

**Public Consultation on  
Annual Review and Proposal for Fees –  
Financial Year 2020**

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

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## 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<sup>1</sup> of the HPRA. Since 2004, the HPRA has implemented a policy of annual fee reviews following consultation with industry.

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 also sets out the current operating environment, the service levels and activities and expected changes in service levels and activities for 2020.

## 2 THE OPERATING ENVIRONMENT

2019 has been a challenging year for both the HPRA and the industry. Brexit has brought considerable uncertainty to the regulatory framework and both industry and the HPRA have expanded their resources in preparation for Brexit. While there has been some increase in regulatory activity, it is primarily related to Brexit (transfers and manufacturing variations), undertaking UK RMS roles and changes from the falsified medicines directive. Other activities reflect budgeted levels but we have seen an increase in product withdrawals in 2019. In terms of costs, the Haddington road reductions and the general public service pay increases have been re-instated. General inflation has been low reflecting prices for food, clothes, alcohol and other consumables. Business expenses such as rent, utilities and IT costs have been increasing beyond the general rate.

Due to increased complexity of regulation and enhanced regulatory and public health offerings, staff numbers continue to increase. As noted above, the biggest impact on activities in 2019 was Brexit. The HPRA committed to the industry that we would work with them to minimise the regulatory burden where possible, to progress Brexit related changes in an expedited manner and to actively work with industry to deliver pragmatic solutions, where possible. In addition, we agreed to take over as Reference Member State (RMS) for any

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<sup>1</sup> 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.

product that the UK previously was RMS and where Ireland was a Concerned Member State (CMS). We are happy that we delivered on and continue to deliver on these commitments but it obviously has had an impact on resources.

Medical devices have also been impacted by Brexit. HPRA have played a leading role in Europe in seeking to address issues arising from the fact that the UK notified bodies are the largest certifiers of medical devices in Europe. The impact of preparing for the new medical device regulation (the MDR), has hugely increased the workload of the Medical Devices department and a number of high profile safety issues such as meshes and breast implants has further contributed to a challenging year.

As noted previously, Government policy in relation to pensions changed and the HPRA was asked in 2018 to make an employer contribution in respect of staff employed, since 2013 under the single service scheme. This contribution, which is up to 17% of the payroll cost of those employees was made for the first time in 2019. 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 would make a contribution and we have flagged in previous fee consultations the long term impact of an unfunded pension scheme. This pension liability is now impacting on fees.

A particular area of concern is increased litigation, both on the personal injury side and judicial review. An unfortunate result of this is increased costs and resources dedicated to work which delivers nothing under our public health remit.

The impact of new legislation continues to be rolled out across the organisation. The Clinical Trials Regulation will be implemented in 2020/2021, and the EU Medical Device Regulation will be implemented in 2020. The regulatory model is becoming more complex, there are more complex medicines and the Pharmacovigilance legislation has led to an increase in the number of referrals and regulatory action arising from the outcome of these referrals. Public scrutiny and the role of the regulator in relation to medicines such as the HPV vaccine has increased, and compliance activity, particularly outside of Ireland, is also increasing. The HPRA expects staff levels to increase in 2020.

### **3 STRATEGIC DIRECTION OF THE HPRA**

The HPRA has commenced the process of developing its new strategy for the period 2021 to 2025. We continue to deliver under our current strategic plan for the years 2016 – 2020 which also aligns with the EMA and HMA joint strategic plan. The high-level strategic goals under this plan are as follows:

- **Access to medicines** (enhancing regulatory support to patient access to medicines)

- **Better informed users** (providing current information to inform choices and decisions made by patients and their healthcare professional)
- **Optimised regulatory system** (keeping pace with product, manufacturing and supply chain developments)
- **Supporting innovation** (providing regulatory support and advice to research and development centres)
- **Internal capabilities** (ensuring strong internal systems, resource and expertise)

While the strategic plan expands on each of these strategic goals, key projects for 2020 include:

- Managing the impact of Brexit across all our strategic initiatives.
- Dedicated project and resources to manage medicines shortages from a regulatory view point.
- The further development of the innovation office and support for early innovation on a global basis.
- The rollout of a new regulatory work flow system, 'Eolas', across the entire organisation which will put the HPRA at the cutting edge in Europe in respect of its IT capabilities.
- European and international projects in pharmacovigilance, crisis management and GMP.
- Increasing our regulatory offering both centrally and in the decentralised system.
- Implementation of the clinical trials directive
- Implementation of the Medical Devices Directive

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

#### **4 PROPOSED CHANGES FOR 2020**

The HPRA, as outlined above, is operating in a challenging environment, particularly in light of Brexit. As outlined above, we committed proactively to supporting the industry and to manage its regulatory obligations in Europe following the still unknown outcome of the UK Brexit negotiations.

Overall income in 2019 has performed satisfactorily due to the Brexit related activity for the first seven months of 2019. However much of this income is once off Brexit related income such as transfers and Brexit variations and will not occur going forward. Outgoing work has increased with the number of UK RMS taken over by the HPRA. This does not significantly increase income as the income was previously incoming (CMS) but has resulted in an increase in workload. Product withdrawals are higher than forecast, which again may be a reflection of Brexit.

As noted above, medical device work load has increased significantly in 2019 without additional income. While we have managed this work load within income levels for 2019, staff

increases in 2019 and 2020 are required to manage this increased work load. This will impact on the funding model which is currently subvented by the Department of Health.

More significantly, the HPRA cost base has been increasing. As noted in previous submissions, payroll remains the most significant part of HPRA being up to 77% of total costs. Payroll costs have increased over the last number of years but will increase particularly in 2020 for the following reasons:

- The impact of the new Public Service Pay increases will result in pay awards of approximately 3%.
- It is estimated in 2020 that an additional 30 staff will be subject to the employer contribution in relation to the single scheme.
- HPRA receives no funding for pensioners under the local government superannuation scheme (LGSS). Previously as a 'young' agency this did not impact significantly but we have seen significant increases in pension costs in the last two years and it now accounts for 4% of payroll.
- Brexit: While the final shape of Brexit is still unknown, it is likely that managing the aftermath of Brexit will still be a significant work load for the HPRA. A longer term effect will be our commitment to taking over a significant amount of work previously carried out by the UK. This will impact on the mix of work HPRA undertakes with a much greater emphasis on outgoing work.

Despite pressures on costs, funding from the Department of Health for Brexit has allowed us to keep the proposed increase in fees to 3% which is, in effect, a cost of living increase. The proposed changes to the fees are as follows

- General fee increase of 3%.
- MR/DCP outgoing supplement for Type IA variations.
- Increase/amendments to Medical Device Classification fees, Summary Evaluation Reports and Clinical Investigations.
- New fees for assessments of Medical Devices under Article 11.13 of 93/42/EEC.
- Removal of the MR supplement for outgoing variations where Ireland is the only country involved in a procedure (has arisen as a result of the UK leaving procedures).
- Alignment of the fees for combined national and MRP procedures with the DCP fees where the MRP follows the national procedure within six months.
- Increase to manufacturing fees to align with increases to product fees in 2019 and to reflect increases in the complexity of the oversight of manufacturers and the global supply chain.

#### **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 2019. The nature of regulatory income is that it is dictated by

industry activity which can change significantly over a period of time. In addition, the uncertainty from Brexit means that forecasting is extremely difficult and subject to change.

However, as noted above, we are experiencing increased workloads and increased costs due to increased staff levels and a reversal of some of the pay costs that arose during the economic down turn. The HPRA are now required to pay significant pension contributions to DPER. Consequently, the HPRA is seeking the fee increase outlined above. As with previous years, the HPRA commits to review the proposed fees during the planning cycle in 2020 and further amend the fees and fee structure, if required, for 2021.

## **5 PROPOSED FEES**

As outlined above there will be a general increase of 3% to all human medicine, compliance, blood, tissue and organs and medical device fees in 2020.

## **6 DETAILED CHANGES TO FEES**

### **6.1 General change to fees**

It is proposed that there will be a 3% increase applied to all fees – human medicine, compliance, blood, tissue and organs and medical device fees other than the specific changes listed below.

### **6.2 Other proposed adjustments to fees - Human Medicines**

#### **6.2.1 New Applications**

It is proposed to introduce the following supplement fees where the MRP is applied for within six months of the national procedure ending in order to bring the fees in line with the Decentralised outgoing fees for new products.

	<b>FEE</b>
Complex – New Active	€15,450
Complex – Reduced Dossier	€10,300
Standard – Reduced Dossier	€6,180

## 6.2.2 Type IA – Outgoing Supplement - €285

It is proposed to introduce a MRP/DCP outgoing supplement for type IA variations. Ireland has significantly increased the number of products that it acts as reference member state (RMS) and while there is still no fee for the assessment of the variation, there is a high administrative cost in bringing these variations through the European process and the HPRA can no longer absorb this cost.

## 6.3 Other proposed adjustments to fees – Medical Devices

### 6.3.1 Assessment of substances ingested or absorbed

It is proposed to apply the current medicinal product/medical device drug consultation fees to the assessment of devices that are composed of substances that are absorbed by or locally dispersed in the human body and that are systematically absorbed to achieve their intended purpose. The medical device regulation 2017/745 (Annex IX, 5.4b) requires, for this subset of 'ingested products', a medicine competent authority to provide an opinion on the compliance of the device.

### 6.3.2 Medical Devices - Determination of classification within the medical devices regulations

It is proposed to restructure the fees relating to the determination of a classification within the medical devices regulations to the following:

	CURRENT FEE	PROPOSED FEE
Determination not requiring a complex technical review (one device per request)	€250	€260
Determination requiring a complex technical review (one device per request)	€1,000	€1,030
Appeal to the determination decision	€250	€600
Arbitration between medical device manufacturers & notified bodies on the determination or qualification of a product	€0	€5,000

There will no longer be a reduced fee for additional products (available at the time of the initial request).

### 6.3.3 Medical Devices – Summary Evaluation Reports

It is proposed to increase the fees for HPRA assessments of evaluation reports submitted by Irish based notified bodies. The level of complexity of review required for these assessments has increased since the introduction of the last revision of the TSE Regulation. The absence of a TSE certificate of suitability of the material used, further increases the work required with an extended review period for EU competent authorities.

	CURRENT FEE	PROPOSED FEE
Medical devices using starting materials for which a TSE certificate of suitability has been submitted	€1,000	€2,500
Medical devices using starting materials without a TSE certificate of suitability	€3,000	€5,000

### 6.3.4 Medical Devices – Clinical Investigations

It is proposed to increase the fees for clinical investigations. The medical device regulation has increased requirements for an assessment moving from 'no objective' to 'authorisation'.

	CURRENT FEE	PROPOSED FEE
Active implantable medical devices	€3,837	€4,300
Class III and Class IIb medical devices	€3,837	€4,300
Class IIa and Class I medical devices	€1,645	€1,900
Technical amendment to a previously approved clinical investigation	€1,129	€1,240
Resubmission of a clinical investigation following a withdrawal or objection	€1,500	€1,900
Non-Commercial	€0	€0

Non Commercial investigations are those which are carried out in academic settings with limited significant funding.

Commercial investigations are all other investigations which either have a commercial sponsor or have sufficient funding.

### 6.3.5 Medical Devices – Assessments under Article 11.13 of 93/42/EEC

It is proposed to introduce the following new fees for assessments conducted by the HPRA under Article 11.13, with a discretionary waiver of the fee when it is being used on compassionate grounds for a single patient, single and multiple use of the same device. Multiple applications for the same device in multiple devices will incur fees. Each application will have a validity period applied and re-application will be required.

ASSESSMENTS UNDER ARTICLE 11.13	PROPOSED FEE
Less than 10 devices	€1,000
Between 10 and 50 devices	€2,000
More than 50 devices	€4,000

## 6.4 Other proposed adjustments to fees – Compliance

### 6.4.1 Blood and Tissue assessment of devices incorporated non-viable human tissues

It is proposed to introduce a new fee of €3,000 for the provision of a scientific opinion from the Tissues & Cells component authority. The new medical device regulation requires the tissue and cells component authority to provide opinion to the notified body on the non-viability of the cells/tissues, donation, procurement, testing and best risk of incorporation of the tissues or cells.

### 6.4.2 Annual Fees – Manufacturers'/Importers' Authorisations

It is proposed to increase the manufacturing annual maintenance fees to align with increases to product fees in 2019 and to reflect increase in the complexity of the oversight of manufacturers and the global supply chain.

SITE SIZE	CURRENT FEE	PROPOSED FEE
Major site (more than 250 employees)	€18,363	€22,000
Large site (150-250 employees)	€12,241	€15,000
Medium site (50-149 employees)	€8,162	€10,000
Small site (less than 50 employees)	€4,079	€4,500

### 6.4.3 Inspection rescheduling fee

It is proposed to introduce a booking fee of €1,000 for a request to change the agreed date of a non-routine (new licence, updates to facility) inspection. This fee would be non-refundable and would be deductible from the final inspection fee provided the inspection takes place on the pre-agreed date.

## 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 31 October 2019. Contributions should be sent by email to [feesconsultation@hpra.ie](mailto: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 and service levels to industry.

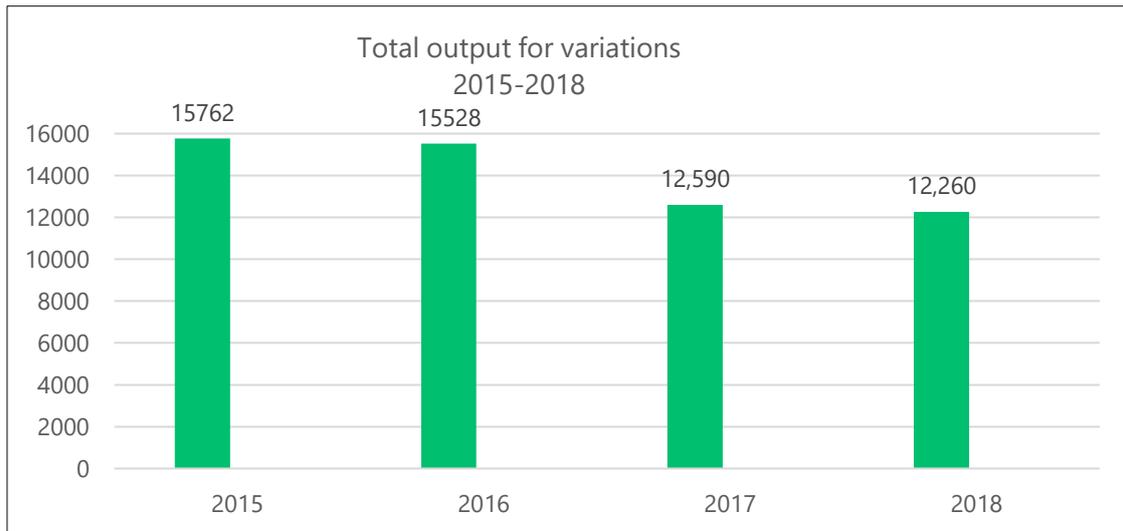
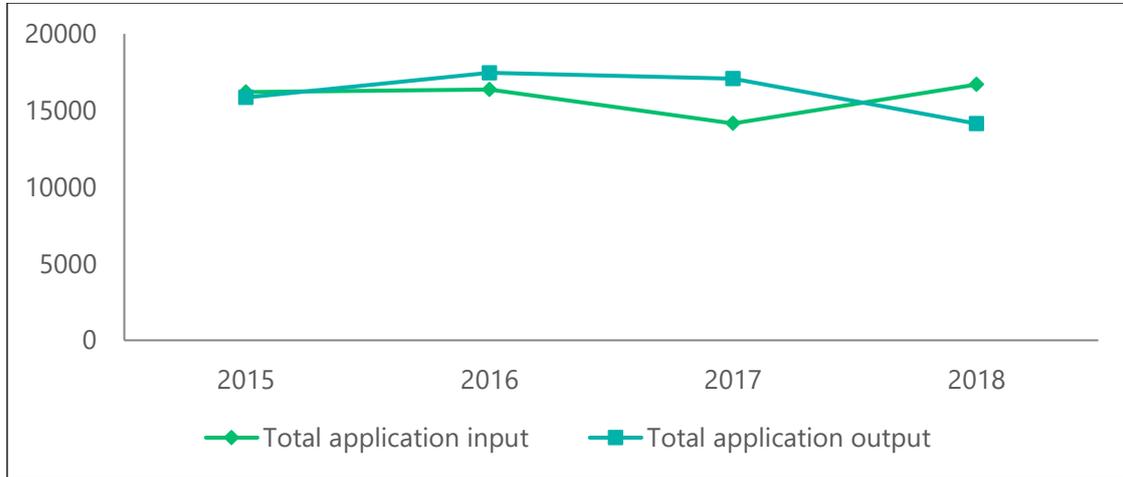
These projects include in summary:

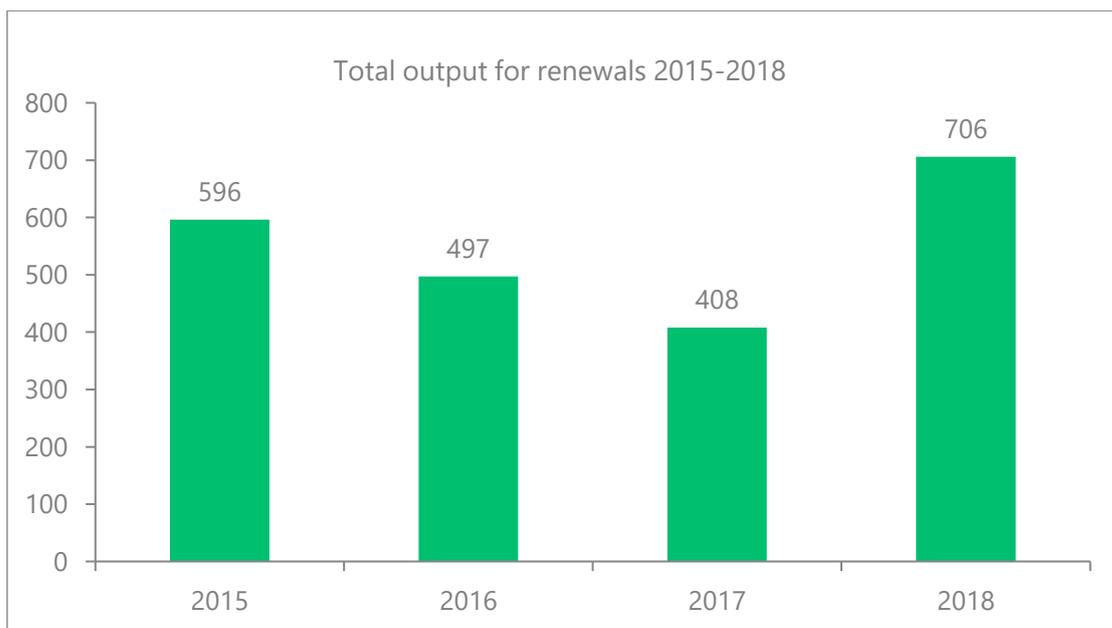
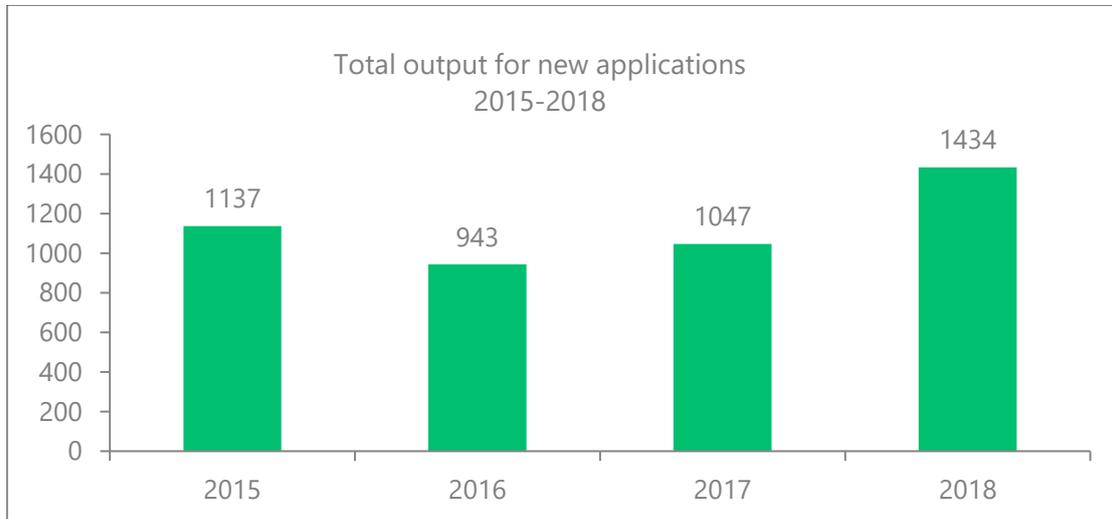
- Readiness to operate as Reference Member State for MR/DCP procedures for both new procedures and those transferring as a result of Brexit related activity.
- A national scientific advice procedure was introduced in 2016. This is to assist applicants in the development of new or existing human medicinal 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. Following some reduction in output upon implementation the organisation has returned and exceeding previous levels. Our focus is on improving our current workflow technology to ensure ongoing delivery of benefits to the organisation 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.
- Introduction of online reporting for adverse reaction and quality defects, accessible to patients, health care professionals and industry.
- Significant system upgrade to the adverse reactions database needed to meet the revised electronic reporting requirements standard (E2B R3 revision).
- Substantial increases in adverse reaction reporting following the introduction of centralised reporting requirements in November 2017, with additional complexities associated with reporting through the EudraVigilance system impacting on workload and interactions to support case processing and data quality.
- Continued customer-focused approach.
- The work on the development of interchangeable medicines to support generic substitution by pharmacists in line with the Health (Pricing and Supply of Medical Goods) Act 2013, has progressed very well. Of the 65 priority substances identified by the Minister or the HSE for inclusion 63 are now incorporated on the list. The two remaining are being assessed. The development of the interchangeable list will continue as a routine

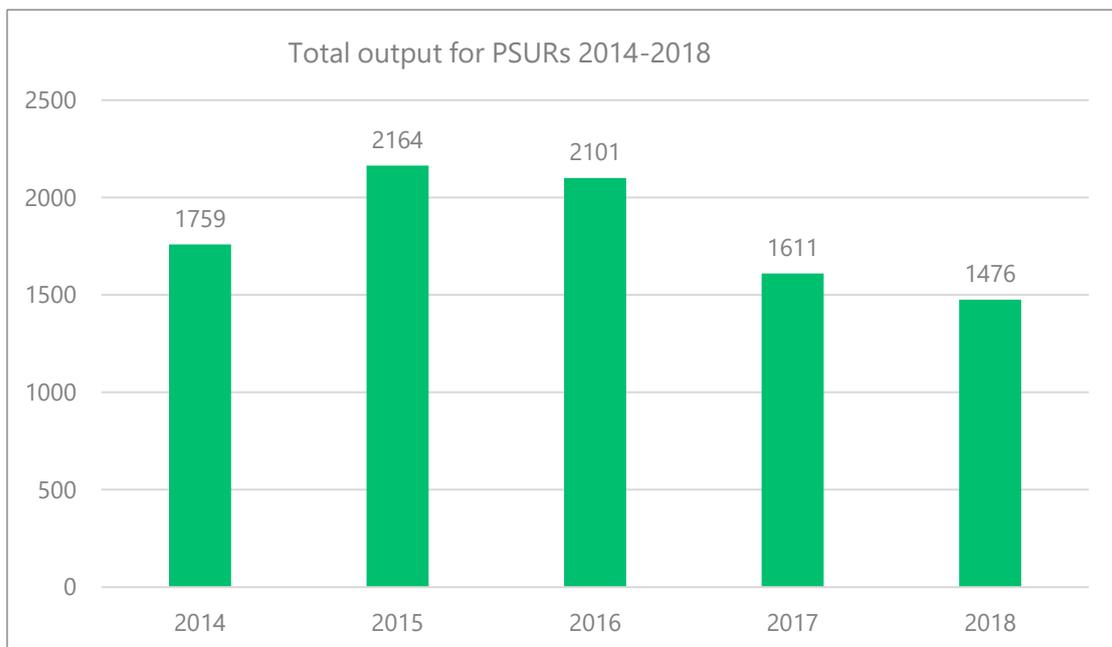
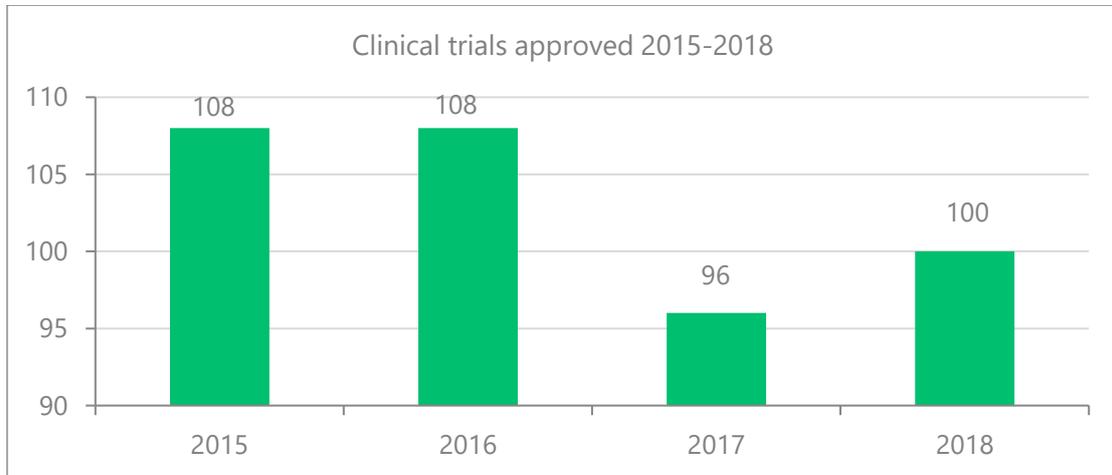
component of our assessment work, whereby industry can proactively make applications to have their product incorporated on to the list; we will also continue to work to include further substances as may be requested by the Minister or the HSE. Further efficiencies will be introduced during 2018-2019 to allow marketing authorisation holders, where appropriate, to incorporate an application for inclusion in a group on the list as part of their marketing authorisation application.

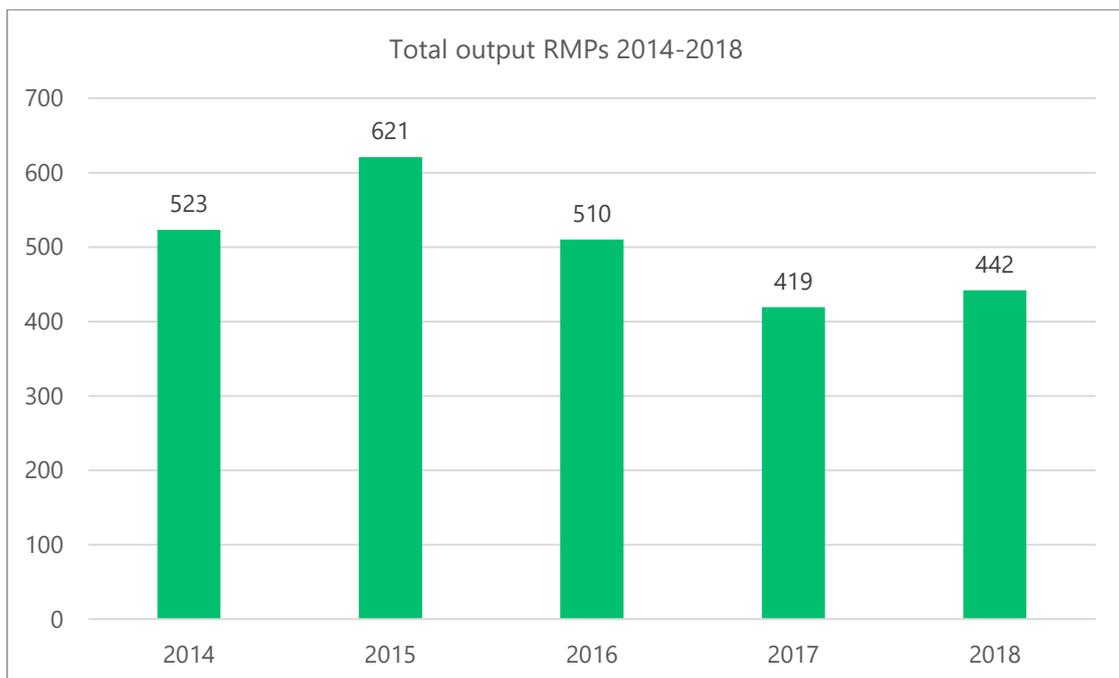
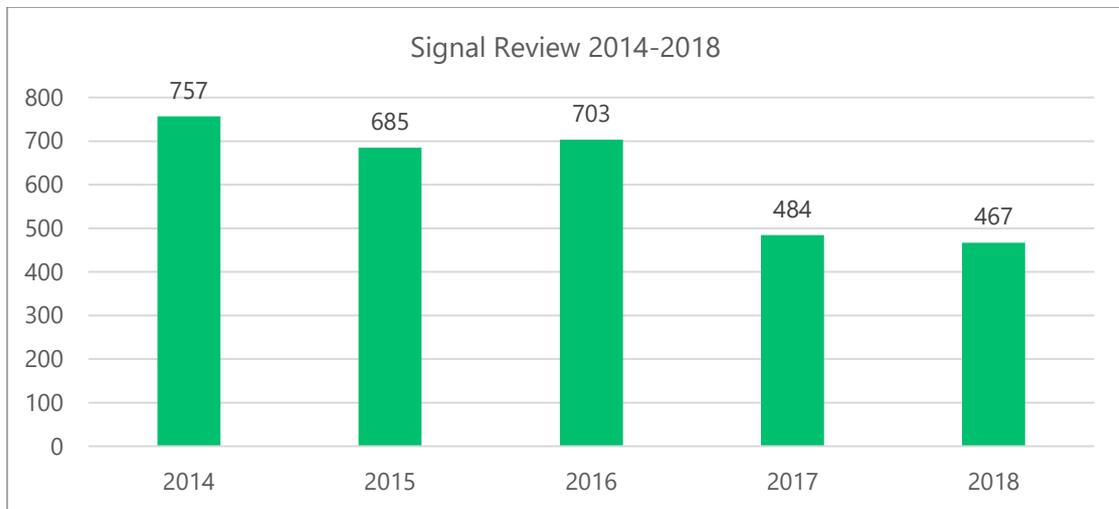
- Focus on the continued provision of guidance and support to industry stakeholders in areas undergoing evolving regulatory development, including:
  - o the new requirements of the Clinical Trials Regulation
  - o the new requirements of the Medical Devices Regulations
  - o the registration of traditional herbal medicinal products
- Continued progression of a public health initiative focused on providing important online information about all medicines licensed by the HPRA. This includes maintaining publication of the summary of product characteristics document, patient information leaflets, ATC codes, interchangeable lists and the legal classification status of all human medicines on the HPRA website ([www.hpra.ie](http://www.hpra.ie)). Since December 2015, all educational materials are published on the website.
- A proactive approach to switching is ongoing. Following a review of policies in this area, and after liaison with the Department of Health, the HSE Health and Wellbeing Directorate and healthcare professionals, the HPRA has taken a proactive approach to the reclassification of medicines since 2014. This has included the publication of a list of active substances currently classified as prescription-only medicines which the HPRA considers could be safely switched from prescription-only medicine to over the counter (OTC) pharmacy sale (not subject to medical prescription). The response from the marketing authorisation holders to this initiative has been disappointing, commercial reasons cited most often. The HPRA continues to engage directly with the industry to establish their interest in submitting applications for the reclassification of prescription medicines and reclassification of medicines currently available for sale through pharmacies, to make these available, where it is considered safe to do so, in general retail outlets. 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.

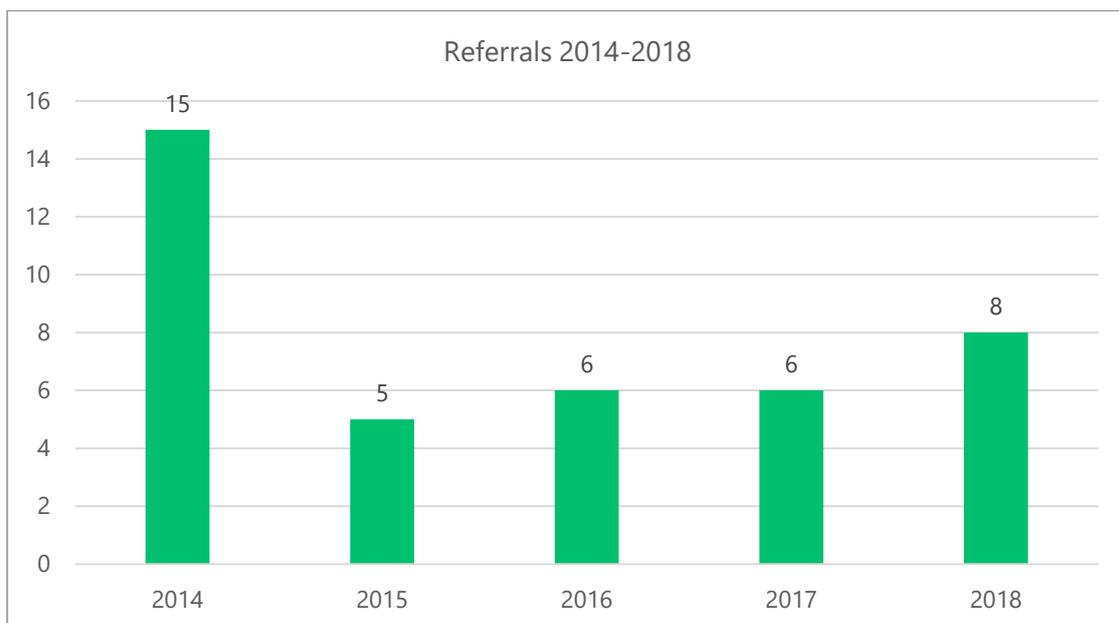
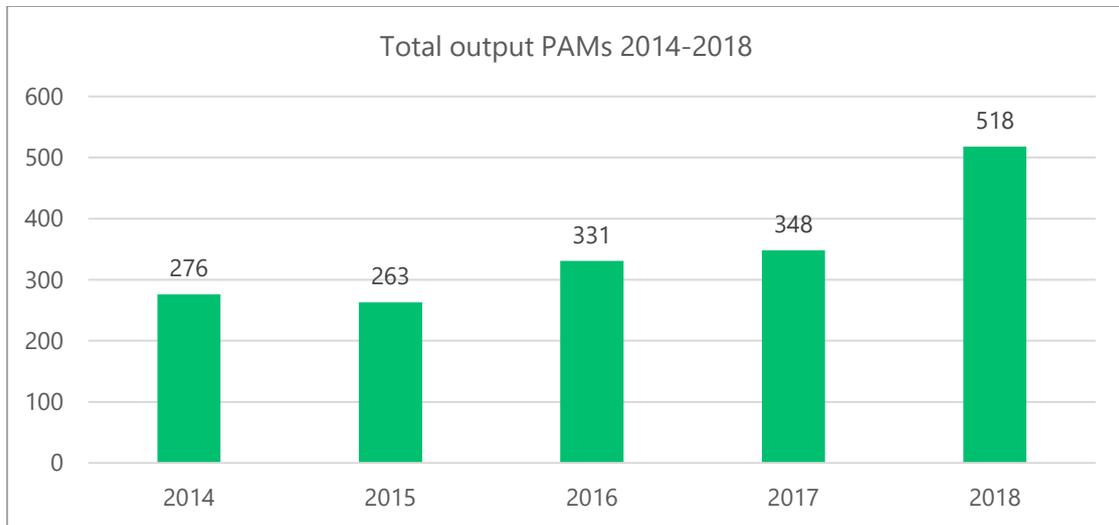
The following graphs outline the output across all application types up to the end of 2018



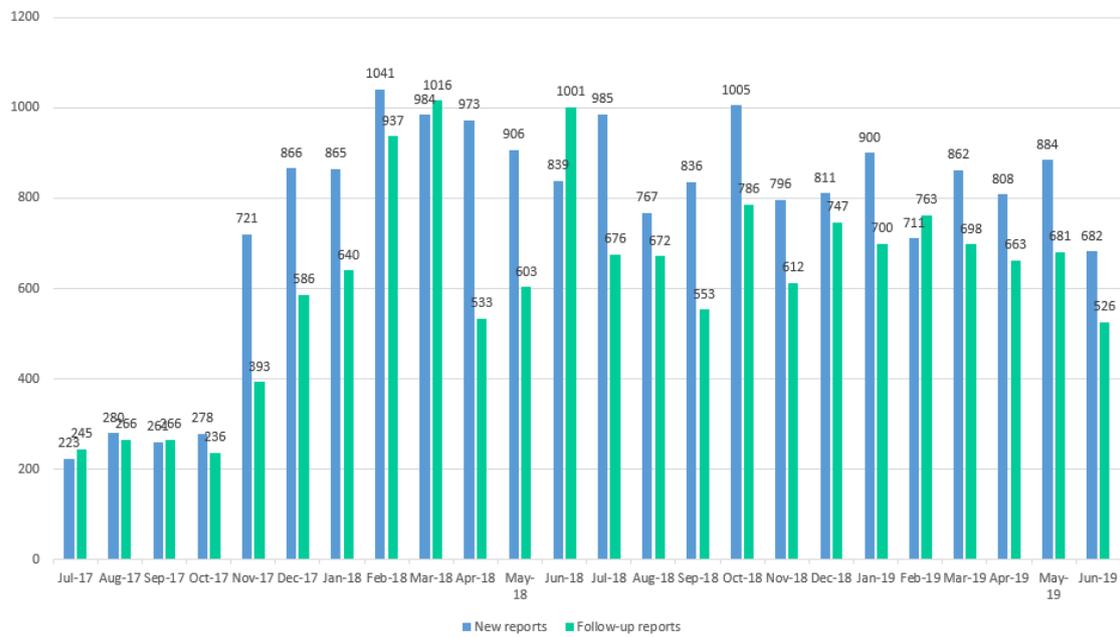








Number of adverse reaction reports received by the HPRA  
2016-2019



## **APPENDIX II SERVICE LEVELS – COMPLIANCE DEPARTMENT**

### **Compliance Department General Activities**

Initiatives undertaken/further developed in 2018/2019 included:

- Preparations for Brexit, in conjunction with other departments across the organisation, have included:
  - o Participation in a stakeholder meeting in February 2019. Following on from that, guidance on Brexit, already published on our website, has been updated.
  - o Meetings with a number of stakeholder companies in order to discuss their Brexit related plans and to clarify issues arising. Such meetings and liaison will continue to be an important focus.
  - o Meetings with industry bodies, and attendance at workshops organised by some of those bodies, in order to consider and clarify Brexit related questions.
  - o Advising potential applicants for authorisations and licences of the requirements and processing of a number of new applications.
  - o Provision of support to the Departments of Health and Agriculture, Food & the Marine, including participation in regular meetings of the Brexit Operations Group and the Brexit Medicines Review Group, both convened by the Department of Health
  - o Liaison with other agencies, including the Health Service Executive and Revenue's Customs Service, on issues of mutual interest.
- On 01 June 2018, the HPRA was listed as a 'capable authority' by the US Food and Drug Administration (FDA) under the EU – US mutual recognition agreement on GMP inspection. On 15 July 2019, the agreement became operational in relation to the majority of medicines for human use. This means that, in the short to medium term, the number of FDA inspections of sites in Ireland manufacturing active substances and the majority of human medicines for supply to the US will reduce considerably. In relation to importation of human medicines manufactured in the USA, the requirement for retesting of each batch on importation to the European Economic Area has been removed by virtue of the MRA becoming operational.
- Continued development of a workflow database for compliance case management to improve efficiency in processing of authorisations/licences/registrations, organisation and follow-up of inspections, quality defects and recall management and other compliance monitoring cases.
- Continued provision of support to the Department of Health on the implementation of national legislation aimed at preventing the entry of falsified medicines into the legal supply chain – transposition of Directive 2011/62/EU ('Falsified Medicines Directive' (FMD)).
- Under the FMD, annual updates to registrations of manufacturers, importers and distributors of active substances and brokers of medicines for human use were processed during 2018 and 2019.

- Also under the FMD, 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 marketing authorisation holders (MAHs) and manufacturers on 09 February 2019. In relation to this, the HPRA has liaised closely with MAHs, manufacturers, wholesale and retail stakeholders which have come together as the Irish Medicines Verification Organisation (IMVO) to implement the so called 'stakeholder model'. 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. In this capacity we chair teleconferences and produce inspection procedures and aides memoire. We also participate in a National Implementation Group, convened by the Department of Health, and including other key stakeholders.

- 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) to the EudraGMDP database.
- Provision of support to the Department of Health on the transposition and implementation of national legislation on quality and safety of human tissues and cells regarding the single European code (Commission Directive (EU) 2015/565 amending Directive 2006/86/EC) and importation requirements (Commission Directive (EU) 2015/566 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells)
- 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 2019.
- 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.
- Provision of support to the Department of Health in the development and implementation of an access programme for cannabis for medical use. In late June 2019, the Minister for

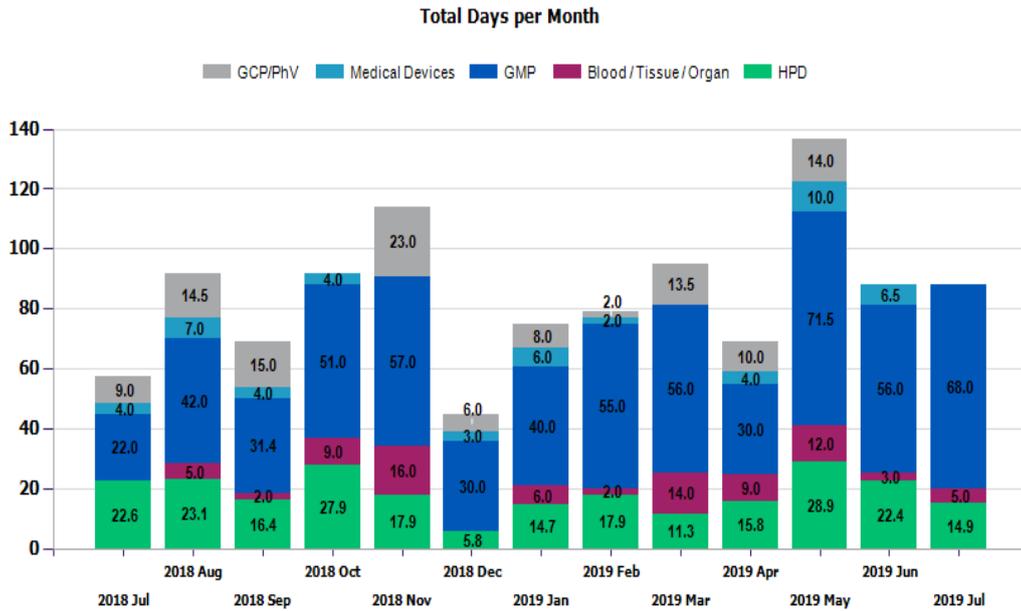
Health signed Regulations to establish the access programme. Following that, the HPRA received and reviewed applications for inclusion of products under the programme. This work is ongoing.

- Monitoring, via inspections, of the implementation of Good Manufacturing Practice requirements, Good Distribution Practice, Good Clinical Practice, and Good Pharmacovigilance Practice standards, and of the required controls relating to Controlled Drugs and Precursors.
- Provision of support to the Department of Health in the development of national provisions relating to the implementation of two European Regulations relating to precursor chemicals.
- Monitoring, via inspections, of the activities of Marketing Authorisation Holder 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 EMA working groups, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Committee and its Expert Circle meetings. The HPRA's Inspection Manager has been Deputy Chair of the PIC/S for 2018 and 2019 and is due to assume the Chair for 2020 – 2021.
- 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 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 is due for implementation during 2019.
- 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 2018 and 2019.
- Continued development of the advertising compliance programme which includes regular liaison with the industry to outline HPRA requirements and to clarify our interpretation of the legislation.
- Further development of the monitoring of 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 has included 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 market place. The Forum develops the market surveillance programme in line with risk based principles and to take account of new legislative and technical progress.

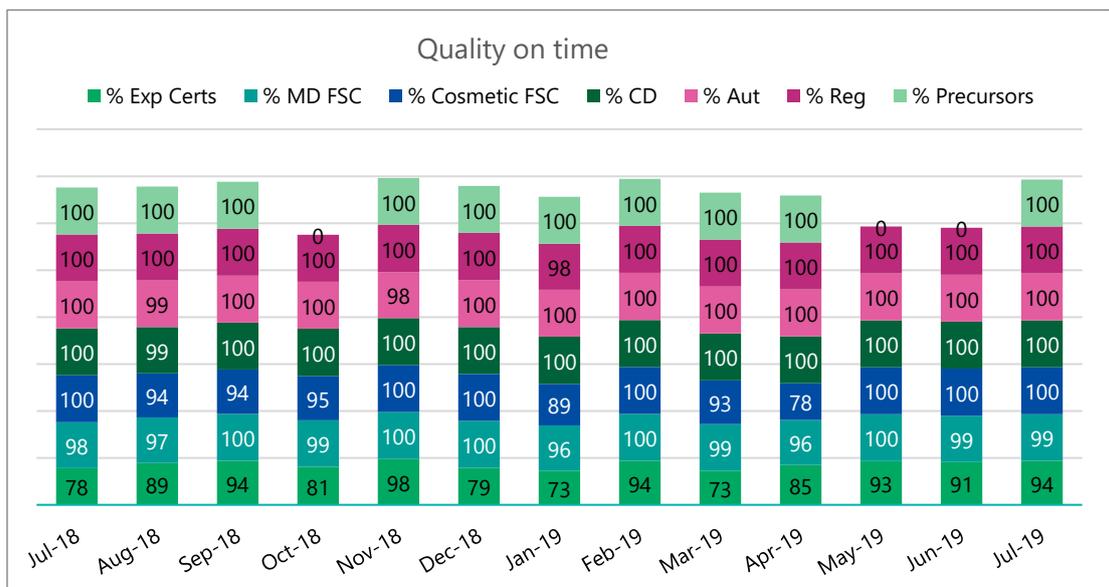
Other activities included:

- Continued interaction and communication with stakeholders, including industry and other representative groups. These included meetings with industry representative bodies and individual companies.
- Continued management of the controlled drugs 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.
- A particular focus on the illegal trade in anabolic steroids and associated products led to a number of significant detentions and prosecutions.
- 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 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 XI, an Interpol-coordinated international operation against illegal supplies, including trafficking, of unauthorised prescription medicines and medical devices via online and social media activities.

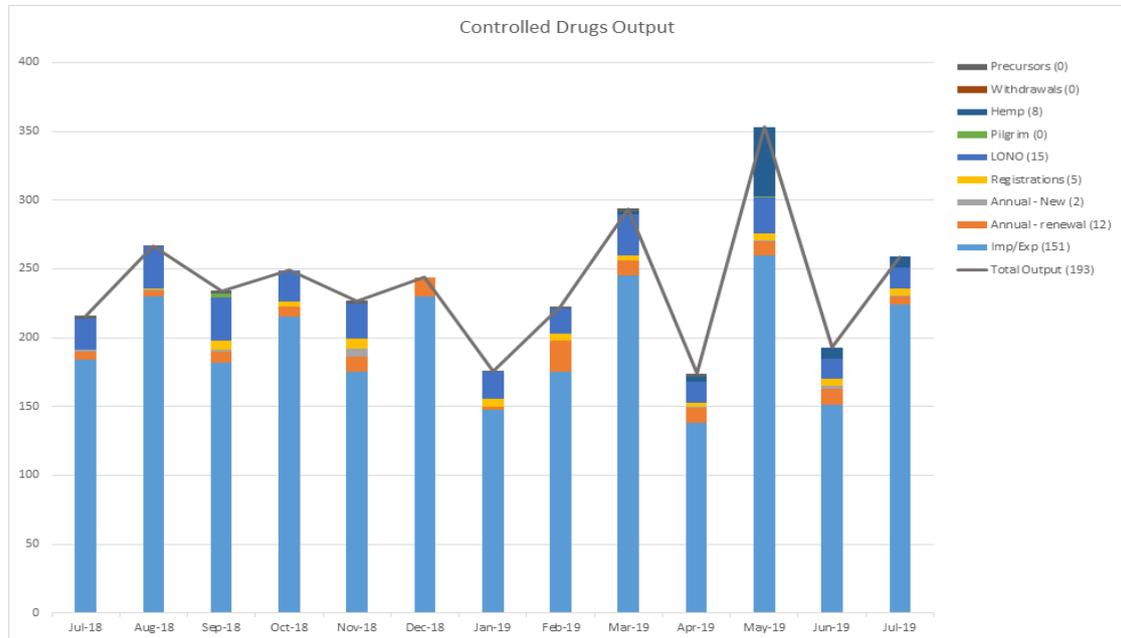
The graph below shows the level of inspection activity over the period July 2018 to month-end July 2019.



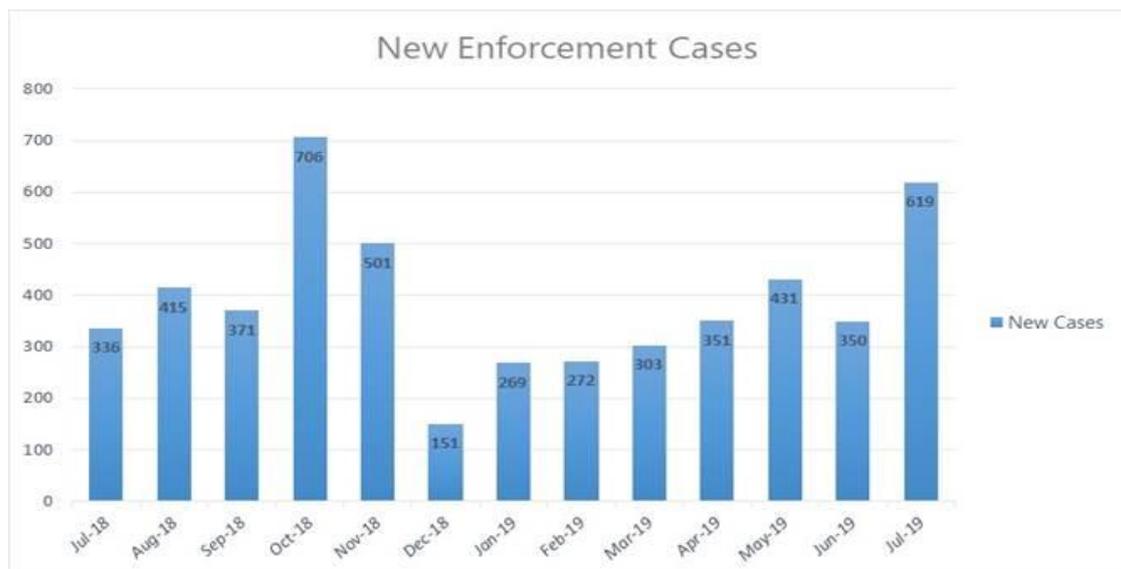
The following graphs show the numbers issued and the percentages issued on time, for export certificates, controlled drugs licences and GDP, GMP and IMP licences, over the period July 2018 to July 2019, inclusive.



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 2018 – July 2019 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.



In 2018 to 2019 the regulated sectors will see further benefits, including:

- Continuing focus on the effective management of resources, activities and relationships with interested parties.
- Continuing application of risk-based planning of inspections in some areas and of risk-based approaches to other activities.
- Greater potential for submission of applications electronically.
- Population of the EudraGMDP database with MIAs.
- Continued focus on clear communication of requirements and expectations.

### **Blood and Tissues & Cells**

During 2018 and 2019 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 ongoing 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. To date, a full 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 Organ Donation and Transplant Ireland (ODTI)) also has competent authority functions in the areas of standards and traceability/registries.

The Organs legislation applies to 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 cannabis access programme, on behalf of the Minister of Health. The Minister retains the final decision to include a product within the cannabis access programme as 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. Of particular note in 2019 has been a significant increase in applications for licences to cultivate hemp.

### **Exempt Medicinal Products**

A significant level of notifications of importation of exempt (unauthorised) medicines continued through 2018 and 2019, to date. We have an electronic system for notification and we continue to work closely with the notifying companies to ensure that data have been uploaded correctly. The notifications are an important source of information particularly when checking on whether products, recalled in other countries, have actually been supplied as exempt in Ireland. With a focus on Brexit, Regulations covering the programme were amended during 2019 to permit authorised wholesalers to source medicinal products from non-EEA countries. Prior to that, such importation could only be carried out by the holder of an MIA.

### **APPENDIX III SERVICE LEVELS - MEDICAL DEVICES**

Caseload volume continued in line with recent trends observed since 2015 in medical devices across the HPRA. 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 other initiatives aimed at developing the regulatory framework. Further details on these issues are outlined below.

#### **Brexit Preparations**

Preparations for Brexit, in conjunction with cross organisational departments, have included participation in stakeholder meetings, development of website and guidance material, registering new organisations establishing in Ireland as a result of Brexit. The HPRA has had extensive communication with manufacturers and authorised representatives at national level to ensure appropriate awareness of the implications of a no-deal Brexit for medical devices. We have also led on EU work with other competent authorities to promote awareness and to prevent adverse impacts on medical devices used in Ireland. HPRA has provided support to the HSE and the Department of Health in the Brexit operations groups.

#### **New EU legislation on medical devices and other regulatory developments and initiatives**

Two new European Regulations (Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/745 on *in-vitro* diagnostic devices) entered into force in May 2017 and will be fully applicable in May 2020. The legislation places new requirements and obligations on the HPRA in addition to other entities operating within the medical device sector.

The improvements and developments of the regulatory framework have improved the system's capacity to ensure medical devices are safe and effective and that public health is protected. Such reinforcement has helped ensure that the regulatory system can facilitate safe innovation of new health technologies with timely and well controlled introduction to the market. Increased emphasis has also been placed on ensuring robust surveillance of medical devices on the market by national authorities. The new legislation will further develop these principles and confer additional responsibilities on national authorities, manufacturers and notified bodies. Robust life-cycle market surveillance of medical devices will help to ensure that each device continues to be safe and to perform effectively throughout its lifespan.

In tandem with this the regulatory system has been considerably developed and secured as a result of the EU Commission's joint action plan. The HPRA remains dedicated to the effective implementation and continued development of this plan. The HPRA has contributed significantly to the joint assessment scheme for notified bodies across Europe. This has included provision of audit, technical and clinical expertise to the joint assessment teams for

five assessments during 2019. The HPRA has also contributed to the coordination group at EU level which is overseeing implementation, development and guidance on the scheme.

The HPRA also continued, during 2018, to conduct a detailed review of medical device activities to ensure that the organisation continued:

- to perform as efficiently and effectively as possible;
- to develop activities in line with regulatory developments, in particular the EU Commission's joint plan for immediate actions;
- to plan and prepare for the new requirements, activities and expectations that will form part of the ongoing medical device legislation.

As a result of this review, a Medical Devices Department was formed and a restructure of medical devices activities was approved in Q1 2019. At national level, the HPRA has continued its monitoring and oversight of notified bodies.

A significant amount of work has been done in the area of user engagement. The approach has focused on three inter-related areas of the dissemination of safety information, the development of the role of 'designated person/vigilance officer' and the encouragement of user reporting. In relation to the dissemination of safety information, the Health Service Executive (HSE) has developed a National Medical Device eAlert System designed to streamline the management of the HPRA medical devices safety notices within the public health system. As the national competent authority for medical devices, the HPRA publishes safety notices highlighting safety concerns related to medical devices. A pivotal part of the success of the eAlert system is the nomination of a 'designated person/vigilance officer' within hospitals and other health facilities to take responsibility for the receipt of the medical device alert notifications and to champion user reporting.

The HPRA places significant emphasis on developing the regulatory network for medical devices across Europe, in order to increase its effectiveness, to increase cooperation and to help avoid duplication by regulatory authorities. An effective network is also important to ensure timely communication, sharing of information and expertise, coordination and joint working on medical device issues. To this end the HPRA has been intimately involved in reviewing the structures and mechanisms which exist at EU level to achieve effective cooperation, namely the Competent Authorities for Medical Device (CAMD) network.

The HPRA is part of the EU delegation (along with France and Germany) of the Management Committee of the International Medical Device Regulators Forum (IMDRF). This forum seeks to clarify and harmonise, where possible, regulatory requirements in each global region and helps facilitate cooperation and communication between regulatory authorities.

The HPRA continued the role of IMDRF National Competent Authority Report (NCAR) exchange secretariat. This involves the management of exchange of medical device safety information among international regulators.

The HPRA is an active contributor to the development of guidance documents for the IMDRF work-stream initiatives.

### **Fee based funding**

Fees for medical devices were introduced in January 2017 following extensive consultation with industry to cover the costs of the HPRA's medical device regulatory activities. The model was amended during 2018 to reflect feedback received from affected stakeholders and is now based on a cost recovery model which relies on subventions from the Department of Health.

### **Case Workloads**

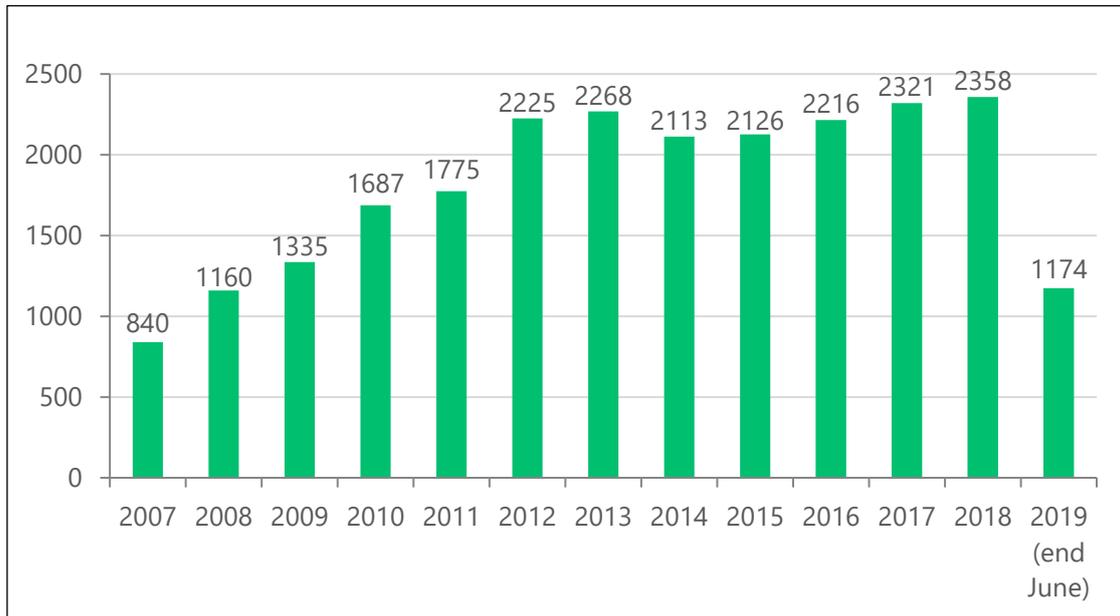
#### Vigilance & Compliance

There has been ongoing work with the HSE in various National Incident Management Teams during 2018 – 2019 and case work continues to lead to the identification of significant issues that require increased monitoring and oversight by HPRA.

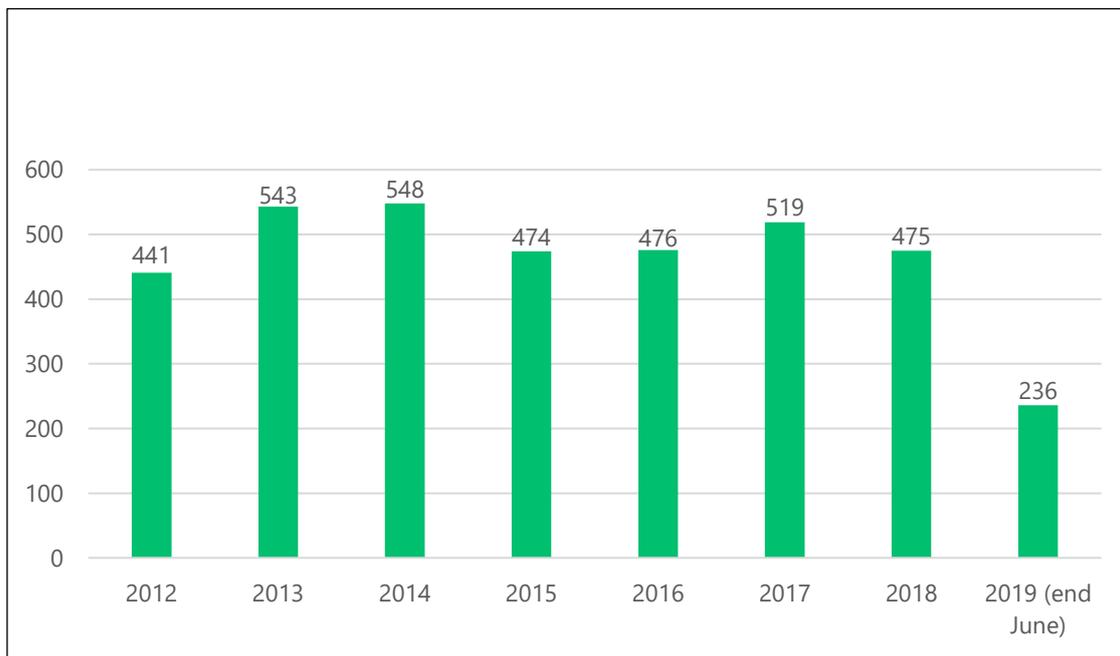
To date in 2019, the vigilance workload continues at consistent levels, with an increase in complexity in relation to vigilance cases. Year to date (January to end June), 1174 vigilance cases were opened and reviewed. Also in this period, among other communications, 23 HPRA safety notices and 45 NCAR's 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 (2007 to end of June 2019)**



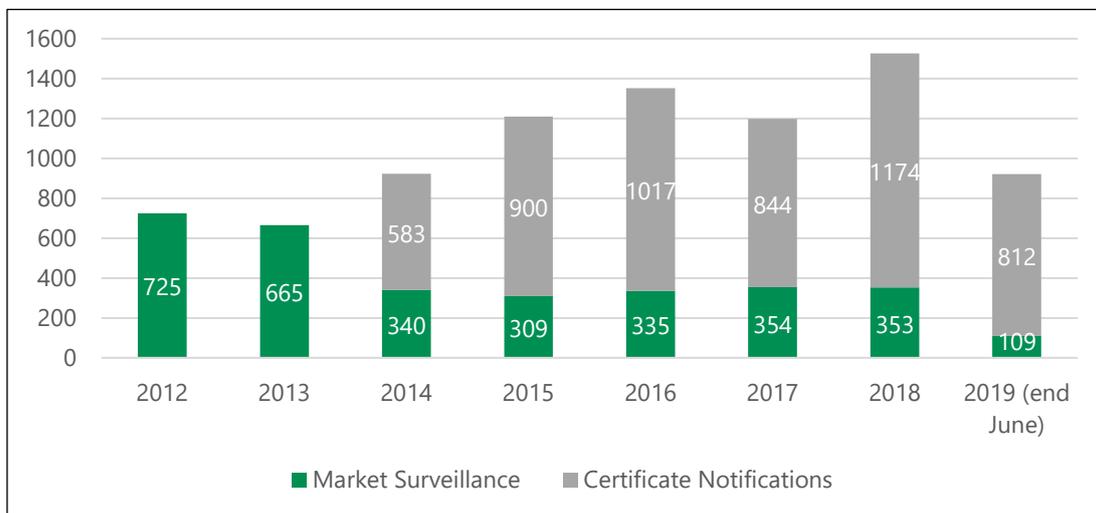
**Graph 2: Number of Field Actions affecting Irish Market (2012 to end of June 2019)**

## Designation and Monitoring of Notified Bodies

### Surveillance Cases

In line with the EU Commission’s 2012 Joint Plan for Immediate Actions, the HPRA has, over recent years, been developing and reinforcing its market surveillance activities for medical devices. The HPRA has implemented a lifecycle approach to surveillance focused on protecting the health and safety of those who use medical devices by ensuring that all devices on the Irish market comply with the relevant European directives.

During 2018, the HPRA continued to develop its lifecycle approach to market surveillance and investigated 353 market surveillance cases.



**Graph 3: Number of Market Surveillance Cases (2012 to end of June 2019)**

Note: in 2014 the HPRA changed its categorisation of market surveillance cases to separate out certificate notifications as a subset of market surveillance cases (whereas previously these were included as market surveillance cases). Presented in the graph above are the cases for 2012 – 2019.

The HPRA has, in particular since 2014, 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 market place 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.

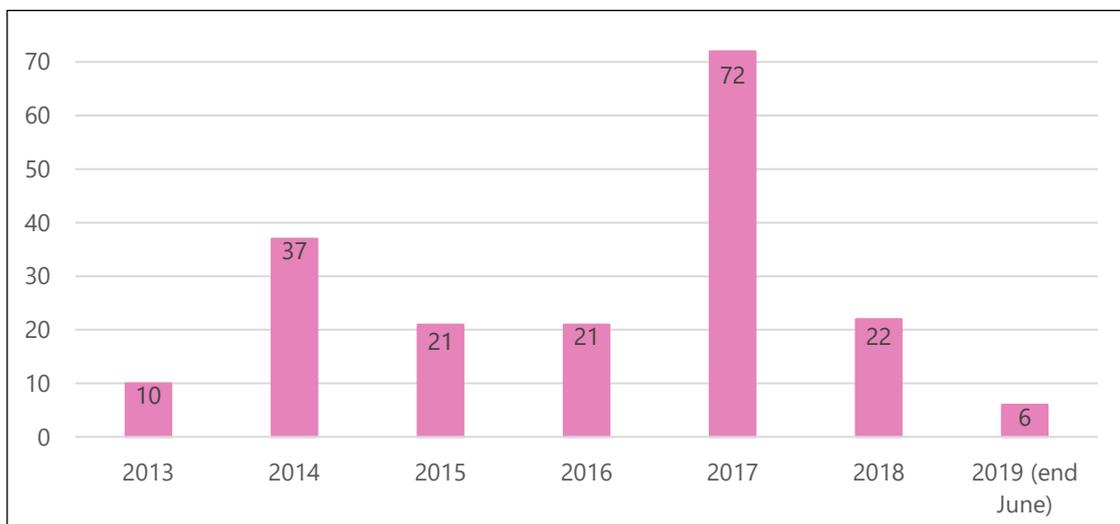
In addition, a significant number of queries for advice on regulatory issues have been processed. In 2018, we conducted 15 audits relating to medical devices. These were comprised of 6 for cause audit and 9 were based on proactive market surveillance projects and notified body surveillance/assessment.

#### Technical file reviews

A total of 22 technical file reviews were initiated in 2018. Technical file reviews require input across the assessment and clinical teams and are related to proactive surveillance work. Reactive cases were also initiated due to concerns raised by external stakeholders regarding products where the manufacturer with legal responsibility for the product is based in Ireland or the product has been certified by the Irish Notified Body.

#### Clinical Evaluation Review

Since 2015, 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 reactively in response to a number of specific device issues highlighted during the year 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 level and European level as part of EU joint assessment activities.



**Graph 4: Number of Technical File Review Cases created (2013 to end of June 2019)**

### Product registrations

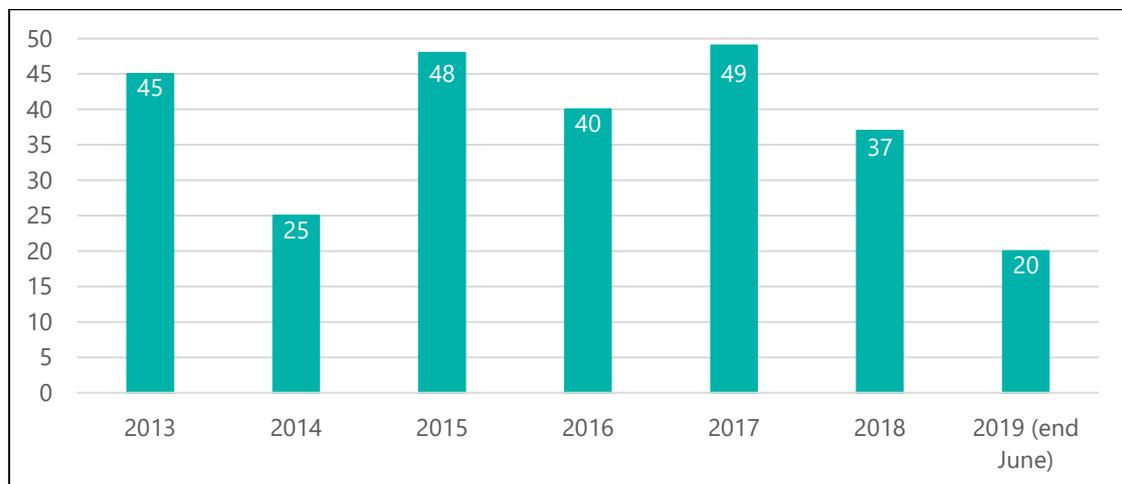
In 2018, the HPRA received 831 notifications of new medical devices to the medical device register. In addition, 50 new organisations as Irish-based manufacturers or authorised representatives for Class I, custom-made, *in-vitro* diagnostic medical devices, as manufacturers of system or procedure packs, or as sterilisers of medical devices, have been notified. Registration of these devices in the Member State in which the manufacturer or its authorised representative is based is required by legislation as there is a self-declaration of conformity made by the manufacturer.

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.

### Classification Requests

The HPRA received 37 applications for classification of medical devices or products queried as medical devices in 2018. 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 5: Classification Requests (2013 to end of June 2019)**

### Clinical Investigation Applications

The HPRA received ten applications for clinical investigations of a medical device to be conducted in Ireland in 2018.

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

### Queries

During 2018, the HPAR medical devices team received 521 queries relating to medical devices. The majority of the queries related to the provision of guidance and interpretation of the legislation, registration, labelling, qualification and classification of devices and distribution.