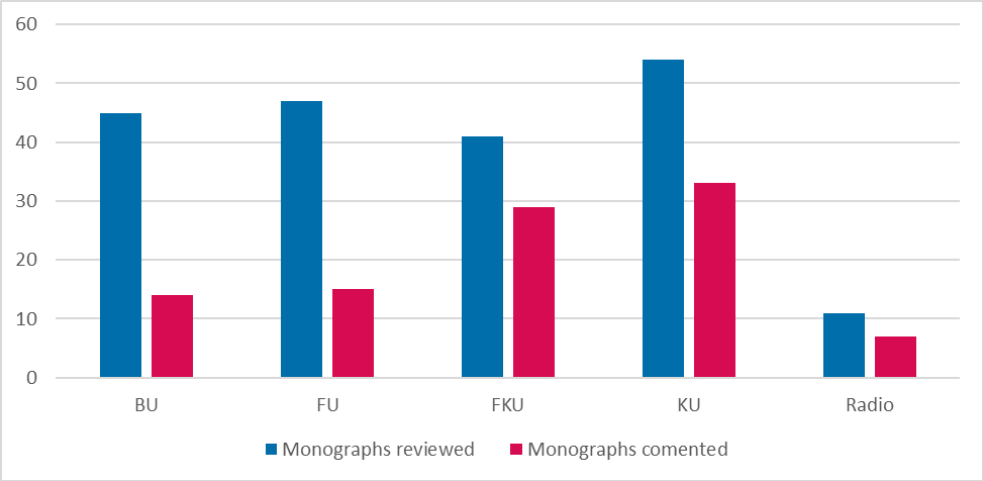
Denmark have 3 delegates in the Ph. Eur. Commission who participate in the tree yearly meetings. The Danish OMCL also participated in a number of the expert groups located under the Ph. Eur.

- 10A: Organic chemistry
- Gr. 14: Radiopharmaceutical
- Gr. 15V: Vet. Vaccines
- CTP WP: Cell Therapy Products
- MAB WP: Monoclonal Antibodies

A substantial part of the Danish activities concerning development of pharmacopoeial monographs (e.g. "Pharmeuropa" evaluation) takes place in the 4 committees for biology (BU), chemistry (KU), pharmacy (FU) and pharmacognosy (FKU). The Danish working group for Radiopharmaceuticals (Radio) have also handled relevant monographs.

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 2022. The number of monographs reviewed and commented is illustrated in Table 3.

TABLE 3
REVIEWED AND COMMENTED MONOGRAPHS IN 2022



The 4 committees for biology (BU), chemistry (KU), pharmacy (FU), pharmacognosy (FKU) and the Danish working group for Radiopharmaceuticals (Radio).

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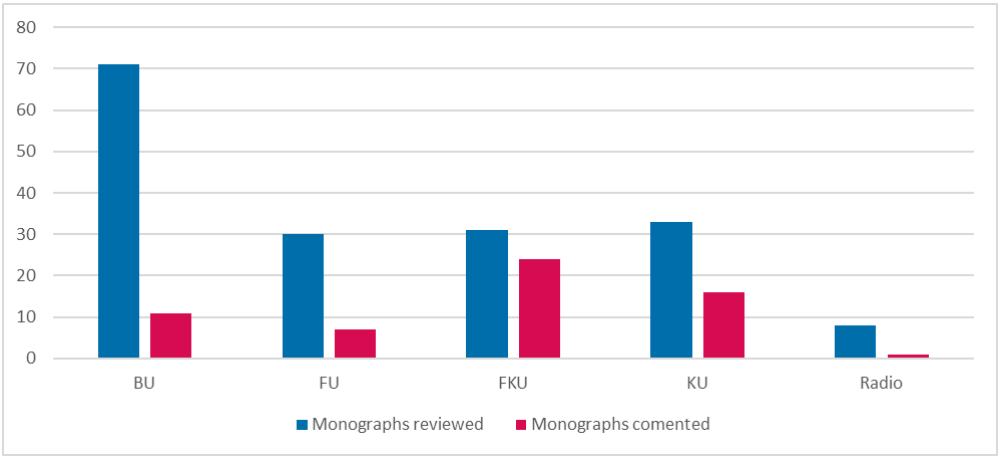

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In 2023 the monograph for Pyrogenicity (5.1.13.) were introduced to the Ph. Eur. Subsequently, a large number of monographs were revised to correct the information and references to pyrogenicity testing. The number of revised monographs for BU in 2023 therefore stand out, see table 4.

4 Method related activities

In this section, we report some of the highlights from the OMCL's method related activities in 2022 and 2023.

Nitrosamines

In 2022/2023 the Danish OMCL developed and validated a method for the determination of N-nitroso dimethylamine (NDMA) and N-nitroso diethylamine (NDEA) in sartan products using LC-MS (QTOF). The Danish OMCL has evaluated the need for a more sensitive triple quadrupole LC-MS for the analysis of nitrosamines, and is currently considering a possible investment.

Monocyte Activation Test:

The Danish OMCL has re-qualified the *in house* MAT assay according to the changes and new requirements in the European Pharmacopoeia (Ph. Eur.) 2.6.30.

Method development

The Danish OMCL has developed and validated an internal method for the determination of steroids in cream products.

Moreover, the OMCL has optimised and revalidated a quantitative/semi-quantitative GC-MS method for the analysis of residual solvents in finished products and API's. The aim for this method is to be used for control projects in 2024 and in the future.

Subvisible particles

In 2022, a HIAC 9703+ particle counter was qualified in order to test for sub visual particles in vaccines and other parenteral preparations. The apparatus has in 2022 and 2023 been used in control project according to Ph. Eur. 2.9.19.

5 Public relation activities

In this section, we report some of the highlights from the OMCL's public related activities in 2022 and 2023.

The new Cannabis Flower monograph were published on EDQM web side in Q4 2023 and will be part of the Ph. Eur. in 2024.

The MSSFP05 study resulted in an article in Journal of Pharmaceutical Sciences, which was published by Elsevier Inc in May 2023.
The title is "Clustering of Tadalafil API Samples According to their Manufacturer in the Context of AP Falsification Detection" by E. Deconinck *et al*. Journal of Pharmaceutical Sciences vol. 112, 2023, 2834−2842

The main focus was performing a multi analytical approach and chemometrics as a tool for the discrimination of manufacturing sources.

This paper reports the results of the active pharmaceutical ingredient (API) fingerprint study, organized by the General European Official Medicines Control Laboratory Network (GEON), on tadalafil. A classical market surveillance study, evaluating compliance to the European Pharmacopoeia, was combined with a fingerprint study, the latter to obtain characteristic data for the different manufacturers, allowing the network laboratories to conduct authenticity tests for future samples, as well as to detect substandard and falsified samples. In total, 46 tadalafil API samples from 13 different manufacturers were collected. For all samples fingerprint data was collected through analysis of impurities and residual solvents, mass spectrometric screening, X-ray powder diffraction and proton nuclear magnetic resonance (1H-NMR).

Chemometric analysis revealed that all manufacturers could be characterised based on the impurity, residual solvent and 1H-NMR data. Future suspicious samples in the network will therefore be analysed with these techniques in order to attribute the sample to one of the manufacturers. If the sample cannot be attributed, a more profound investigation will be necessary to reveal the origin of the sample. In cases where the suspect sample is claimed to be from one of the manufacturers included in this study, analysis can be limited to the test distinguishing that manufacturer.

The Biological Laboratory participated in the validation of a qPCR method for determination of viral genome titres of AAV2-based vector preparations. This work was combined in the article: “Validation of a qPCR method for determination of viral genome titres of AAV2-based vector preparations” by V. Ridoux *et al.* Pharmeuropa Online, Pharmeuropa Bio & Scientific Notes, august 2023.

Abstract: The viral genome titre is universally used for the dosing of adeno-associated virus (AAV)-based vectors used for gene therapy. To standardise this determination, the development of a common method would be valuable to facilitate comparison of viral doses used in the clinic and in the subsequent quality control of the products. A collaborative study was initiated by the Gene Therapy Working Group of the General European Official Medicines Control Laboratories Network in order to validate a qPCR-based method targeting the ITR2 sequence common to a broad variety of AAV vectors, independently from the serotype of the capsid or from the specific transgene. Five preparations of AAV vectors from various serotypes, including the AAV2/2 (RSS2) and AAV2/8 (RSS8) Reference Standard Stocks (American Type Culture Collection, USA) were used in the study. A plasmid carrying the ITR2 sequence was used to prepare standard curves. Its digestion outside the ITR regions facilitated melting of the hairpin ITR sequence during PCR, allowing better accessibility to the DNA polymerase. The results show that this qPCR method is satisfactory in terms of accuracy and precision. The reproducibility is also acceptable when compared with other similar studies, as it was shown previously that titres obtained by qPCR generally show higher inter-laboratory variability. The use of RSS2 or RSS8 as normalisation control in each assay demonstrated a promising help to identify potential sources of variation in a given laboratory or to smooth out inter-laboratory variations, thus improving reproducibility.

6 Future planning

6.1 National

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

The OMCL will participate i the audit programme among the GMP inspectorates for human and veterinary medicines agencies known as the Joint Audit Programme (JAP) in September 2024 and in November 2024 in the benchmarking programme among the human and veterinary medicines agencies known as the Benchmarking of European Medicines Agencies (BEMA).

The OMCL is continuously developing our risk assessment model. We are planning to include “drug formulations” as part of the model.

6.2 Network

The Nordic OMCL network will focus on spilt tests OTC products with common Nordic labelling.

7 Difficulties encountered

The OMCL's difficulties related to testing activities.

The Danish OMCL regularly encounter challenge with receiving material from MAH, as well as vendors at expected time. This may lead to delay in delivering results on the CAP testing to the EDQM.