HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Public Consultation on
Annual Review and Proposal for Fees – Financial Year 2024

Human Medicines, Compliance Activities, Blood, Tissue Establishments and Organs and Medical Devices

October 2023

CONTENTS

1 INTRODUCTION

The Health Products Regulatory Authority (HPRA), since its establishment in 1996, has successfully run its regulation of human medicines authorisation, manufacturer and wholesaler operations without recourse to exchequer funding, and has established sufficient reserves to allow it to fund capital and IT expenditure and deal with unexpected costs as these arise. This is both a requirement under the Irish Medicines Board Act and a stated objective of the Authority[1] of the HPRA. Since 2004, the HPRA has implemented a policy of annual fee reviews following consultation with industry. For medical devices, cosmetics, blood tissues and cells, the HPRA receives a partial subvention from the Department of Health but also commits to ensure that the income received matches the costs of those functions.

As stated in previous consultations, it is a priority for the HPRA to match resources from fee income, with current work volumes and to plan for future activity. The second aim, in respect of fee income, is to provide predictability, stable timelines and ability to fund the cost of the regulatory system that we operate.

To ensure that we manage the business properly, we have agreed to review our fees on an annual basis to reflect changes to our cost base and service levels. This document summarises the outcome of our review of fees, and it sets out the current operating environment, the service levels and activities and expected changes in service levels and activities for 2024.

2 THE OPERATING ENVIRONMENT

In 2023 the operating environment, following the difficulties during and after COVID-19, stabilised in the HPRA. Hybrid working is established within the organisation, enabling 350 staff to return to the office while continuing to facilitate homeworking. While the hybrid model continues to be reviewed, the organisation is adapting to the new way of working.

During 2023 the pandemic officially ended and while work continues on COVID-19 vaccines and therapeutics, it has become business as usual. However, 2023 was a busy year as work that had been put on hold during the pandemic years restarted. Volumes of transactions were high and significant amounts of legislation are in the process of being implemented (the Clinical Trials Regulation (CTR), the *In vitro* Diagnostic Medical Devices Regulation (IVDR)), in negotiation (Substances of Human Origin Regulation (SoHO)) or published (the pharmaceutical package). In relation to Brexit, the publication of the Windsor Framework (WF) at the start of the year, combined with the expiry for the Brexit exemptions in the end of 2024, brought Brexit to the

[1] The term 'Authority' is used to refer to the persons appointed under section 7 of the Irish Medicines Board Act, 1995, and previously referred to as the 'Board' of the IMB.

forefront and implementing plans to address the full impact of Brexit/WF has commenced. Overall, human medicine income and other income categories remain at expected levels with the exception of compliance income which is below planned levels.

In 2024, authorisation and inspection volumes are expected to be consistent with 2023 and costs are expected to increase. Payroll costs were significantly less than planned in 2023 as full employment in the market, resource constraints and delays in approvals meant that positions were unfilled for a large part of the year. In 2024 we expect significant increases in the cost of payroll related both to increases in staff numbers and pay increases, although the latter have not yet been agreed. The increase in staff numbers is due to delays in recruiting in 2023 and greater staff turnover. However, additional staff are also required to deliver in the CTR, the level of Mutual Recognition Procedures (MRP) / Decentralised Procedures (DCP) in the system and the need for more centralised assessors. The medical device department continues to need additional staff as the MDR/IVDR is rolled out and acknowledged overall lack of resources in the EU system. Big projects such as the website redevelopment, the pharmaceutical legislative project and the sodium valproate inquiry will also impact resourcing. Costs in 2023 increased in line with inflation. General inflation remains high and is expected to impact costs for 2024.

Due to the increased complexity of regulation and enhanced regulatory and public health offerings, staff numbers continue to increase.

As noted previously, since 2019, the HPRA makes an employer contribution in respect of staff employed since 2013, under the single service scheme. This contribution is up to 17% of the payroll cost of those employees. By its nature, it will increase exponentially as all new staff are covered by this obligation and this means that as longer serving employees leave, they are replaced by a more expensive resource. It is appropriate, in common with all pension schemes that the employer makes a contribution and we have flagged in previous fee consultations the long-term impact of an unfunded pension scheme. This pension liability continues to impact on fees.

A particular area of concern is increased litigation, in the areas of both personal injury and judicial review. This unfortunately results in increased costs and resources dedicated solely to work which delivers nothing under our public health remit.

Public scrutiny and the role of the regulator in relation to medicines has increased in the areas of global supply and shortages, vaccines and vaccine hesitancy, and availability and access to innovative therapies.

3 STRATEGIC DIRECTION OF THE HPRA

During 2020-2021, the HPRA developed a new strategic plan for the period 2021-2025. Following extensive consultations and a detailed review of the environment within which we operate, we have identified the themes and activities which we believe are relevant to the development of our

regulatory activities over the next five years. The high-level strategic goals under the current plan are as follows:

- **Health system partnerships** (strengthening our collaborations across all areas of the health system)
- **Progressive regulation** (increasing our use of proportionate and adaptive approaches for better patient outcomes)
- **Communication and engagement** (improving our models of engagement to strengthen public trust and confidence)
- **Enabling innovation** (enhancing our supports for innovation from discovery through to regulatory approval)
- **Great people, great processes** (developing our organisation and people to successfully achieve our goals)

The key projects for 2024 will include:

- Building on relationships with key stakeholders within the health system. The HPRA will continue to develop relationships with health service providers and policy makers to discuss significant issues relating to health products and related risk mitigations.
- Continue to progress activities under the shortages framework.
- Developing further capacity in clinical trials under the CTR, MRP/DCP and centralised assessment.
- Replacing the existing HPRA website with a new website with greater functionality. This is a major development project with a cross organisational team and external service supplier.
- Developing plans (including capital investment) to deliver on the Government sustainability plans for 2030.
- Engaging with clinical researchers to support innovative research in Ireland.
- Implementation of the IT strategy to ensure longevity and resilience in the system.
- Implementation of the new people strategy.
- Contributing to the planned inquiry into sodium valproate
- Participating in a number of workstreams under the EU Health4Europe initiatives.
- Participating in the review nationally and at a European level with the new legislative pharmaceutical package published by the Commission.
- Continued implementation of the Clinical Trials Directive, Medical Devices and IVD regulations
- Participation in European and international working groups and initiatives such as Accelerating Clinical Trials in the EU (ACT EU), IncreaseNET, CORE-MD, tactical group on resourcing, simultaneous national scientific advice, crisis management, GMP WG, ICMRA, PQKMS among others.

All the above initiatives will provide real and tangible benefits to our stakeholders.

4 THE OUTLOOK FOR 2024

Operating environment for 2023
In a period of high inflation, the operating environment remains challenging.

New legislation
In 2022 the HPRA implemented three new regulations: the New Veterinary Regulation (NVR), the CTR and the IVDR. The HPRA will continue to implement these regulations in 2023 as the transition provisions expire. Further legislation is expected in the areas of substances of human origin. The pharmaceutical package containing a directive and regulation was published Q1 2023. The legislative package updates existing legislation for human medicines, paediatrics and orphan medicinal products. This is an extensive body of legislation and will be a significant workload in the coming year.

A new directive, the 'Resilience of Critical Entities Directive', has been published and has implications for medicines and medical devices. The impact of this directive is currently being worked on.

The workload of the medical device department has increased significantly. The importance of the role that medical devices play in healthcare delivery and the related challenges in their regulation was highlighted in recent years by the COVID-19 pandemic. The Medical Device Regulation (MDR) and IVDR are both applicable. Significant work remains in providing support to stakeholders to aid their understanding and support their implementation of the regulations.

The new regulations place very explicit obligations on regulatory authorities in relation to their activities, resources and capabilities. In addition, growth in specific technological areas, such as digital health products and *in-vitro* diagnostics will necessitate reallocation, re-purposing and development of our staff. This means that staff increases in 2023/2024 are required to manage this increased workload. This will impact on the funding model, which is currently subvented by the Department of Health.

Implementation of new legislation does not just impact the departments concerned, their impact is felt across the organisation as management, legal, HR, IT and financial support is necessary for the successful delivery of the new legislation.

Financial outturn for 2023
The outturn for 2023 will be positive. This reflects the income levels operating as expected and significantly lower costs, principally around payroll caused by the inability to bring the expected levels of staff on Board in the first half of 2023.

Financial impacts on 2024
It is expected that there will be a substantial increase in costs for 2024. This reflects the high level of recruitment in Q3/Q4, planned additional staff in 2024 and a continuing increase to costs reflecting the continuing high levels of inflation. Income levels are expected to hold in 2024.

Payroll
The key drivers of payroll increases in 2024 will be:
- Additional staff numbers related to expanded functions, increased levels of work.
- The impact of the 1.5% increase from October.
- Pay increases 2024 (not yet known but under negotiation).
- Increased pension costs.

Other costs
Other costs continue to increase as activity levels are returning to pre-pandemic levels. The current energy crisis significantly increased costs in 2023 and will have a knock-on impact in 2024, although there is evidence of steadying energy costs. While inflation (which has been running as high as 9% in 2022) has reduced to 6% in 2023, it will still have a significant impact on projected costs.

The HPRA expects that 2024 will be another challenging year in managing costs for the reasons outlined above.

4.1 Risks and uncertainties in relation to the fee model

The fee proposal outlined above is based on the volumes and patterns of submissions seen in the first seven months of 2023. The nature of regulatory income is that it is dictated by industry activity, which can change significantly over a period of time.

As with previous years, the HPRA commits to review the proposed fees during the planning cycle in 2024 and further amend the fees and fee structure, if required, for 2025.

5 PROPOSED FEES

While the cost base of the HPRA will increase in 2024, the HPRA acknowledge that the costs, in particular payroll, were below budget in 2023 and this resulted in a positive financial outcome. To reflect this, and taking the two years together, the HPRA propose to impose only a minor inflationary adjustment of 1.5% in 2024. This 1.5% is only intended to cover the agreed payroll increase in October 2023 and which will be in place for all of 2024. It will not cover other cost increases which will be reviewed as part of the 2025 fees.

6 DETAILED CHANGES TO FEES

6.1 General change to fees

As outlined above there will be a minor 1.5% adjustment to fees for the year 2024.

6.2 Other proposed adjustments to fees – clinical trials

6.2.1 Clinical trial fees under the Clinical Trials Regulation (CTR) – the HPRA fee and NREC fee

A single fee is charged by Ireland (the HPRA and the National Office for Research Ethics Committees (NREC) Office) for each clinical trial application (CTA) or substantial modification (previously known as substantial amendment). The sponsor pays the total fee to the HPRA at the time of application on the Clinical Trails Information System (CTIS) and following validation the HPRA will transfer the corresponding portion to the NREC Office.

The HPRA and the NREC Office are not proposing to increase the current CTR fees.

Please note for clinical trials authorised under the Clinical Trials Directive (CTD), fees charged by both the HPRA and NREC are not linked and therefore payment of fees is made to each organisation based on each organisation's set of fees. The HPRA is not proposing to increase fees in 2023 for CTD amendments to clinical trials. For information on NREC fees, see https://www.nrecoffice.ie/about/national-office/.

6.2.2 Non-commercial / academic clinical trials under Regulation No: 536/2014

NREC and the HPRA have proposed not to charge for non-commercial/academic clinical trials from 2024 and the following fee codes will be removed. The removal of these fees has been taken to encourage non-commercial research.

Fee code	New Description
1006	Authorisation under Regulation No. 536/2014 Clinical Trial Regulations – Non-commercial / Academic Trials
1014	Substantial Modifications (Parts 1 & 2 or Part 1 only) – Non-commercial / Academic Trials
1019	Substantial Modifications – Part II only – Non- commercial / Academic Trials
1021	Appeal to a Clinical Trial decision non-commercial

6.2.3 Appeal of a clinical trial decision

It is proposed to include the HPRA appeal fee of €690 along with the NREC appeal fee portion of €1,200 resulting in a total appeal fee of €1,890.

6.3 Other Proposed adjustments to fees – Medical Devices

6.3.1 MDR Article 51(2) / IVDR Article 47(2) referral for decision

It is proposed to increase the fee for MDR Article 51/IVDR Article 47 referral for decision from €5,000 to €10,000. In 2023, HPRA received its first applications under these Articles since the EU Medical Device Regulations became fully applicable. The fee was set before HPRA had any experience of carrying out this process. Having received our first applications, it is apparent that the level of assessment resource required to conclude an Article 51/Article 47 decision, means that a fee of €10,000 is required to cover the cost of the procedure.

6.4 Other Proposed adjustments to fees – Compliance

6.4.1 Tissue Establishment (TE) – supplying multiple international organisations responsible for human application (ORHA) or other international TE's/distributors for onwards distribution

It is proposed to charge an annual fee to tissue establishments supplying multiple international organisations responsible for human application or other international TE's/distributors for onward distribution to over 50 organisations.

The annual fee proposed is €945 to cover the biannual review of updated details in relation to the international ORHAs/TE's/distributors.

7 CONSULTATION

The HPRA welcomes comments on these proposals and invites respondents to comment.

Contributions to the consultation on these proposals may be provided to the HPRA by 27 October 2023. Contributions should be sent by email to feesconsultation@hpra.ie.

APPENDIX I SERVICE LEVELS – HUMAN PRODUCTS AUTHORISATION, REGISTRATION AND SAFETY MONITORING

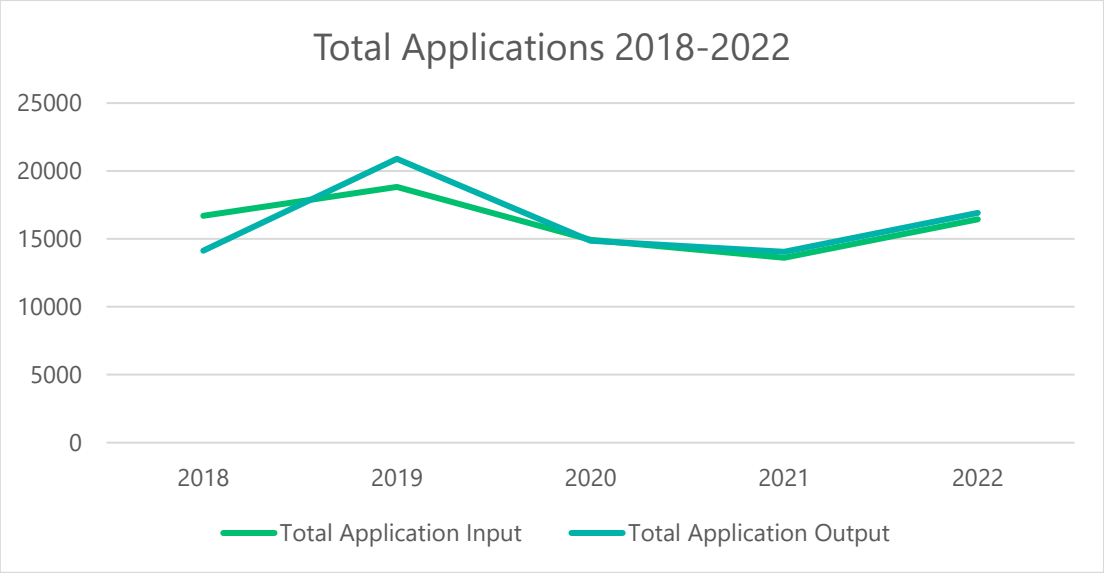
The most significant projects undertaken by the HPRA in the last number of years were driven by the requirement to maintain and further improve patient safety, protect access to medicines and service levels to industry.

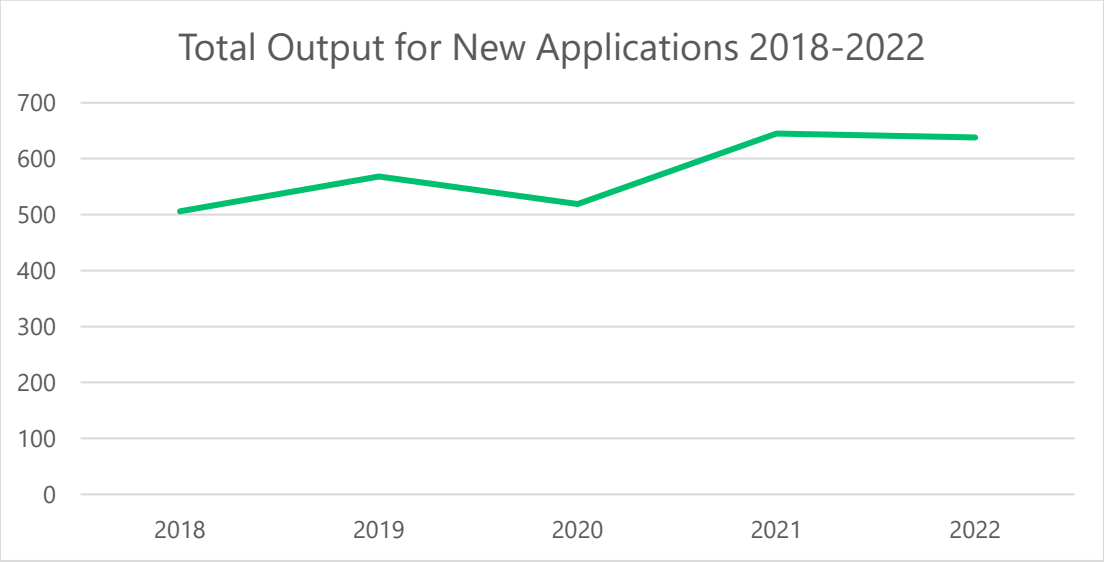
These projects include in summary:

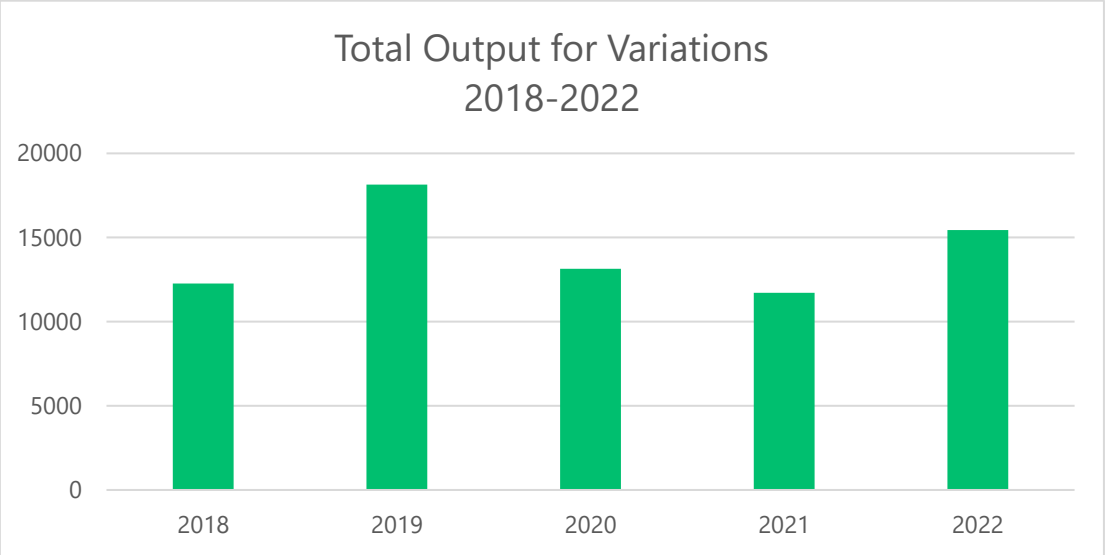
- Readiness to operate as Reference Member State for both MR and DCP new procedures.
- A national scientific advice procedure was introduced in 2016. This assists applicants in the development of new or existing human medicinal products by taking into account the current knowledge of a given condition, targeted patient population, existing treatment modalities and specificities of the product being developed.
- Progress has been made in the development of a new HPRA workflow system. Our focus is now on further optimisation of this workflow technology to ensure ongoing delivery of continued benefits to the organisation and stakeholders in the tracking and managing of workloads. Further development of capabilities in using key performance indicators to allow for more effective monitoring of timelines will improve utilisation of resources and drive further efficiencies.
- Integration of the online reporting system for adverse reactions with the HPRA adverse reaction database which is accessible to patients and health care professionals in tandem with further streamlining of current adverse reaction processing procedures to allow for improved case processing efficiencies. This work supported the significant increase in adverse reaction reports submitted directly to the HPRA arising from the COVID-19 pandemic, including vaccines and therapeutics.
- Continued customer-focused approach.
- Work on the list of interchangeable medicines to support generic substitution by pharmacists in line with the Health (Pricing and Supply of Medical Goods) Act 2013 continues, and is a routine component of our assessment work. We review substances as requested by the Minister for Health or the HSE. In addition, we review applications made by industry to have their products incorporated on to the list.
- Focus on the continued provision of guidance and support to industry stakeholders in areas undergoing evolving regulatory development, including:
    - the new requirements of the Clinical Trials Regulation
    - the new requirements of the Medical Devices Regulations
- A proactive approach to reclassification of the legal status of medicines (switching) continues. The HPRA is open to discussing innovative switches.
- Raising awareness of the regulation of medicines and important safety considerations via publications and contributions to undergraduate programmes in the medical and paramedical fields.

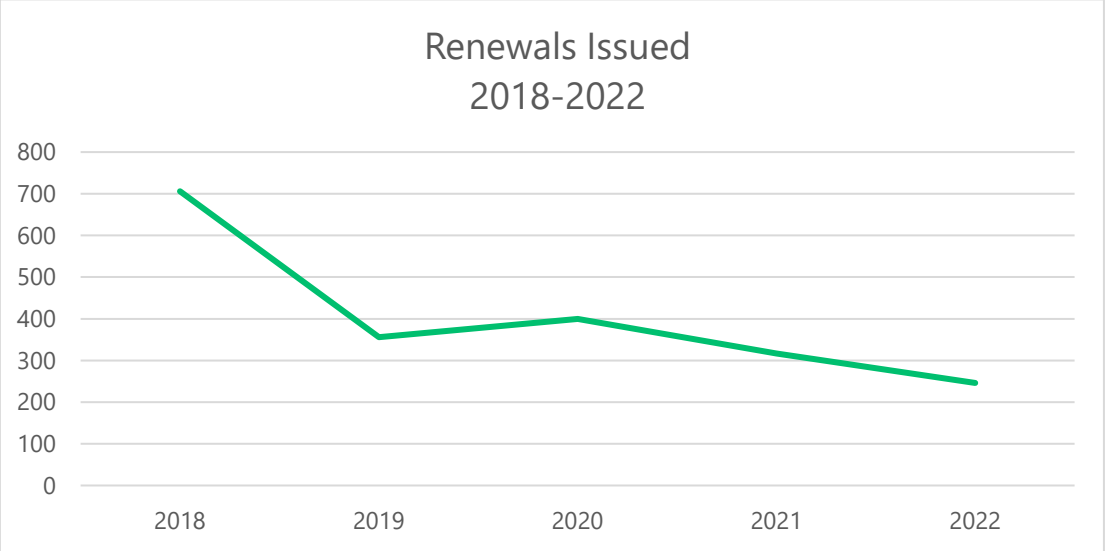
- Enhanced patient engagement through the Patient Forum which facilitates dialogue and exchange on topics relevant to patients regarding the regulation of medicines and medical devices.
- Enhanced monitoring of vaccines and therapeutics related to COVID-19. The substantial increase in the number of direct reports to the HPRA continue to be made available to marketing authorisation holders (MAH) via EudraVigilance.

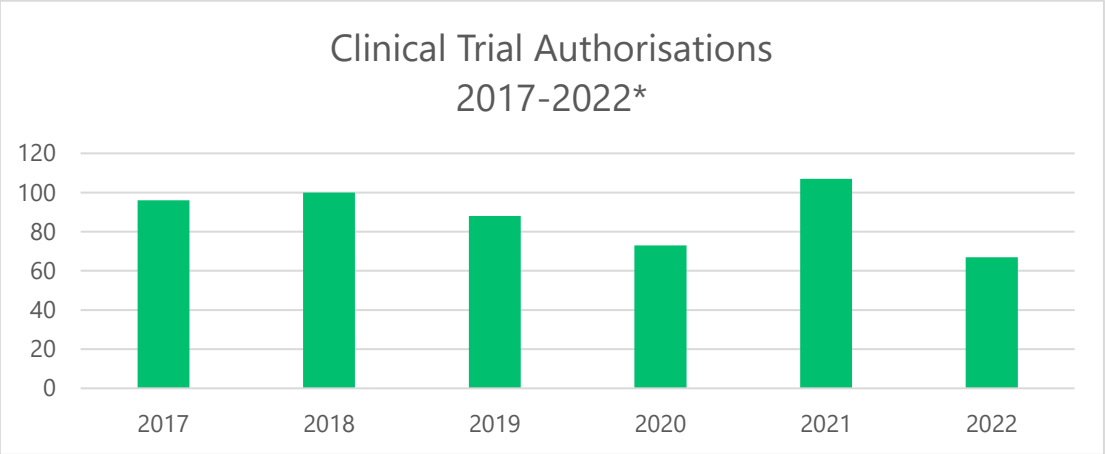
The following graphs outline the output across all application types up to the end of 2022.

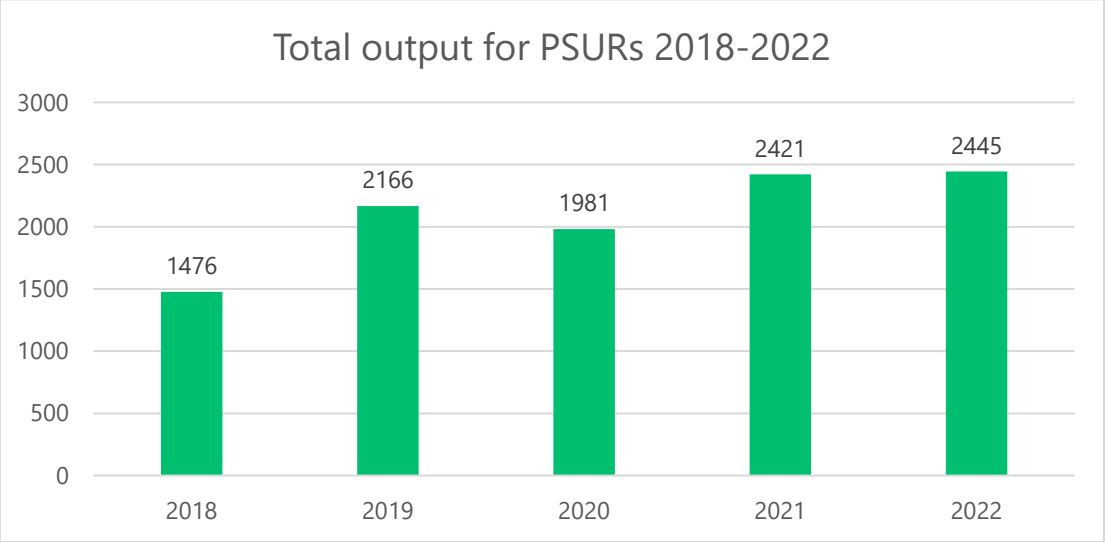


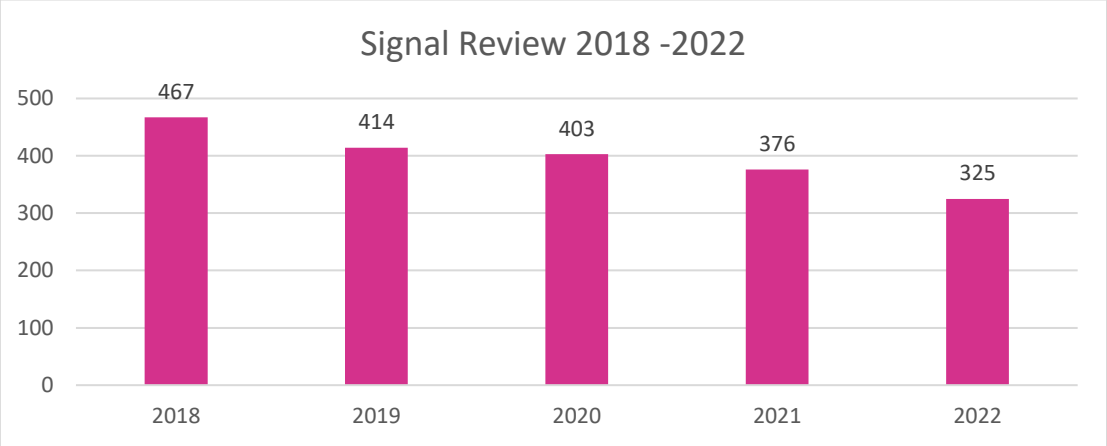


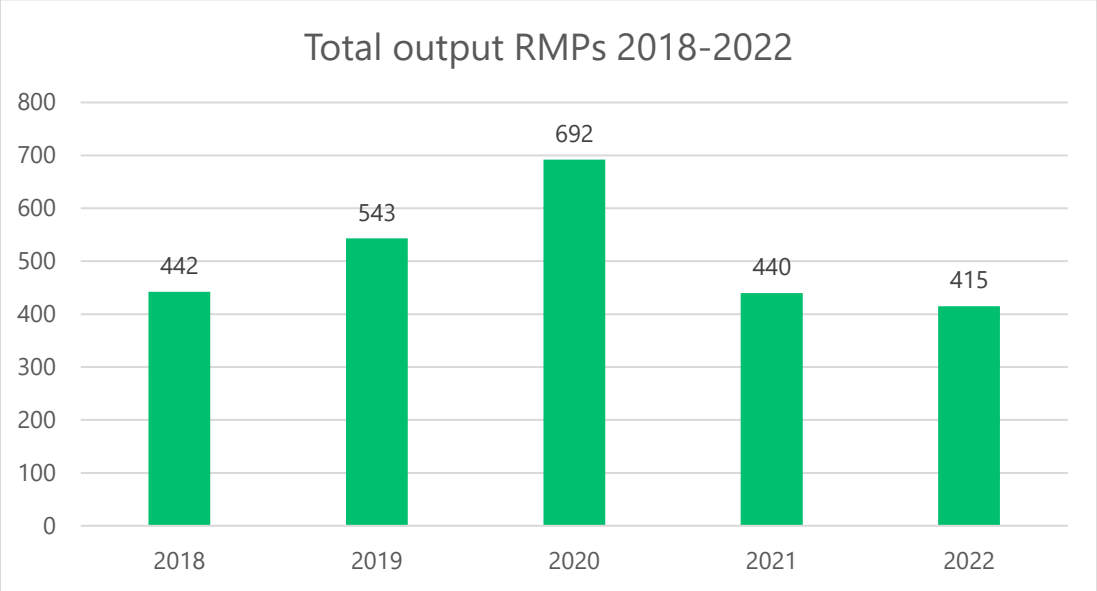

Total Output for Variations
2018-2022
20000
15000
10000
5000
0
2018
2019
2020
2021
2022

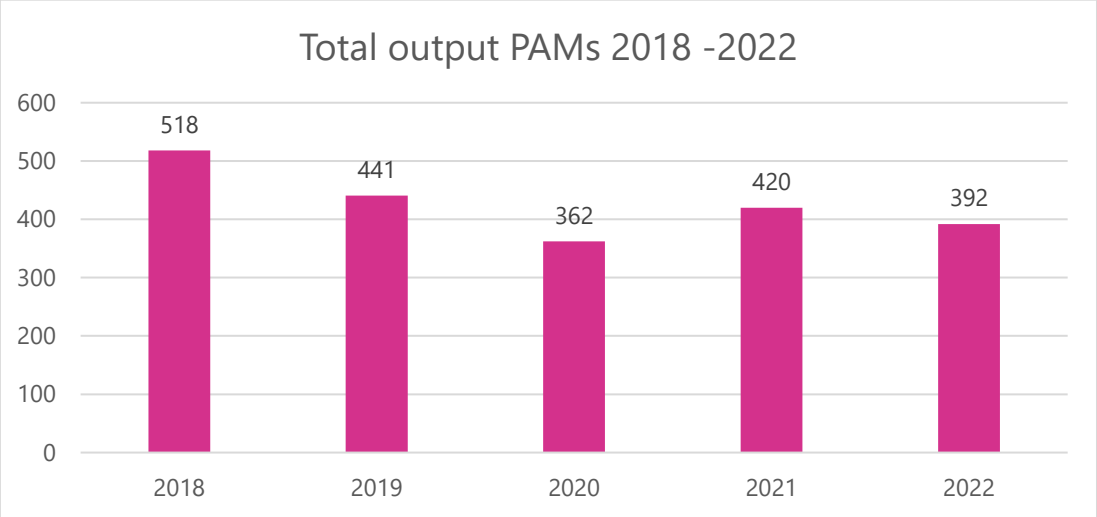

Renewals Issued
2018-2022
800
700
600
500
400
300
200
100
0
2018
2019
2020
2021
2022

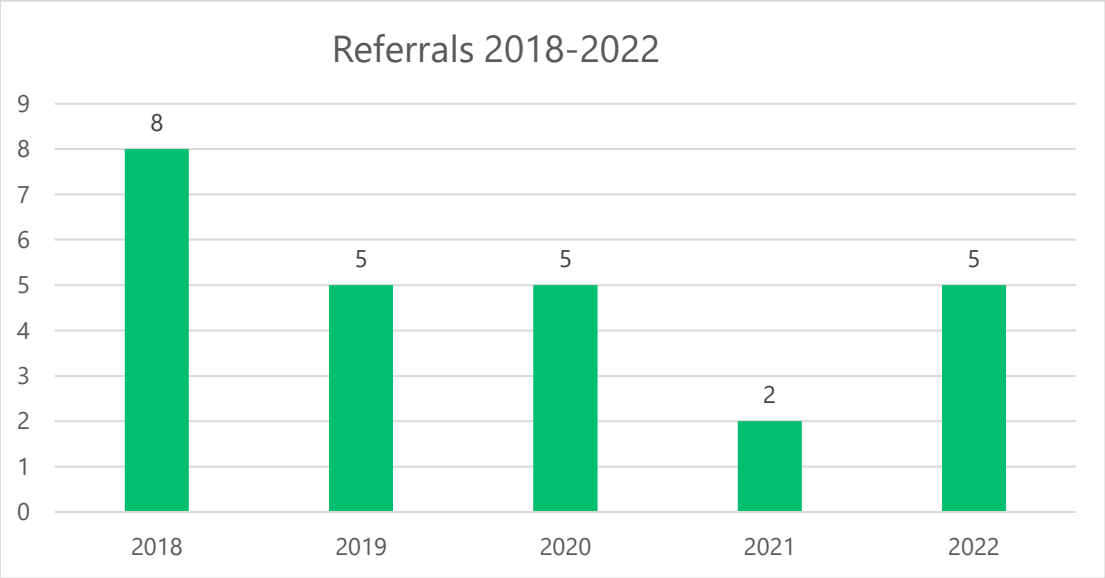

Clinical Trial Authorisations
2017-2022*
120
100
80
60
40
20
0
2017
2018
2019
2020
2021
2022

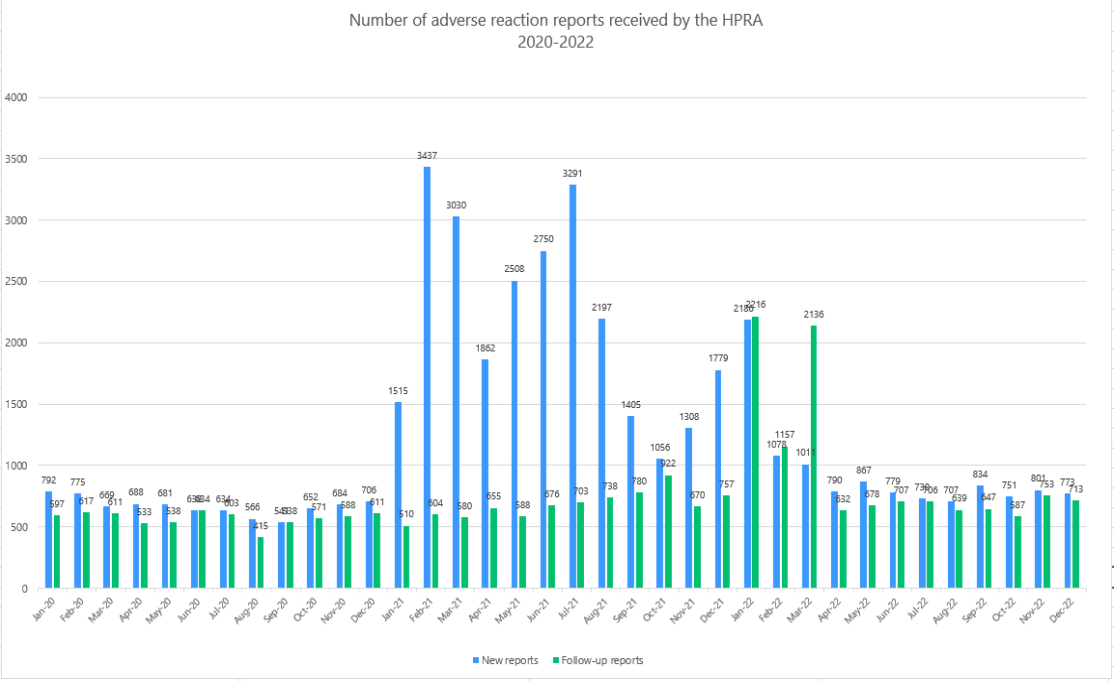

Total output for PSURs 2018-2022
3000
2500
2000
1500
1000
500
0
1476
2166
1981
2421
2445
2018
2019
2020
2021
2022


Signal Review 2018 -2022
500
400
300
200
100
0
467
414
403
376
325
2018
2019
2020
2021
2022


Total output RMPs 2018-2022
800
700
600
500
400
300
200
100
0
442
543
692
440
415
2018
2019
2020
2021
2022


Total output PAMs 2018 -2022
600
500
400
300
200
100
0
518
441
362
420
392
2018
2019
2020
2021
2022


Referrals 2018-2022
9
8
7
6
5
4
3
2
1
0
8
5
5
2
5
2018
2019
2020
2021
2022


Number of adverse reaction reports received by the HPRA
2020-2022
4000
3500
3000
2500
2000
1500
1000
500
0
New reports
Follow-up reports

APPENDIX II SERVICE LEVELS – COMPLIANCE DEPARTMENT

Initiatives undertaken/further developed in 2022/2023 included:

- Preparations for Brexit, in conjunction with other departments across the organisation, have included:
  - Continued engagement with stakeholders with the primary purpose of maintaining supplies of health products through and beyond Brexit.
  - Meetings continued with stakeholder companies to discuss their Brexit related plans and to clarify issues arising. Such meetings and liaison will continue to be an important focus.
  - Regular liaison with key wholesalers to clarify ongoing stock levels of medicines, plans for replenishment, identify any particular difficulties in the supply chain and, if necessary, to assist in remediating those.
  - Meetings with industry representative bodies, and attendance at workshops organised by some of those bodies, to consider and clarify Brexit related questions.
  - Advising potential applicants for authorisations and licences of the requirements and processing of a number of new applications.
  - Provision of support to the Department of Health and the Department of Agriculture, Food and the Marine (DAFM), including participation in regular meetings of the Brexit Operations Group and the Brexit Medicines Review Group, both convened by the Department of Health.
  - Liaison with other agencies, including the HSE and Revenue's Customs Service, on issues of mutual interest.
- Continued provision of support to the Irish Medicines Verification Organisation (IMVO) on the implementation of national legislation aimed at preventing the entry of falsified medicines into the legal supply chain – implementation of Directive 2011/62/EU (Falsified Medicines Directive (FMD)).
- Annual updates to registrations of manufacturers, importers and distributors of active substances and brokers of medicines for human use were processed during 2021 and 2022.
- HPRA staff continued to participate in an expert group on safety features convened by the European Commission. A Commission Delegated Regulation, which sets out the requirements around safety features on the majority of prescription medicines for human use, was implemented by relevant MAHs and manufacturers on 9 February 2019. In relation to this, the HPRA has liaised closely with the IMVO to implement the systems. This has included the development of a national database (repository) for batches of human medicines bearing safety features that are placed on the Irish market and a system for authentication of packs at various points in the supply chain, principally at point of dispensing. The purpose is to guard against falsified medicines reaching patients.

While not part of the governance structure of the IMVO, we continue to liaise closely with it. We have an oversight role in relation to the repository and have taken on the role of lead of the EU working group on supervision of the repositories. We also participate in a National Oversight Group made up of key stakeholders and convened by the IMVO. Implementation of authentication was not straightforward and, accordingly, was approached in a 'use and learn' mode. Gradual transition to full implementation, as per the Delegated Regulation, had commenced during the first quarter of 2021 but had to be postponed due to the advent of the COVID-19 pandemic. The 'use and learn' phase officially concluded on the 30 May 2023.

- Continued upload of post-inspection good distribution practice (GDP) certificates to the EudraGMDP database. All existing Wholesale Distribution Authorisations (WDAs) had already been uploaded to the database and upload of new or varied WDAs continued.
- Continued upload of Manufacturers'/Importers' Authorisations (MIAs) and post inspection good manufacturing practice (GMP) certificates to the EudraGMDP database.
- The NVR (2019/6) was implemented in January 2023. Work is ongoing with colleagues from the Veterinary Sciences department, the legal section and the DAFM to ensure smooth implementation of the new regulation.
- Provision of support to the Department of Health on the implementation of national legislation relating to the Children and Family Relationships Act, Human Tissue Bill and Health (Assisted Human Reproduction) Bill which overlaps with the human tissues and cells legislation for which HPRA are the designated competent authority.
- Continued support to the Department of Health on the implementation of national legislation regarding quality and safety of human organs intended for transplantation – Directive 2010/53/EC. This included monitoring of authorised procurement and transplant centres, via inspections and other follow up measures. The framework for quality and safety of organs for human transplantation, developed in conjunction with Organ Donation and Transplant Ireland (ODTI), is used in evaluating these centres. Review and updating of this framework, in conjunction with ODTI, continued in 2023.
- A system for reporting and assessment of serious adverse events/reactions relating to organs for human transplantation remains in place.
- Continued support to the Department of Health on the development and implementation of national legislation regarding controlled drugs. An upgraded system for processing of licence applications and collation of statistics became fully operational in Q1 2022 and has provided a much-improved service to stakeholders.
- Continued provision of support to the Department of Health in the implementation of an access programme for cannabis for medical use. The HPRA continue to receive and review applications for inclusion of products under the programme. A number of products have been recommended to the Department for inclusion under the programme. This work is ongoing.
- Monitoring, via inspections, of the implementation of GMP requirements, GDP, Good Clinical Practice (GCP), and Good Pharmacovigilance Practice (GvP) standards, and of the required controls relating to controlled drugs and precursor chemicals.

- Provision of support to the Department of Health in implementing two European regulations relating to precursor chemicals.
- Monitoring, via inspections, of the activities of MAH companies with respect to their obligations under the Medicinal Products (Control of Placing on the Market) Regulations, 2007 to 2019.
- Active participation in harmonisation of standards and inspection practices through European Medicines Agency (EMA) working groups and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Committee and its Expert Circle meetings.
- Active participation in the work of the Official Medicines Control Laboratories (OMCL) network to promote risk-based approaches to surveillance programmes and effective work-sharing programmes. The HPRA also led on an initiative within the Heads of Medicines Agencies (HMA) Group on developing a new risk-based approach to the sampling and analysis of mutual recognition, decentralised and centralised medicines which was finalised during 2018 and implemented during 2019. Work on extending this initiative to the post marketing phase began in 2020.
- The HPRA continues to participate in optimisation of the processes used by EEA medicines competent authorities for the management of quality defects, recalls and rapid alerts. This has included implementation of revised (more risk-based) versions of the relevant EEA procedures during 2020 and 2021.
- Continued focus on the advertising compliance programme which includes regular liaison with industry to outline HPRA requirements and to clarify our interpretation of the legislation.
- Further development of the monitoring of the availability of medicines in non-pharmacy retail outlets with appropriate follow up where unauthorised or pharmacy confined/prescription only medicines are identified.
- Continued development of our role as competent authority for cosmetics. This includes maintenance of effective working relationships with the Department of Health, HSE and the Competition and Consumer Protection Commission, and the implementation of a coordinated national approach to market surveillance and testing of cosmetics.
- The National Cosmetics Safety Forum was continued by the HPRA and the HSE for the purpose of reviewing the safety of cosmetic products available within the Irish marketplace. The forum develops the market surveillance programme in line with risk-based principles and takes account of new legislative and technical progress.

COVID-19 pandemic:

- Processing of controlled drugs licences, export certificates and the various authorisations continued throughout.
- The pandemic meant that all inspection activities had to be suspended during March 2020. Since then the HPRA has led in the development of EU guidance on remote inspections/distant assessments.

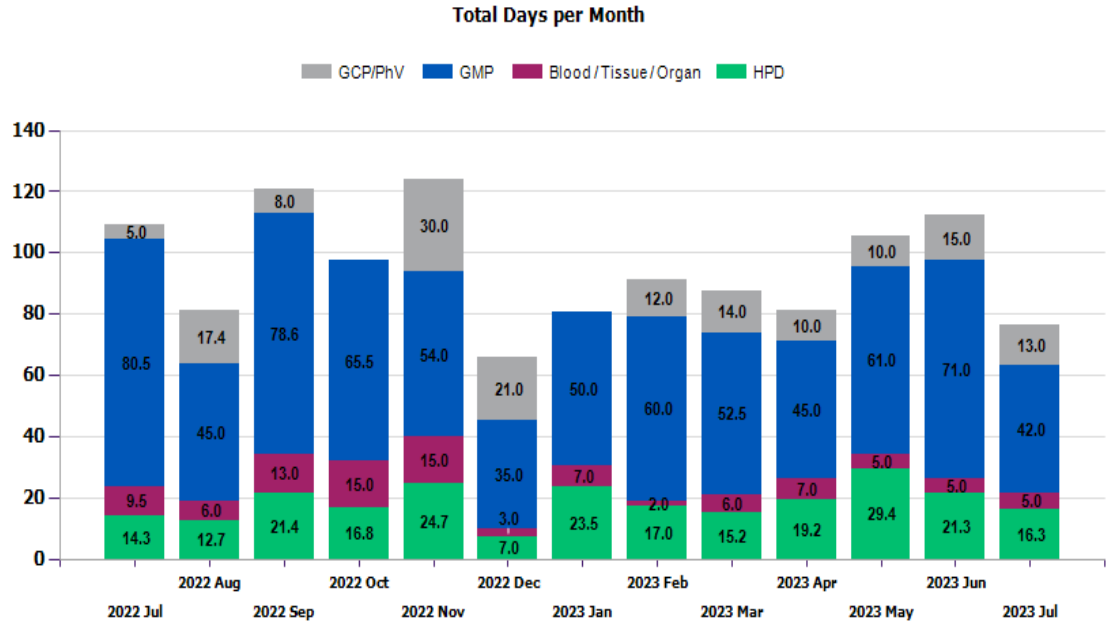
- Guidance was drawn up for safe return of inspectors to regulated sites and training was completed. A hybrid inspection model, comprised of remote and focused onsite elements was used, where necessary.
- All other activities of the Compliance department continued as normal throughout the pandemic.
- In conjunction with colleagues from the Medical Devices department, the Enforcement section monitored for illegal supplies of test kits for diagnosis of COVID-19 and treatments for the virus. Monitoring for illegal supplies of medicines continues. Co-operation from Revenue's Customs Service and An Garda Síochána was of great assistance in this monitoring and, where necessary, in the investigation of suspected illegal activities.

Other activities included:

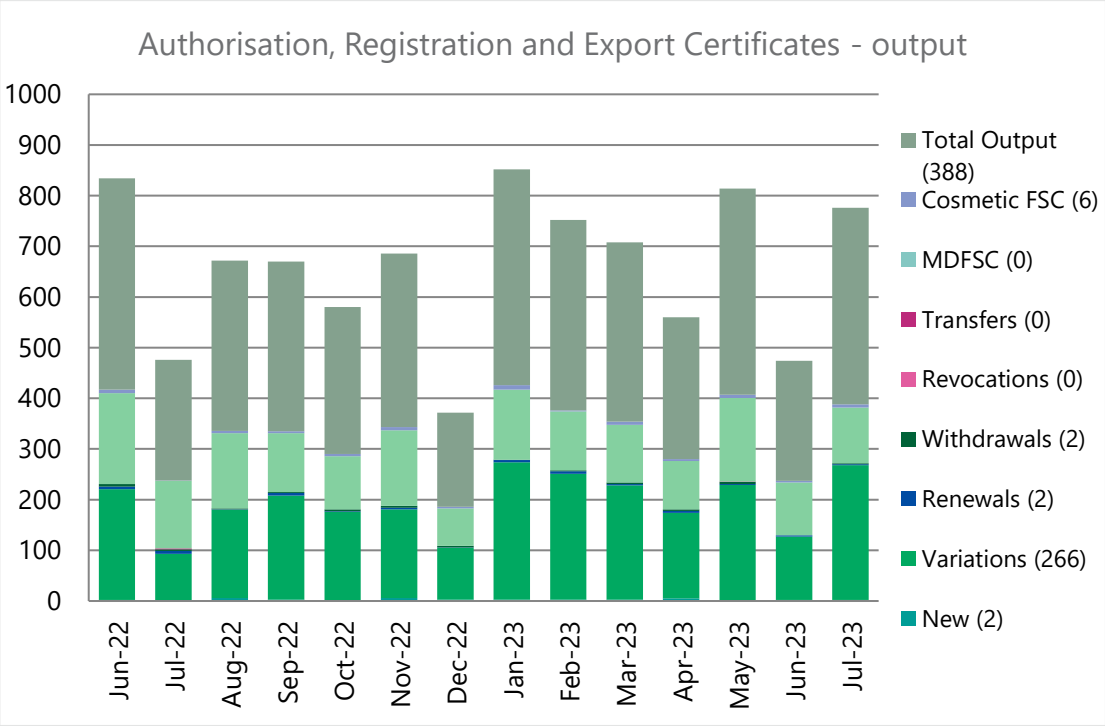
- Continued interaction and communication with stakeholders, including industry and other representative groups. These included meetings (virtual) with industry representative bodies and individual companies.
- Continued management of the controlled drugs licensing function on behalf of the Department of Health.
- Continued management and use of the exempt medicinal products importation/supply data that are notified to the HPRA by wholesalers sourcing exempt products. These data continue to serve as a source of relevant information for the quality defect and recalls programme.
- Efficient turnaround of applications for variations to manufacturers' and wholesalers' authorisations, and for export certificates (medicines, medical devices and cosmetics) and controlled drugs licences.
- Further development of good clinical practice, bioequivalence and pharmacovigilance inspections.
- Full programme of good practice inspections of blood, tissue and organ establishments.
- Continued strong focus, through good distribution practice inspections and enforcement activities, on the legitimate supply chain to prevent infiltration of falsified products.
- Continued monitoring of the parallel trading of medicines by wholesalers based in Ireland, particularly relative to ensuring that the needs of Irish patients are met.
- The particular focus on the illegal trade in anabolic steroids and associated products has continued.
- In co-operation with Revenue's Customs Service, ongoing detection and detention of illegal supply, including mail-order importations of prescription-only medicines.
- Co-operation with Revenue's Customs Service, An Garda Síochána, Sport Ireland, and the Food Safety Authority of Ireland (FSAI) to identify and disrupt medicinal products/food supplements supply among sport and leisure participants that are, in particular, considered to present a risk to human health.

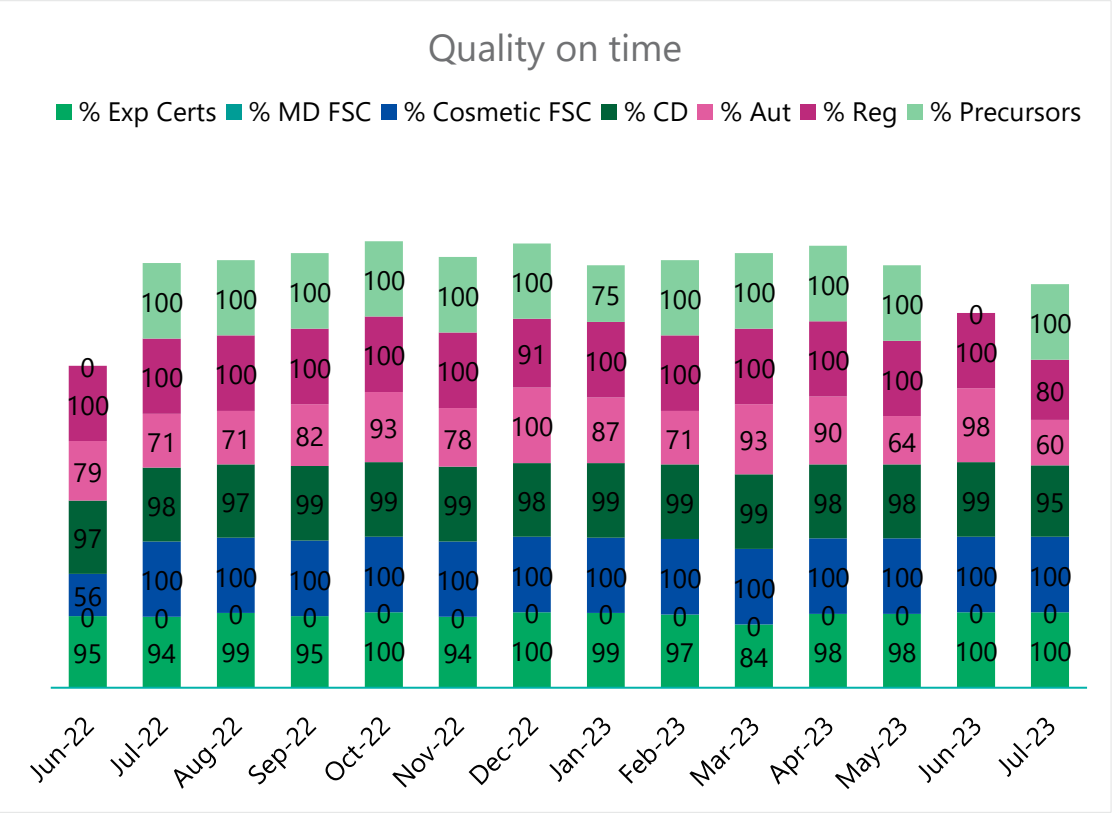
- Co-operation with An Garda Síochána and the Pharmaceutical Society of Ireland (PSI) to detect and stem the flow of unauthorised medicinal products and leakage of authorised medicinal products from the legitimate supply chain for illicit supply and use.
- Enhanced level of intelligence-led enforcement operations with An Garda Síochána, Revenue's Customs Service and enforcement agencies worldwide on Operation Pangea XIII, an Interpol-coordinated international operation against illegal supplies, including trafficking, of unauthorised prescription medicines and medical devices via online and social media activities.

The graph below shows the level of inspection activity for the period July 2022 to July 2023 inclusive. HPD refers to GDP and Controlled Drugs inspections.

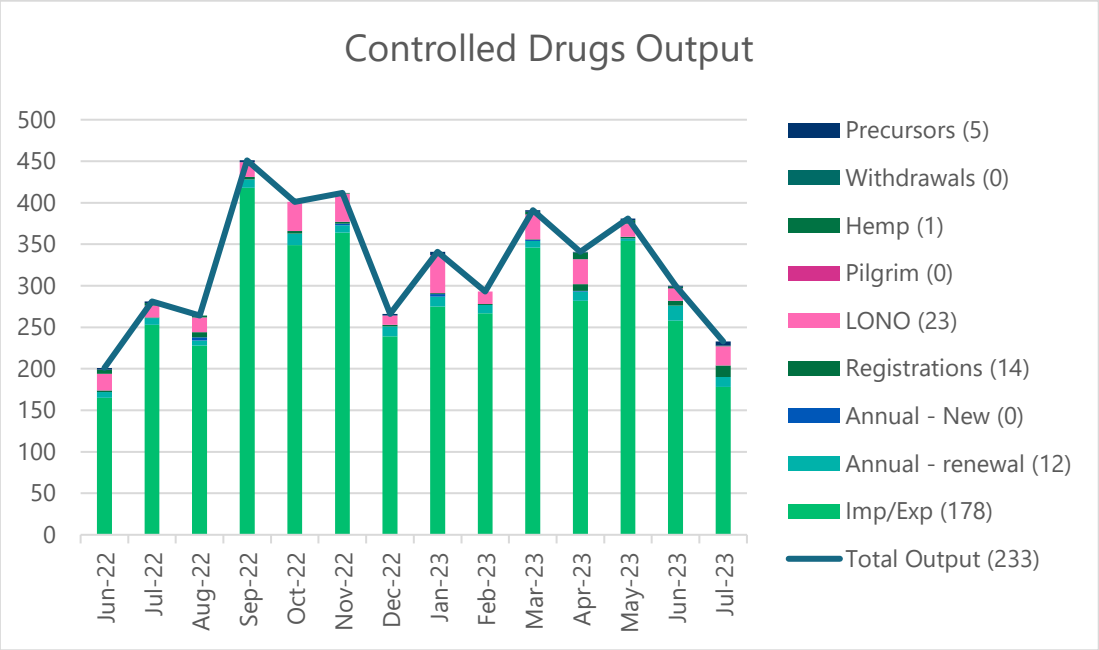


The following graphs show the numbers issued and the percentages issued on time, for export certificates, controlled drugs licences and GDP, GMP and IMP licences, over the period July 2022 to July 2023, inclusive.

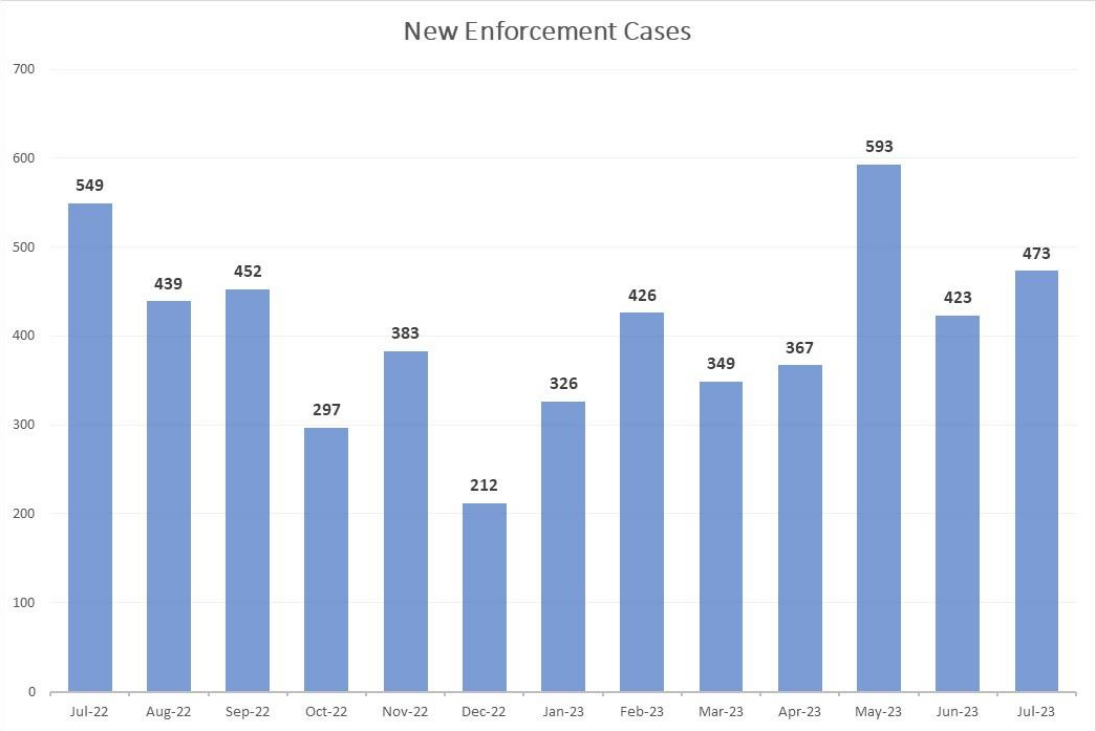




The graph below shows the output of licensing of controlled drugs, by category of licence.



The graph below shows the number of enforcement cases for the period July 2022 – July 2023 inclusive. The majority of these relate to attempts to illegally import prescription-only medicines, an amount of which are falsified. The remainder involve the supply by wholesale and retail sale of prescription only medicinal products which are authentic, but diverted and falsified medicines.



Blood, tissues and cells

During 2022 and 2023 to date, a full inspection programme for blood establishments (i.e. involved in the collection, testing, processing, storage and distribution of blood) was carried out. Annual reports from all blood banks were received and reviewed during both years.

The HPRA also continued its interaction with the National Haemovigilance Office (NHO) in relation to haemovigilance reporting requirements and updates.

The tissues and cells legislation requires all sites involved in the procurement, testing, processing, storage and distribution of tissues and cells to be authorised. A programme of inspections of tissue establishments has been carried out.

The HPRA also continued to operate the tissues and cells vigilance system, participating at EU activities and training to support development of further harmonisation initiatives across the EU.

Human organs for transplantation

Directive 2010/53/EC was transposed into Irish legislation via Statutory Instrument No. 325 of 2012. Under this legislation, the HPRA is the competent authority responsible for the inspection and authorisation of organ procurement and transplant centres and for serious adverse event and

reaction reporting. The HSE (via ODTI) also has competent authority functions in the areas of standards and traceability/registries.

The organs legislation applies to the donation, procurement, testing, characterisation, transport and transplantation of organs. A programme of inspections of procurement and transplant centres was carried out with follow up, as appropriate. The HPRA continued to liaise with the HSE lead and ODTI colleagues in relation to the vigilance system in place for reporting of suspected serious adverse reactions and events, in accordance with the legislative provisions in place.

Controlled drugs

The HPRA continues to be responsible for management of the application and issuing processes for all controlled drugs licences, with the Department of Health retaining a signatory role for all official documentation. In 2019, the HPRA took on responsibility for managing applications for products to be included within the Medical Cannabis Access Programme (MCAP), on behalf of the Minister of Health. The Minister retains the final decision to include a product within the MCAP and this requires the schedule to a statutory instrument to be amended. Inspections related to import, export and holding of controlled drugs and drug precursors have been implemented and continue to be developed.

Exempt medicinal products

A significant level of notifications of importation of exempt (unauthorised) medicines continued through 2022 and 2023, to date. The HPRA has an electronic system for notifications and continues to work closely with notifying companies to ensure data has been uploaded correctly. The notifications are an important source of information, mainly when checking on whether products recalled in other countries have been supplied as exempt medicines in Ireland.

APPENDIX III SERVICE LEVELS – MEDICAL DEVICES

As the national competent authority for medical devices, the HPRA is the authority responsible for notified bodies and the market surveillance authority for medical devices in Ireland. The HPRA carries out a range of classification, registration, surveillance, assessment and compliance activities. We also review clinical investigations, inspect manufacturing sites and authorised representative facilities, designate and oversee notified bodies, and investigate activities associated with non-compliant supply and manufacture of medical devices. Our aim is to ensure that these health products perform as intended and do not compromise the health and safety of the patient or the person using them.

Caseload volume continued in line with recent trends observed since 2015 in medical devices. There continues to be a focus on vigilance cases and field actions (recalls, device modifications, etc.) relating to devices on the Irish market. These cases are increasing in complexity and significance in terms of assessing the impact on public health. In addition, the HPRA has engaged significantly and developed its activities relating to medical device market surveillance, notified body oversight and technical and clinical assessment. Another key area of focus during the past year has been our contribution to ongoing legislative and policy initiatives aimed at developing the regulatory framework as well as our involvement in supporting the Department of Health, the HSE and industry in managing medical device relates aspects of the COVID-19 pandemic. Further details on these issues are outlined below.

Authorisation and registration

The HPRA is focused on ensuring effective and consistent designation and oversight of notified bodies at national and European level. In 2022, we:

- Concluded our review of an application for designation under Regulation (EU) 2017/746 on IVDR. During the year, we reviewed actions taken following the implementation of a corrective and preventive action (CAPA) plan, ensured open questions from the European joint assessment team were addressed and tabled the application to the HPRA Management Committee and the Medical Devices Coordination Group (MDCG) for approval. The formal designation and notification steps of the process concluded in early 2023.
- Continued our schedule of oversight of the notified body in Ireland based on ongoing assessment, surveillance and observed audits. This included a surveillance assessment under Regulation (EU) 2017/745 on medical devices (MDR) in January 2022.
- Contributed as national experts as part of two European Joint Assessment Teams (JATs) for reassessment and designation applications under the MDR and IVDR at bodies located in Germany and Finland. Two other joint assessments could not be fulfilled due to staff availability and proposed changes by the Commission to reassessment frequency which affected assessments scheduled later in 2022.

- Continued to support the development of EU coordination of notified body designation and oversight through participation in the EU Notified Bodies Oversight (NBO) group and the MDCG.
- Worked with the European Commission and the Competent Authorities for Medical Devices (CAMD) on initiatives to gather data on notified body capacity and certification workload associated with MDR and IVDR.

Supporting innovation and research of new technologies is a key strategic priority for the HPRA medical devices team. In 2022, this support included:

- The review of applications to conduct clinical investigations of medical devices in Ireland under the new medical device regulations. The number of clinical investigations for innovative devices increased with 14 new applications, 13 amendments to ongoing investigations and 17 post-marketing clinical investigations. The HPRA anticipates that these numbers will increase further in the future.
- A continued focus on ensuring regulatory requirements and processes are clear and accessible to potential applicants. As part of our commitment to encourage engagement during product development and innovation of medical technologies, we offer pre-submission meetings. Activity in this area increased in 2022, with eight groups of innovators engaging with the HPRA to discuss potential clinical investigation applications.
- The provision of technical, clinical and regulatory support in respect of medical devices related queries received by the HPRA Innovation Office.
- Manufacturers of certain medical devices and in-vitro diagnostics (IVDs) are required to register with the HPRA via the European medical device database (EUDAMED). In 2022, the HPRA registered 199 medical device economic operators (for example manufacturers, authorised representatives) on the national database. 290 economic operators were validated on EUDAMED by the HPRA. A total of 1,838 medical devices were also registered. This represented a decrease in economic operator registrations when compared to previous years. During 2022, the HPRA estimates that around 19% of the economic operators registering in Ireland were due to Brexit.

Safety and quality

We continue to develop and reinforce our market surveillance activities, with particular emphasis on proactive rather than reactive actions. Of note in 2022:

- We further developed our lifecycle market surveillance strategy and planning mechanism to allow for more effective management and reporting of these activities.
- A total of six notifications were sent by the HPRA to the European network relating to medical device compliance concerns.
- The HPRA supported the European network of authorities via the Market Surveillance Working Group and lead on an initiative to develop common evaluation principles for market surveillance.

- There were 414 market surveillance cases undertaken in 2022, a decrease compared to 2021.

We continued to focus our vigilance activities during 2022 on the areas of user reporting and dissemination of HPRA medical device safety communications. This included:

- The receipt and assessment of 3,935 medical device vigilance cases, an increase compared to 2021. This increase is attributable to significant number of reports received in relation to a specific SARS-CoV-2 Antigen test. Of the reports received in 2022, manufacturers accounted for 50%, users for 41% while 9% came from other competent authorities. Of the 3,180 incident reports notified directly to the HPRA, 51% came from users of medical devices.
- There were 323 field safety corrective actions (FSCA) associated with the national market including 99 product removals conducted in Ireland during 2022.
- We issued 93 national competent authority reports and two vigilance enquiry forms to other European authorities.
- We also issued three safety notices in relation to medical device issues and 15 direct to healthcare professional communications.
- Virology devices, infusion devices and implants accounted for 66% of the total vigilance reports (see next page for accompanying graph). Reports continue to be received relating to in-vitro diagnostic devices in the area of clinical biochemistry (4% of reports), medical devices in the areas of surgical devices (8% of reports), orthopaedic devices (4% of reports), and respiratory devices (5% of reports).

The HPRA also adopted the role of co-chair of the European Working Group on Post-market Surveillance and Vigilance, a subgroup of the Medical Devices Coordination Group. As part of its market surveillance activities, the HPRA undertakes proactive and 'for-cause' inspections of manufacturers, notified bodies, importers, distributors and authorised representatives with the objective of monitoring compliance of devices emanating from Irish based organisations. During 2022, 20 such inspections were performed all of which were based on proactive market surveillance projects and notified body surveillance/assessment.

During the year, we also continued development work on signal detection of medical device issues.

Product types (Top 10)	Number of reports
IVD – Virology	1,533
INFU - Infusion devices	708
IMPL - Implants	343
SURG - Surgical devices	305
IVD - Clinical biochemistry	163
RESP - Respiratory devices	107

EMCY - Emergency devices	95
VSM - Vital signs monitoring	88
DIAL – Dialysis devices	50

Legislation and regulation

Regulation (EU) 2017/746 on in-vitro diagnostic medical devices (IVDR) became fully applicable in May 2022. Our work during 2022, continued to help ensure an effective and timely implementation of both EU device regulations for medical devices and in-vitro diagnostic medical devices at a national and European level particularly with regard to gathering data on the notified body capacity challenges. This included:

- Working with the Department of Health on escalating mechanisms, identifying and proposing solutions for the lack of regulatory system readiness. This included drafting a non-paper with France and Germany calling out some proposed mechanisms to resolve the short-term immediate challenges.
- Supported the Department of Health in preparing for two EPSCO interventions calling out the need for focused solutions to the lack of system readiness and the need for a focused discussion on the root causes of the longer-term challenges.
- Engagement with key stakeholders in the sector to ensure awareness of the impact of the regulations incorporating the provision of information, the development of guidance and specific information sessions on MDR/IVDR implementation.
- Working with the Department of Health and relevant stakeholders on national policy and national provisions to ensure transposition of the national requirements into Irish law.
- Contributing to the European Commission's development of the secondary legislation relating to implementation of both regulations.
- Participating in the EU MDCG. Chaired by the EU Commission, this group is responsible for the overall coordination and governance of the regulatory system.
- Participating in the EU Working Groups tasked with developing guidance for specific functional areas.

The HPRA continues to play a significant role in the development of EU regulatory systems and mechanisms to promote co-ordination, co-operation and consistency. In 2022, this included:

- Continued participation in the Executive Group of the CAMD network.
- Participation in MDCG discussions on improving the coordination and consistency of the implementation of the new EU Regulations and prioritising implementation activities in the short, medium and long term.
- Continuing to take a leading role in number of taskforces of the MDCG working groups to help identify solutions to key practical challenges with implementation.

Throughout the year, our focus remained on identifying and promoting discussions and development of practical measures to ensure the regulatory system operates effectively in practice. Addressing the short term notified body capacity issues was a particular focus for the HPRA. We were also engaged in ensuring that medium- and long-term issues are prioritised and discussed within the EU network to work towards a sustainable effective implementation of the regulations.

The HPRA chaired a number of meetings of the medical devices core group of the HMA. The focus of the core group during 2022 was to prioritise the capacity challenges for notified bodies in the EU network and to work together on identifying solutions to these challenges.

At national level, we further developed our fee-based funding model for medical devices to recover costs associated with our medical device activities.

We continued to participate actively in initiatives to promote regulatory convergence and harmonisation of medical devices globally through the International Medical Device Regulators Forum (IMDRF). This involved:

- Participation in the IMDRF Management Committee as part of the European delegation (along with the EU Commission and Germany).
- Continuing to act as the IMDRF secretariat for the National Competent Authority Report (NCAR) Exchange programme and providing training to the incoming Secretariat.
- Participation in the clinical evaluation working group of the IMDRF.
- Contributing to discussions and development of the Medical Device Single Review Programme, which relates to product review.

Stakeholders and partners

Our work to encourage the direct reporting of incidents and medical devices issues by device users and members of the public continued throughout 2022. We also continued our engagement with health services and healthcare professionals to encourage reporting and raise awareness of the roles and activities of the HPRA.

The HPRA undertook a number of communication initiatives to raise awareness of the impact and requirements arising from the new EU Device Regulations. During 2022, we:

- Hosted a webinar for stakeholders on IVDR implementation, including the impact of new timelines adopted for staggered transition.
- Updated the HPRA website and social media channels to provide information and guidance regarding the new EU Regulations.
- Delivered briefings, advice and workshops on the new regulations to a range of different stakeholders including the HSE, industry and clinical associations.

Throughout the year, we engaged in ongoing strategic, operational and communication initiatives on a bilateral and multilateral basis with European and international authorities, and the EU Commission. We also further developed our bilateral partnerships with a number of those authorities. In addition, we participated in operational and strategic discussions on developing cooperation between the CAMD and the HMA networks.

The HPRA continues to deliver a programme of presentations and talks to a range of external stakeholders.

The HPRA are contributing to a Horizon 2020 funded project (Co-ordination of Research and Evaluation of Medical Devices) CORE-MD. The project runs from 2021-2024 and the HPRA is leading a work package and is also part of the project board. The mid-term technical report was completed and submitted to the Commission in 2022.

Case Workloads

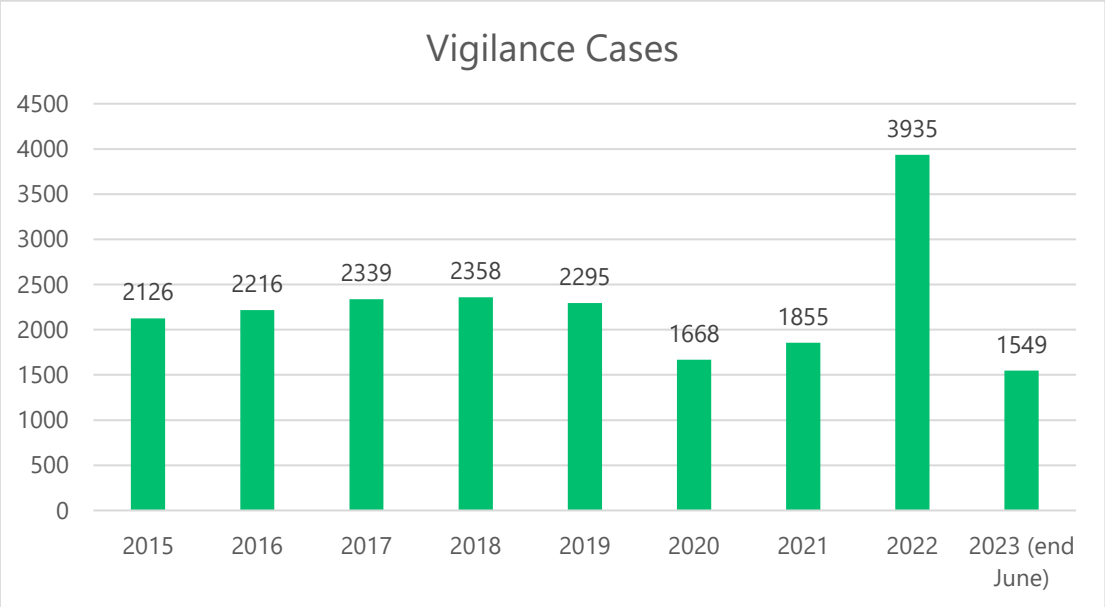
Vigilance and Compliance

There has been ongoing work with the HSE in various National Incident Management Teams during 2019- 2022 and case work continues to lead to the identification of significant issues that require increased monitoring and oversight by HPRA.

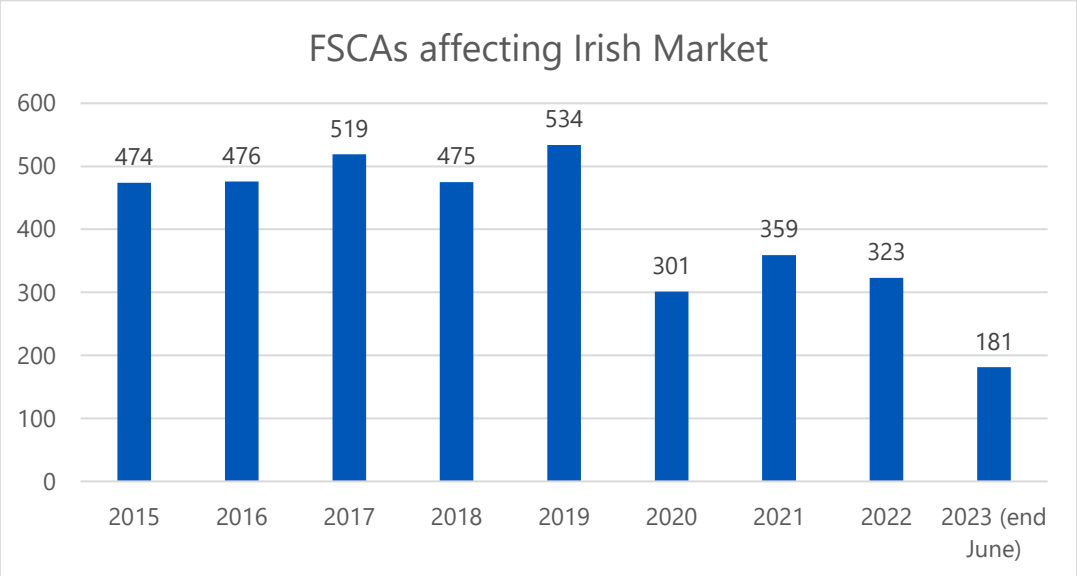
Our vigilance workload continues at consistent levels, with an increase in complexity in relation to vigilance cases, where in 2023 to date (January to end June) 1549 vigilance cases were opened and reviewed. Also in this period, among other communications, 64 NCAR's were issued nationally, across Europe and internationally. The HPRA continues to be very active at a European level in the area of vigilance.

Work has continued to enhance the vigilance function through the introduction of a signal detection and trend analysis system on medical device vigilance data. The aim of this system is to analyse the data on all vigilance reports received to identify trends, patterns or signals relating to medical devices at an earlier stage and to further enhance the contribution of the vigilance function to the overall regulatory system for medical devices.

See charts showing activity levels below.



Graph 1: Number of vigilance reports received (2015 to end of June 2023)

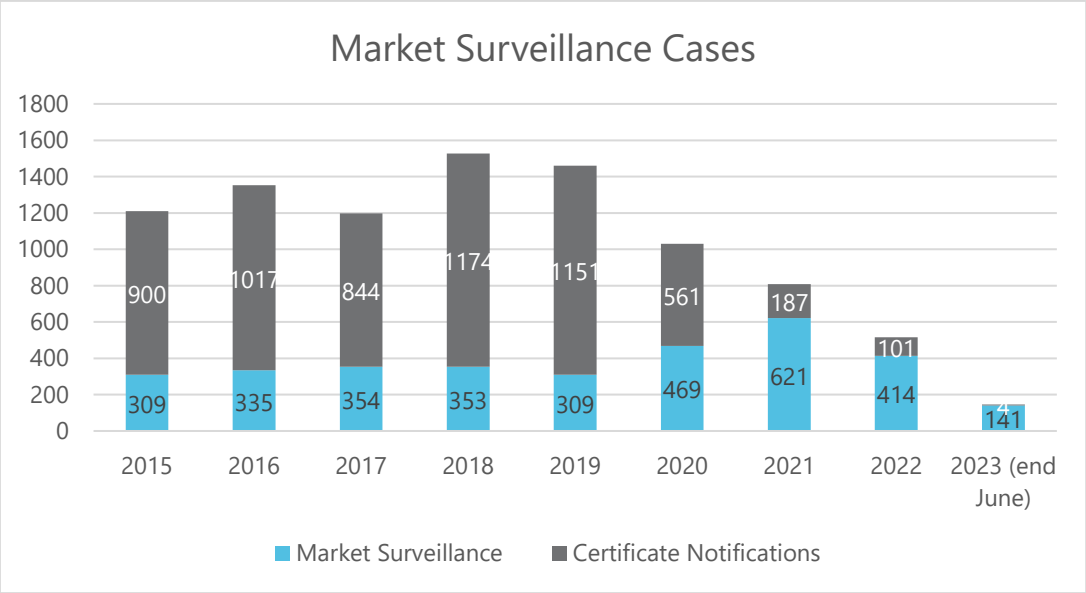


Graph 2: Number of field actions affecting the Irish market (2015 to end of June 2023)

Designation and monitoring of notified bodies

Surveillance Cases

During 2022, the HPRA continued to develop its lifecycle approach to market surveillance and investigated 414 market surveillance cases and received 101 certificate notifications from notified bodies.



Graph 3: Number of market surveillance cases (2015 to end of June 2023)

The HPRA has increased its level of proactive market surveillance activities to check conformance of marketed medical devices with the essential requirements defined in the legislation to help ensure performance and safety and to protect public health. In addition to documentation and labelling checks, this has also included an increased emphasis on sampling and analysis of products from the marketplace and detailed reviews of technical and clinical documentation. These proactive activities include assessment of specific devices, groups of devices or issues identified through the review of scientific data and literature.

The HPRA intends to continue to increase its level of proactive market surveillance activity for medical devices to help ensure that all medical devices placed on the Irish and European market are safe and meet the requirements of the legislation and to help prepare and provide guidance on new legislative requirements arising from the new EU Regulations.

As part of its market surveillance activities, the HPRA undertakes proactive and 'for-cause' audits of manufacturers, notified bodies and authorised representatives with the objective of monitoring compliance of devices emanating from Irish based organisations.

During 2022, inspections were performed at notified bodies, medical device manufacturers and authorised representative facilities, all of which were based on proactive market surveillance projects and notified body surveillance/assessment.

Clinical evaluation review

The HPRA has increased its activities further in the assessment of clinical data presented by manufacturers to support the safety and performance of their device. The work was undertaken both reactively in response to a number of specific device issues over time and proactively as part of our ongoing market surveillance activities. This work also formed a significant part of our notified body designation and oversight activities both at national and European levels as part of EU joint assessment activities.

Product registrations

In 2022, a total of 1,838 medical devices were registered. In addition, 290 new organisations as Irish-based manufacturers or authorised representatives for class I, custom-made, *in-vitro* diagnostic medical devices, as manufacturers of system or procedure packs, or as sterilisers of medical devices, have been notified.

This increase in new organisations registering has already impacted on the number of market surveillance activities undertaken with regard to the register and it is expected that it will continue to be an ongoing focus of the market surveillance activity. In the first five months (up to May) of 2023, 114 medical device economic operators have registered with the HPRA. 88 economic operators have been validated on Eudamed.

Classification requests

The HPRA received 24 applications for classification of medical devices or products queried as medical devices in 2022. This included many complex queries relating to borderline or combination products. The queries emanated from other medical device competent authorities in Europe, from medical device manufacturers, distributors and legal firms.

On foot of a number of these enquiries and as a result of HPRA investigations, a number of products were up-classified to a higher device classification.

Graph 4: Classification requests (2015 to end of June 2023)

Clinical investigation applications

The HPRA received 14 applications for clinical investigations and 13 amendments to a clinical investigation of a medical device to be conducted in Ireland and 17 post-marketing clinical investigations in 2022.

In addition, 13 compassionate use procedures were completed in this period.

Queries

During 2022, the HPAR medical devices team received 1069 queries relating to medical devices.

Certificates of free sale

During 2022, the HPRA issued 5361 certificates of free sale compared with 4482 in 2021.