HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Public Consultation on
Annual Review and Proposal for Fees – For Financial Year 2017

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

DATE 29 September 2016

CONTENTS

1 INTRODUCTION

The HPRA (formerly the Irish Medicines Board (IMB)), since its establishment in 1996, has successfully run its core 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 IMB 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.

After a period during which the country experienced an economic crisis, there are signs of an economic recovery. However, despite the projected growth in the economy, the effects of the economic crisis and the resulting difficult economic environment are still being experienced by both the HPRA and stakeholders. The HPRA continues to face increased workloads arising from both European and new national legislation.

The impact of new legislation continues to be rolled out across the organisation and the preparation for the new Clinical Trials regulation will commence in 2017 for implementation in 2018. 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. Compliance activity, particularly outside of Ireland, is also increasing and the HPRA expects staff levels to increase across all areas in 2017. As noted in previous consultations the HPRA has absorbed the cost resulting from additional requirements and greater regulatory complexity for falsified medicines, pharmacovigilance and generic substitution without increasing its fees. In 2017 HPRA will become the competent authority for controlled drugs and will also commence the rollout resulting from the new medical device legislation (subject to a separate consultation).

During 2015 the HPRA developed a new strategic plan for the years 2016 – 2020 which also aligns with the EMA and HMA joint strategic plan. Following extensive consultations, detailed review of the environment within which we operate and management discussions, we have identified the themes and activities which we believe are relevant to the development of our regulatory activities over the next five years. High-level strategic goals have been determined 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)

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

- **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 2017 include:

- Dedicated project and resources to manage medicines shortages from a regulatory view point.
- The implementation of a virtual innovation office.
- The rollout of a new regulatory work flow system 'Eolas' across the entire organisation which will put HPRA at the cutting edge in Europe in respect of its IT capabilities.
- European and international projects in pharmacovigilance, crisis management and GMP.

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

As previously stated, it is a priority for the HPRA to match resources from fee income with current work volumes and 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 2016 review of fees and it also sets out the current service levels and activities and expected changes in service levels and activities for 2017.

2 REVIEW OF THE 2016 FEES

2.1 The 2016 fees

In 2016 the HPRA kept fees at 2015 levels and continued to absorb the additional costs of the new European legislation without increasing the fee base.

3 SUMMARY OF PROPOSED CHANGES FOR 2017

The HPRA, like all its stakeholders, is operating in a difficult economic environment

A review of income levels across all categories has shown both increases and decreases in various income categories. It seems however that the fall in income experienced over the last number of years has halted and there are some signs of recovery in certain sectors. Given the increased responsibilities, the planned increases to staff numbers, future pension liabilities and the fact that we have not increased fees since 2010 and have reduced fees in 2011 and 2012, we are not in a position to further reduce the fees generally. We will however continue the freeze of fees for a further year and reduce certain fee categories. The proposed key changes are:

- General fee freeze;
- Reduced fee for the assessment of the same active substance master file (ASMF) for a number of products from the same applicant submitted at the same time;
- Reduced fees for bulk transfer applications;
- Introduction of fees for national scientific advice;
- A change to the way fees for Audit/Inspection of medical device manufacturers and cosmetic companies are applied;
- New fees for the inspection of medical device distributors in line with the new legislation.

3.1 Medical Devices

This document contains a consultation on the small number of medical device fees that already exist as part of our fee structure. A completely new fee model for medical devices (for those previously outside the scope of the existing fees regulations has been developed and was subject to a separate consultation which can be found on the consultations 2015 page of our website www.hpra.ie.

That new fee proposal has been approved by the Department of Health and will be implemented from 1 January 2017. The proposed new fee model was subject to an extensive consultation both directly with stakeholders and via the published consultation (see reference above). As all medical device companies will be required to register, a system to facilitate company registration will be available on our website shortly Omitting to register may result

in either being charged at the wrong rate or accumulating outstanding liabilities over a period of time as fees will be backdated to the date of introduction.

3.2 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 2016. 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 being experienced by both the Irish and worldwide economies means that forecasting is extremely difficult and subject to change.

The HPRA has been able to freeze fees due to the continued management of our cost base. However, as noted above, we are experiencing increased workloads and we will have to re-appraise the situation in 2017 for the 2018 fees. The HPRA therefore commits to review the proposed fees during the planning cycle in 2017 and further amend the fees and fee structure, if required, for 2018.

4 FINANCIAL POSITION IN 2016

New national applications have remained the same as last year with a decrease in new DCP and MR incoming applications. There has also been a decrease in national variations, however we have seen a corresponding increase in DCP/MR variations. We are still seeing a reduction in parallel import applications to date. Overall income levels are as expected. General costs have stabilised which reflects the fact that the HPRA had negotiated costs downwards to reflect the prevailing economic climate. However, our cost base is approximately 70% staff costs and in recognition of the additional responsibilities undertaken by the HPRA in 2015 and 2016 we have increased staff numbers and have absorbed these additional costs without increasing fee levels. It should also be recognised that the salary cost of the HPRA has been artificially suppressed with substantive pay cuts across all grades for the last five years and with a recovering job market the HPRA is already starting to lose key senior members of staff as salaries are falling below the market place. If the HPRA is to continue to deliver the service industry requires we will need to be in a position to recruit staff with the relevant expertise at the appropriate salary level. It is likely that some of the pay cuts imposed under the various agreements will be reversed or reversed in the coming years. This will impact directly on the HPRA future cost base. Although we expect to show a surplus at the year-end,' following an IT strategic review of the organisation's needs and existing IT framework, we have commenced a very significant IT project 'EOLAS. Our existing workflow systems are now over 10 years old and can no longer be supported. Given the importance of IT in our service delivery we started a three-year programme in 2015 to replace all the workflow and stakeholder facing systems to continue providing a 'best in class' service. The investment in IT and infrastructure has delivered and will continue to deliver long-term savings and efficiencies.

As noted above, the HPRA saw a reduction on payroll costs from the Haddington Road agreement but, as stated, we believe that without some change to this the current levels of salaries have the capacity to impact negatively on the ability of the HPRA to retain staff. It should also be noted in relation to payroll costs that the HPRA has a significantly unfunded pension liability and it is proposed that savings arising from salary reductions will be allocated against future pension liabilities.

5 FINANCIAL CHALLENGES IN 2017

The HPRA will face further financial challenges in 2017.

As noted above, government restrictions on pay and employment ceilings have artificially reduced the HPRA payroll and staff numbers and some of these reductions are due to reverse in 2017. We have been working closely with our parent Department and will be in position to increase staff numbers in 2017 with a corresponding increase in our cost base. As outlined in the introduction, the increased complexity of the European regulatory model, the ongoing implementation of new directives such of the falsified directive, the implementation of the new clinical trials directive and expanded deliverables under the strategic plan mean that the HPRA continues to require additional resources to deliver our goals and objectives. The HPRA also has increased activity in areas funded by the state but there has been considerable pressure on exchequer funding over the last number of years. A further side effect of the ongoing economic recovery is a projected increase to certain cost levels. While inflation remains low, certain costs were artificially low during the crisis, particularly in the service industries, as companies sought to survive and we predict increases above the expected inflation rates for 2017 in some of the categories. The impact of Brexit on the economy is a further unknown which needs to be managed.

The HPRA continues to manage the requirements under the Health (Pricing and Supply of Medicinal Goods) Act, 2015 where the HPRA is responsible for developing the list of interchangeable medicinal products. While the legislation provides for a fee, much of this work, by direction of the Department of Health, is not funded.

Despite the challenges arising from the economic climate and the increased regulatory responsibilities, the HPRA must also continue to invest in and deliver services to stakeholders. As outlined above, in 2017 the HPRA will make a substantive investments in our new 'best in class' IT systems. We will also use our resources to maintain and improve our existing levels of service to all stakeholders.

6 PROPOSED FEES

As noted above there will be a freeze on fees for the year 2017 notwithstanding the increased costs planned in 2017.

7 DETAILED CHANGES TO FEES

7.1 General change to fees

It is proposed that there will be **no general** increase applied to any fees.

7.2 Other proposed adjustments to fees - human medicines

7.2.1 Annual maintenance fee

It was stated in the 2016 consultation document that the HPRA would consider an increase in the annual maintenance fee in 2017 for active licences to reflect the additional responsibilities arising from recent legislation.

While an increase was considered we have decided to leave the fee at the existing levels, but we will do a full review in 2017 for the 2018 fees.

7.2.2 Transfers of MAH – Divestments and Bulk Transfers

a) Divestments
   It is proposed that the current transfer of ownership fees would apply to applications concerning divestments of products.

b) Bulk Transfer applications
   It is proposed to reduce fees for bulk transfer applications. Currently, to avail of the lower rate, the products are required to be within the same MA range.

   It was agreed that where the bulk transfers are notified in advance, the first ten MA's are charged at the normal rates and thereafter are charged at the reduced fee of €321 per transfer. For products that would have been subject to the full fee this represents a decrease of between 64% and 75% depending on whether the transfer is between a related or related company.

7.2.3 National Scientific Advice

In 2016 the HPRA introduced, for the first time, a pilot for providing scientific advice. In the absence of a fee code the daily technical rate was applied to these applications. In 2017 the following fee structure in respect of different types of advice is proposed. These rates are low in relation to the service delivered and are designed to support innovation in Ireland.

Quality or preclinical development only	€2,200
Clinical development only	€2,800
Quality & Clinical development, Preclinical & Quality, Clinical & Preclinical	€3,500
Quality, Preclinical and Clinical development	€4,500

7.2.4 Clinical Trials

(a) Amendments

As noted in previous years the fees for clinical trials were considerably lower than the cost of delivering the service. We had previously indicated that we would review the fees in 2016. However, in light of the implementation of the new clinical trials regulation, we are keeping the fees at their existing levels and will review as part of the project to implement the Regulation. The HPRA continues to charge no fees for academic trials, consistent with our desire to support clinical trials in Ireland.

7.2.5 Active Substance Masterfile (ASMF) Assessment

It is proposed and agreed to apply a reduced fee when assessing the same ASMF for a number of products from the same applicant submitted at the same time. Currently reduced rates only apply to products within the same range.

7.2.6 Medical Devices

It was noted that a proposal for new fees has been approved by the Department of Health. In relation to the existing fees the following change is proposed:

Notified Body – Annual Maintenance Fee

It is proposed, due to the level of additional work in maintaining certificate notifications and queries relating to devices certified by the Notified Body, to introduce an annual maintenance fee. The fee will cover the continued maintenance of a notified body's designation and its required continuous monitoring. In addition, the new legislation will require proactive sampling of medical devices certified by the Notified Body.

It was proposed to charge an annual fee for €3,000.

7.2.7 Controlled Drugs

The HPRA will become the competent authority for controlled drugs in 2017 and it is proposed that a new fees structure will be put in place (fees for controlled drugs are unchanged from the 1980s).

It is proposed that the current fees will be reviewed during 2017, once the legislation is enacted.

7.2.8 Cosmetic and medical device Inspections / audits

It is proposed that the inspection fee for cosmetic and medical device companies will apply to companies with five employees or more. However, if a company feels that they should be exempt from this fee due to their size/turnover, they may make a submission to the HPRA to apply for a reduced fee based on fee code 190 – service item fee.

7.2.9 Audits of Medical Device Distributors

It is proposed to charge for inspections of medical device distributors in line with the new legislation. The current daily and hourly inspection fee will apply to all medical device distributors.

8 CONSULTATION

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

Contributions to the consultation on this proposal may be provided to the HPRA by 30 October 2016. Contributions should be sent by e-mail 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 three years were driven by the requirement to maintain and further improve patient safety and service levels to industry.

These projects include in summary:

- Continued refining of the HPRA's operations to more effectively meet the needs of our stakeholders. Use of lean six sigma processing and capacity based resource allocation has facilitated improved management and increased efficiency of the assessment processes. Objectives included:
  - improved efficiency with maintenance of quality,
  - streamlined procedures and processes
  - improved transparency and standardisation of approach
  - ongoing increased productivity, and the continued management and reduction of backlogs.

  As a result of meeting these objectives, the Human Products Authorisation and Registration (HPAR) department has seen faster turnaround times and a considerable reduction in the number of human medicine applications overdue.

- Significant progress has been made in the development of a new HPRA workflow system. Our focus is on improving and extending 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 drug reactions and quality defects, accessible to patients, health care professionals and industry.

- 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 50 priority substances identified by the Minister for inclusion 47 are now incorporated on the list. The remaining three will be addressed as a matter of priority. 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 Department of Health or the HSE. Further efficiencies will be introduced during 2016-2017 to allow marketing authorisation holders, where appropriate, to incorporate an application for inclusion on the list as part of the submission to have the product licensed for the Irish market.

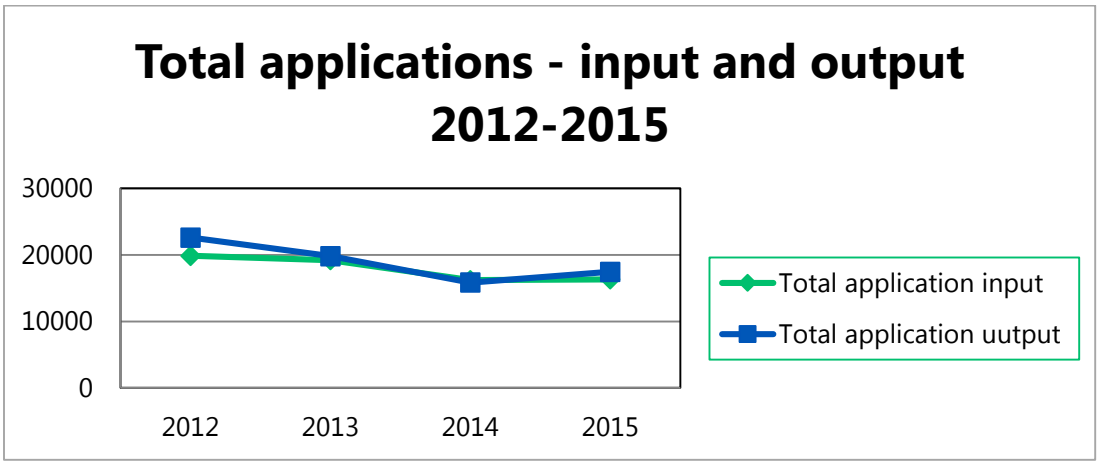
- Focus on the continued provision of guidance and support to industry stakeholders in areas undergoing evolving regulatory development, including
  - the new requirements under the Pharmacovigilance legislation
  - the new requirements of the Clinical Trials Regulation
  - the new requirements of the Medical Device Regulation
  - the registration of traditional herbal medicinal products.

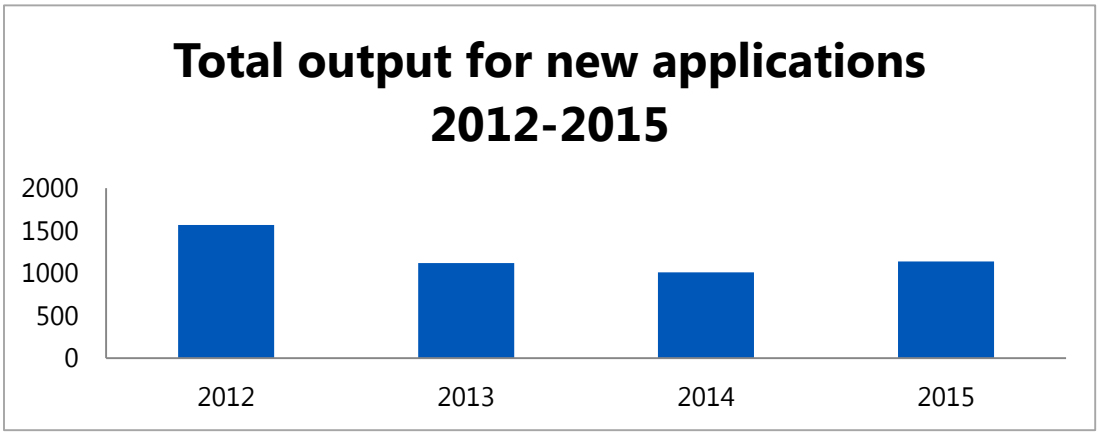
- Continued progression of a public health initiative focused on providing important online information about all medicines licensed by the HPRA. This includes maintaining publication of the summary of product characteristics document, patient information leaflets, ATC codes, interchangeable lists and the legal classification status of all human medicines on the HPRA website (www.hpra.ie). Since December 2015 all educational materials are published on the website.

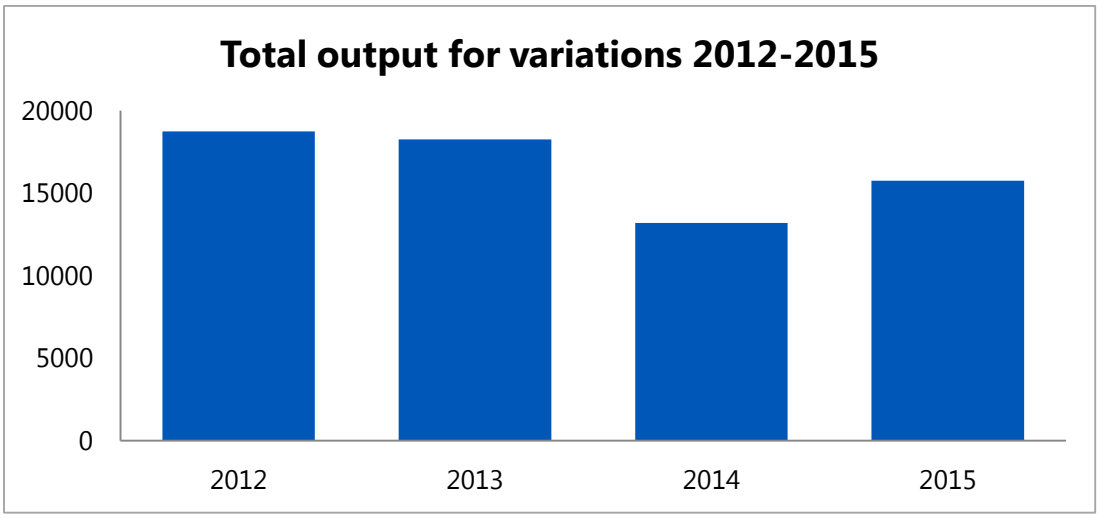
- Proactive approach to switching: following review of policies in this area, and liaison with the Department of Health, the HSE Health and Wellbeing Directorate and healthcare professionals, the HPRA has taken a proactive approach to the reclassification of medicines since 2014. This has included the 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. In 2016 the HPRA continued 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.

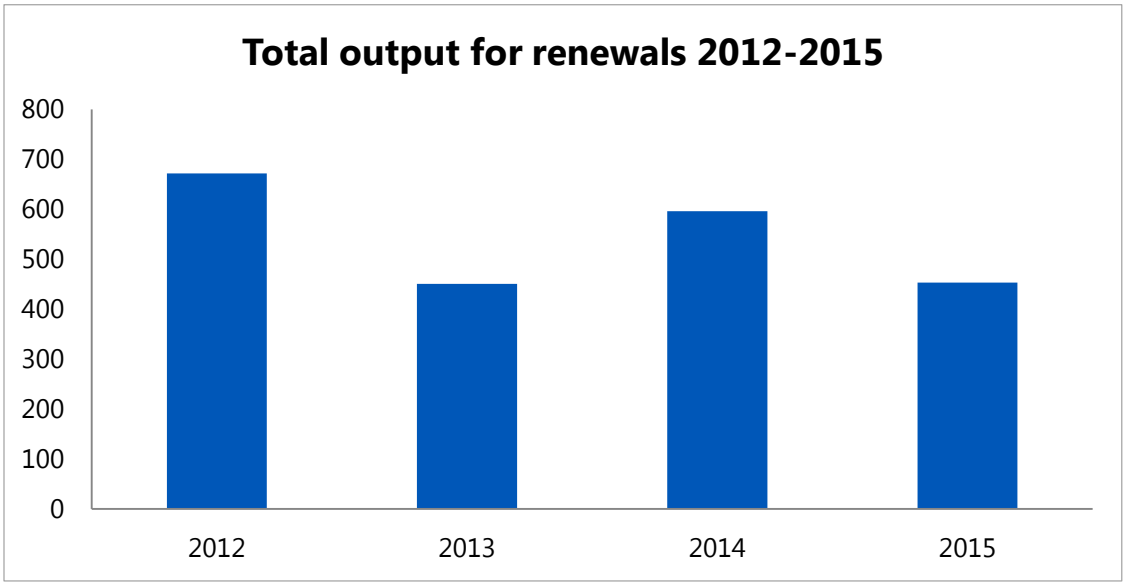
- Raising awareness of the regulation of medicines and important safety considerations via publications and contributions to undergraduate programmes in the medical and paramedical fields.

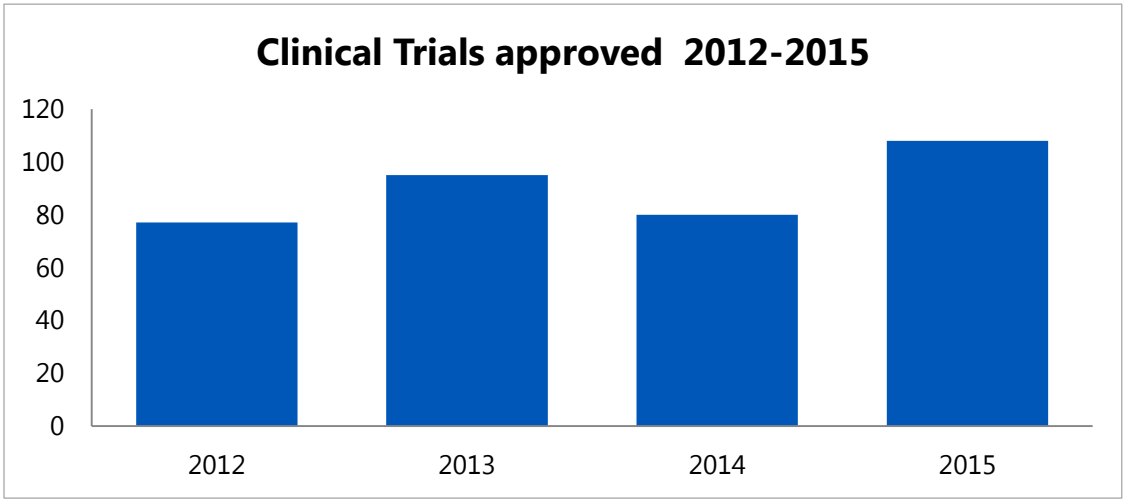
The graphs below outline the output across all application types up to the end of 2015.

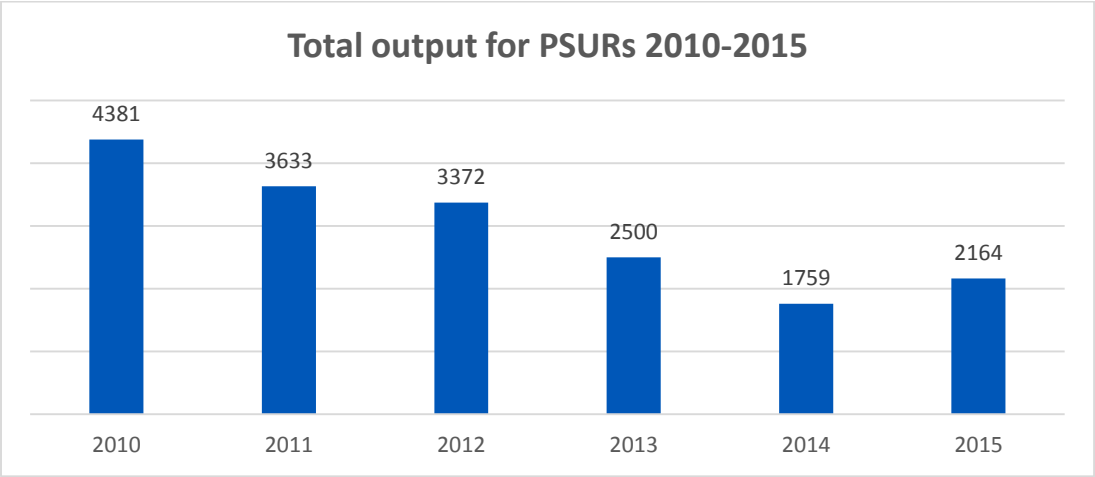

Total applications - input and output 2012-2015
30000
20000
10000
0
2012
2013
2014
2015
Total application input
Total application uutput

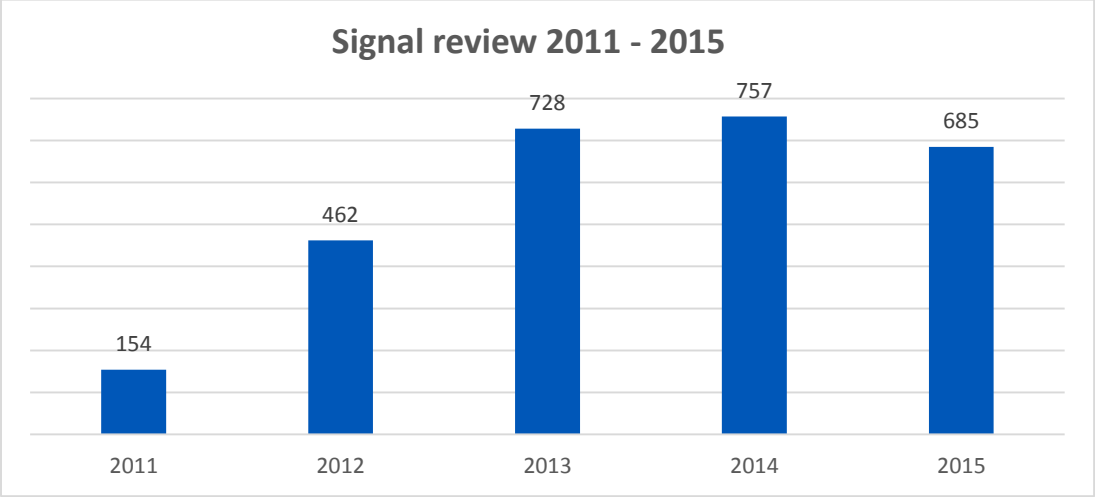

Total output for new applications 2012-2015
2000
1500
1000
500
0
2012
2013
2014
2015

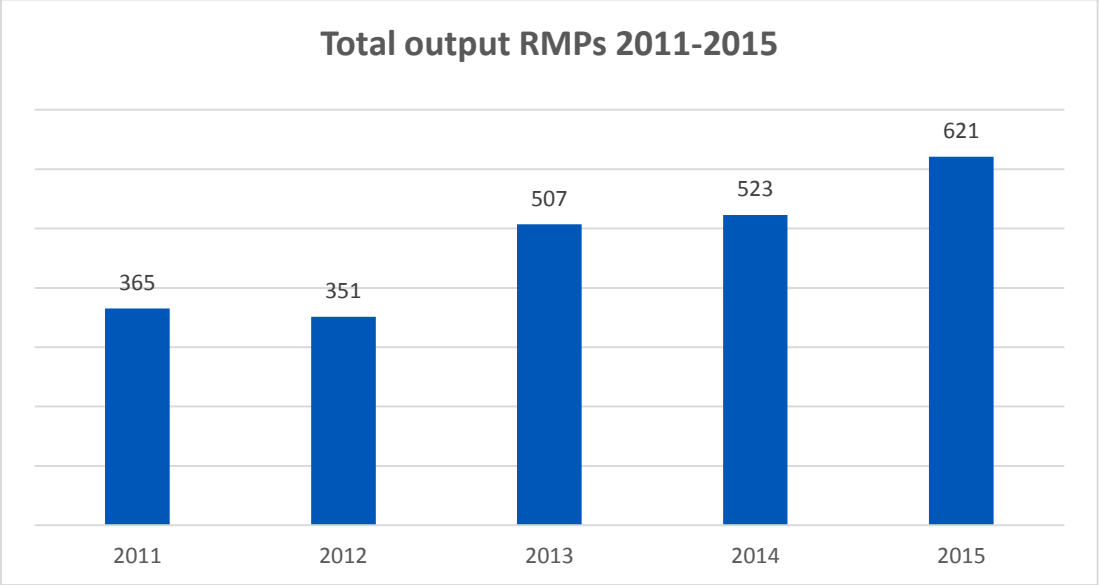

Total output for variations 2012-2015
20000
15000
10000
5000
0
2012
2013
2014
2015

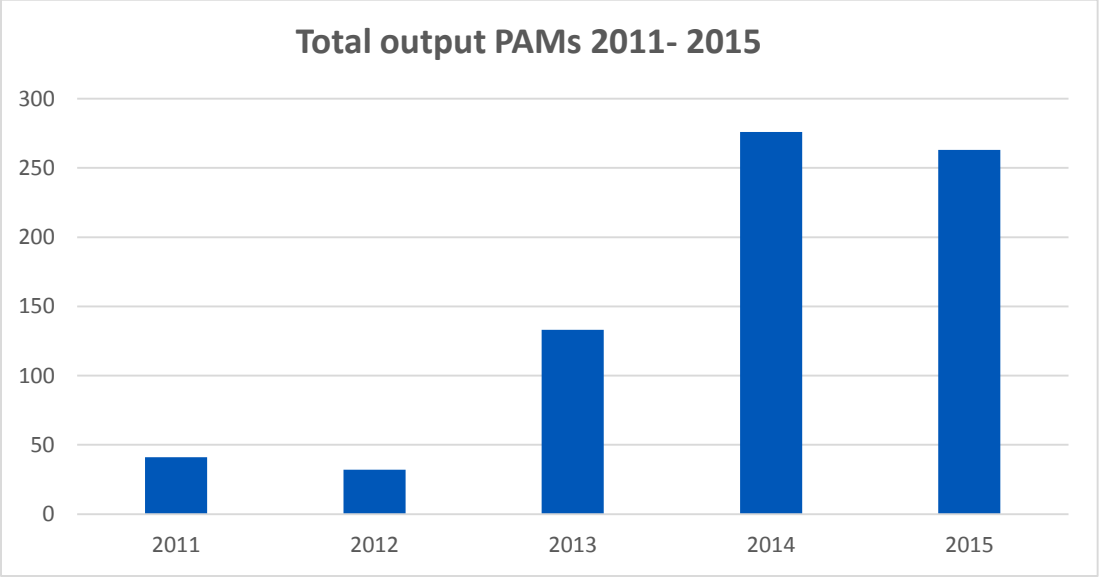

Total output for renewals 2012-2015
800
700
600
500
400
300
200
100
0
2012
2013
2014
2015

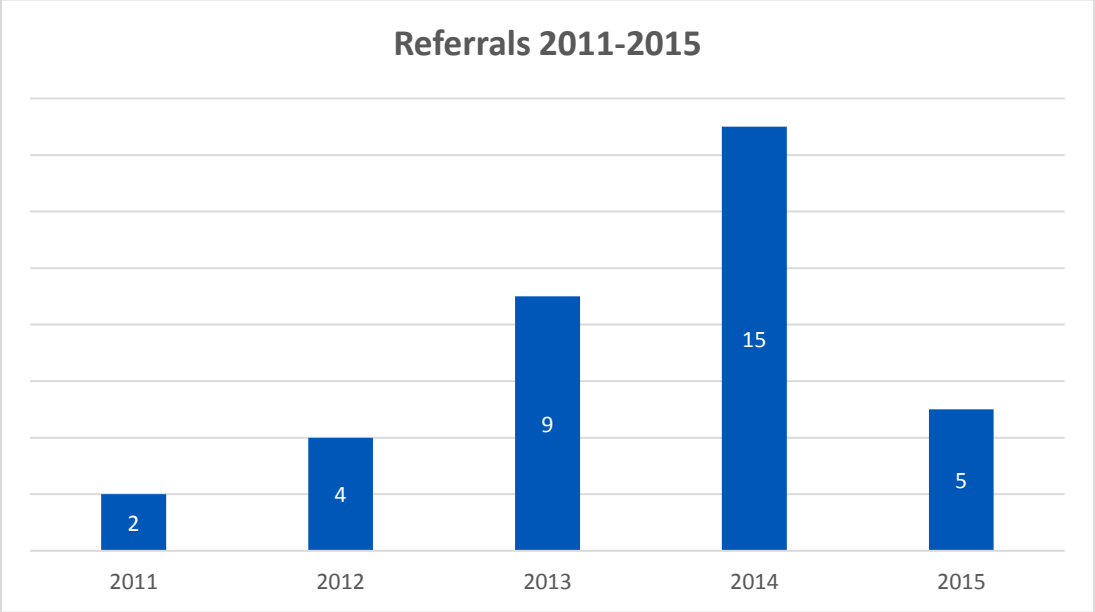

Clinical Trials approved 2012-2015
120
100
80
60
40
20
0
2012
2013
2014
2015


Total output for PSURs 2010-2015
4381
3633
3372
2500
1759
2164
2010
2011
2012
2013
2014
2015


Signal review 2011 - 2015
154
462
728
757
685
2011
2012
2013
2014
2015


Total output RMPs 2011-2015
365
351
507
523
621
2011
2012
2013
2014
2015


Total output PAMs 2011- 2015
300
250
200
150
100
50
0
2011
2012
2013
2014
2015


Referrals 2011-2015
2
4
9
15
5
2011
2012
2013
2014
2015

APPENDIX II SERVICE LEVELS – COMPLIANCE DEPARTMENT

Compliance Department General Activities

Initiatives undertaken / further developed in 2015/2016 included:

- 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 2015 and 2016.
- Also under the FMD, HPRA staff continued to participate in an expert group on safety features convened by the European Commission. This included completion of the Commission Delegated Regulation which sets out the details around safety features and their implementation. This was finalised in February 2016 with a three year timeframe for implementation. In relation to this, the HPRA has liaised closely with industry, wholesale and retail stakeholders which have come together to implement the so called stakeholder model. This will include 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. While not part of the governance structure of this stakeholder body (the Irish Medicines Verification Organisation), we will continue to liaise closely with it. It is also envisaged that we will have an oversight role in relation to the repository.
- 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)
- Provision of 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. Following evaluation of applications for authorisations from procurement and/or transplant centres, via inspections and other follow up measures, all four were authorised. The framework for quality and safety of organs for human transplantation, developed in conjunction with Organ Donation and Transplant Ireland, was used in evaluating these centres. A system for reporting and assessment of serious adverse events / reactions remains in place.

- Continued liaison with wholesalers on the implementation of revised EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use. A number of applications from wholesalers that 'procure and supply' (i.e. do not handle the medicine) were processed and wholesale distribution authorisations were granted. Clarification was also provided to the industry around the requirements applying to 'procure and supply'.
- 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.
- Contributed to the European Commission's work in producing new guidelines for operators in the area of precursor chemicals.
- Provision of assistance to the Department of Health in the development of national provisions relating to the implementation of two European Regulations relating to precursor chemicals.
- Provision of assistance to the Department of Health on an introduction of new controlled drugs legislation.
- 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, as amended.
- 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.
- 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 sampling and analysis of mutual recognition and decentralised medicines
- Continued development of the advertising compliance monitoring 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,

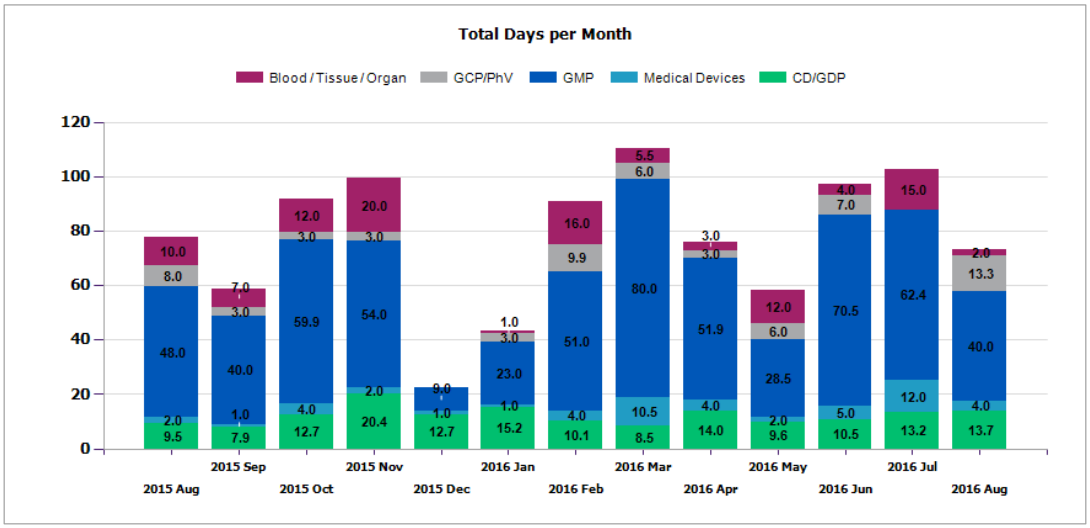
HSE and the Competition and Consumer Protection Commission and the implementation of a coordinated national approach to market surveillance and testing of cosmetics.

- The National Cosmetic 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.
- The Cosmetics Regulation, 1223/2009, came into force in July 2013. Accompanying national legislation, the European Union (Cosmetic Products) Regulations, 2013 (S.I. No 440 of 2013) came into force in November 2013. The HPRA continues to work with the HSE and the cosmetics industry on the implementation of these pieces of legislation.

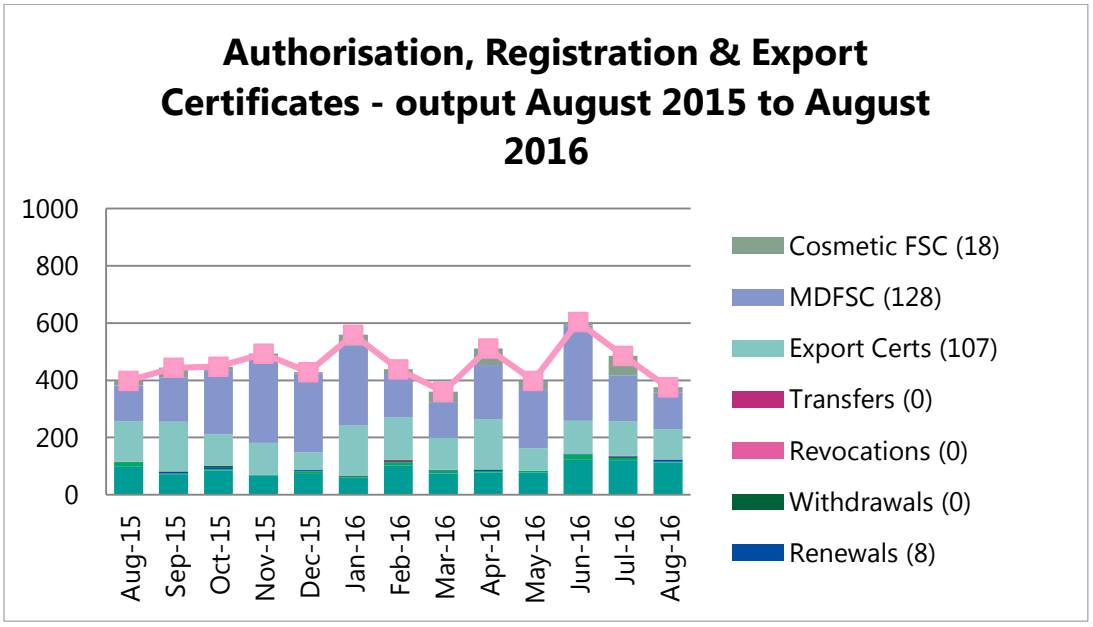
Other activities included:

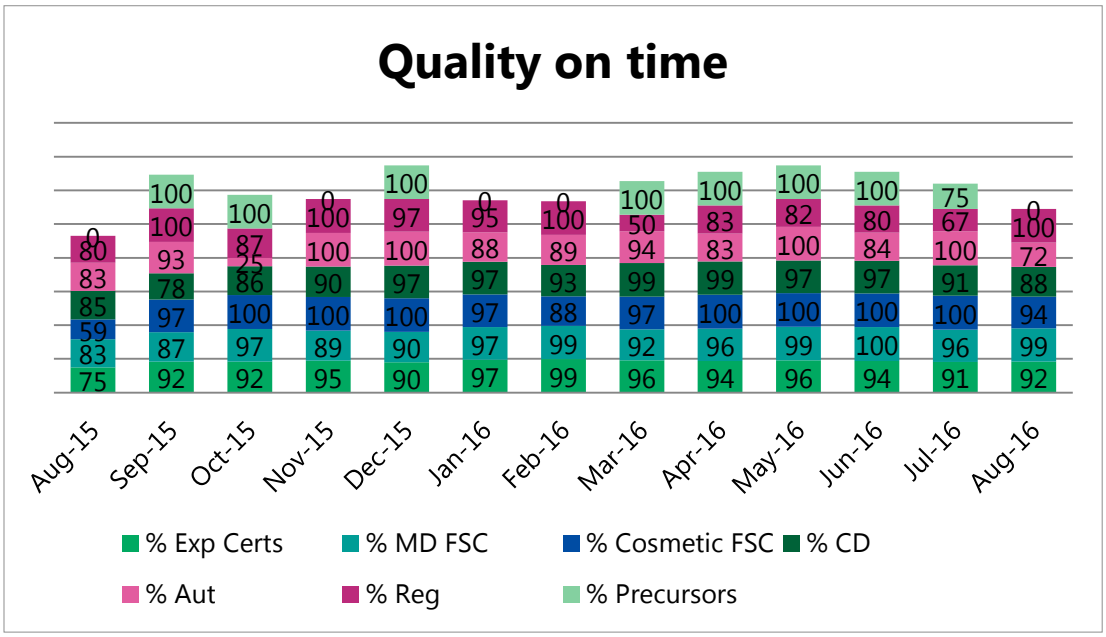
- Continued interaction and communication with stakeholders including industry and other representative groups. These included meetings with industry representative bodies and individual companies.
- Continued management of the controlled drugs function on behalf of the Department of Health.
- Continued management and use of the Exempt Medicinal Products importation/supply data that are notified to the HPRA. These data may be a source of relevant information for the Quality Defect and Recall programme.
- Rapid turnaround of applications for variations to manufacturers' and wholesalers' authorisations, and for export certificates and controlled drugs licences.
- Further development of good clinical practice 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.
- In co-operation with Revenue's Customs Service, ongoing detection and detention of illegal mail-order importations of prescription-only medicine. Co-operation with Customs, An Garda Síochána and enforcement agencies worldwide on Operation Pangea IX, an Interpol-coordinated international week of action against illegal supplies of unauthorised prescription medicines via the internet.

The graph below shows the level of inspection activity over the period September 2015 to month-end August 2016.

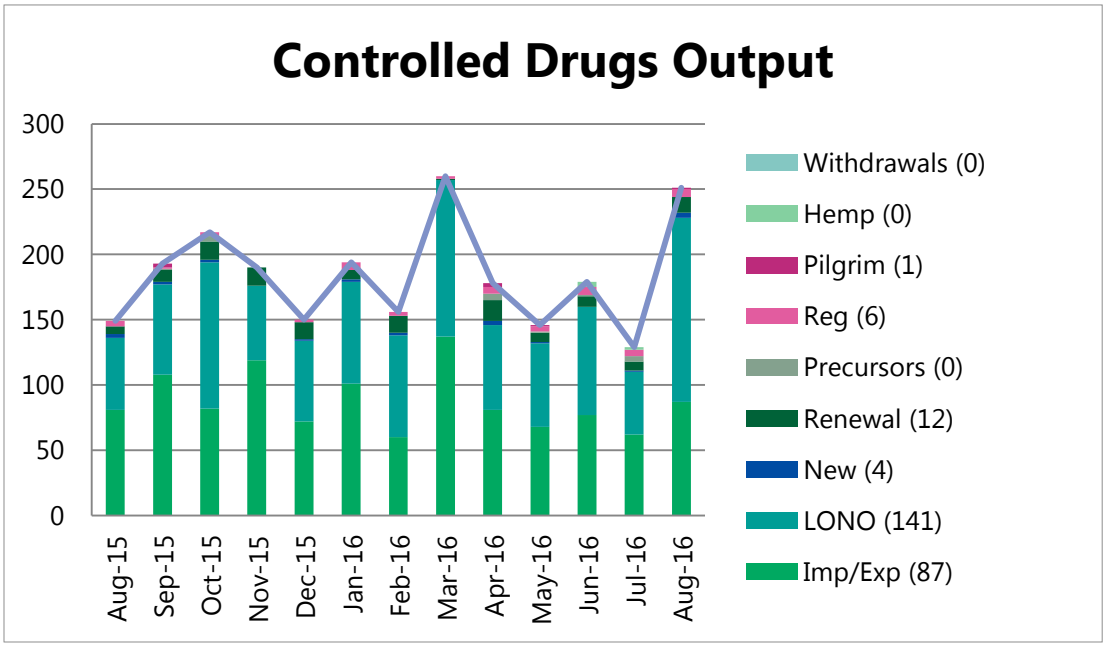


The graphs below show the numbers issued and the percentages issued on time, for export certificates, controlled drugs licences and GDP, GMP and IMP licences, over the period August 2015 to August 2016, inclusive.

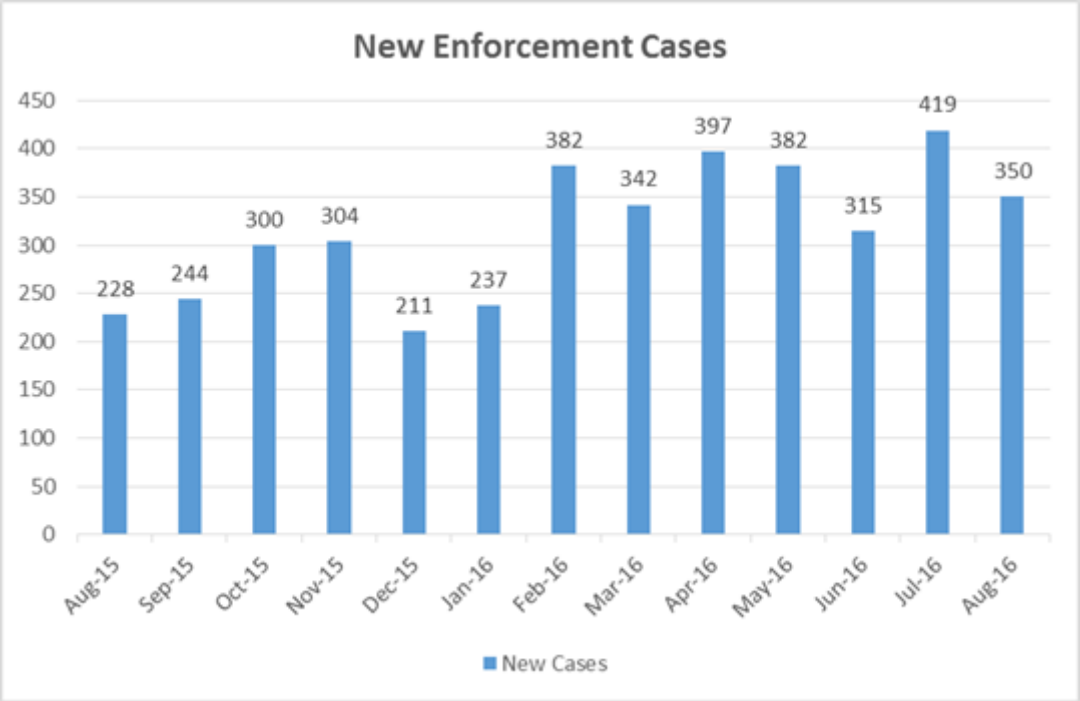




The graph below shows the output of licensing of controlled drugs, by category of licence.



The graph below shows the number of enforcement cases for the period August 2015 – August 2016 inclusive. The majority of these relate to attempts to illegally import prescription-only medicines, an amount of which are falsified.



In 2016 - 2017 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 2015 and 2016, 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 tissues and cells legislation requires all sites involved in the procurement, testing, processing, storage and distribution of tissue and cells to be authorised. To date, a full programme of inspections of tissue establishments has been carried out.

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.

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. 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 2015 and 2016, to date. We have an electronic system for notification and we continued 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.

APPENDIX III SERVICE LEVELS – MEDICAL DEVICES

Caseload volume continued to remain high during 2015 within all of the teams involved in medical devices across the HPRA. There continue to be a high number of vigilance cases and an increasing number of field actions (recalls, device modifications etc.) relating to devices on the Irish market. These cases are increasing in complexity and significance in terms of 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.

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

There has been considerable change and development of the medical device regulatory system over the last number of years and this can be expected to continue into the future with a substantial revision to the medical devices legislation being agreed in June 2016. Two new European Regulations (one on medical devices and another on *in-vitro* diagnostic devices) have been agreed and it is anticipated that these will be published by the end of 2016. The legislation will place 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 six assessments during 2015. 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 2015, 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.

At national level the HPRA has continued its monitoring and oversight of notified bodies. The Irish notified body has been subjected to joint assessments in 2013 and 2015.

Also at a national level 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 was invited by the EU Commission to become 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.

In 2014 the HPRA commenced 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 a member of the IMDRF Working Group on Regulatory Product Submissions and from February 2015, was requested to act as interim Chair for the Table of Contents (TOC) working group. The HPRA returned the Chair to Health Canada at the end of 2015, having reached agreement and published the Assembly and technical guide and the folder structure guidance in preparation for the IMDRF Table of Contents (TOC) .The HPRA is an active contributor to the development of guidance documents for the IMDRF work-stream initiatives

leading in areas such as regulatory products submissions and participation through its observer status, in others, such as, the Medical Device Single Audit Program (MDSAP).

Fee based funding

The HPRA is committed, following instruction by the Department of Health, to introduce fees at national level to cover the costs associated with all of its medical device activities. Following discussion with interested parties over a number of years and in particular during 2014 and 2015 the HPRA launched its public consultation in relation to introduction of a national model for fees in July 2015. Since then and based on further discussions and responses to the consultation the HPRA has added clarifications to its proposed national fee model and submitted these for further consideration by the Department of Health.
It is intended that such fees, to cover all of the costs of the HPRA's medical device regulatory activities will be introduced at national level from January 2017.

Case Workloads

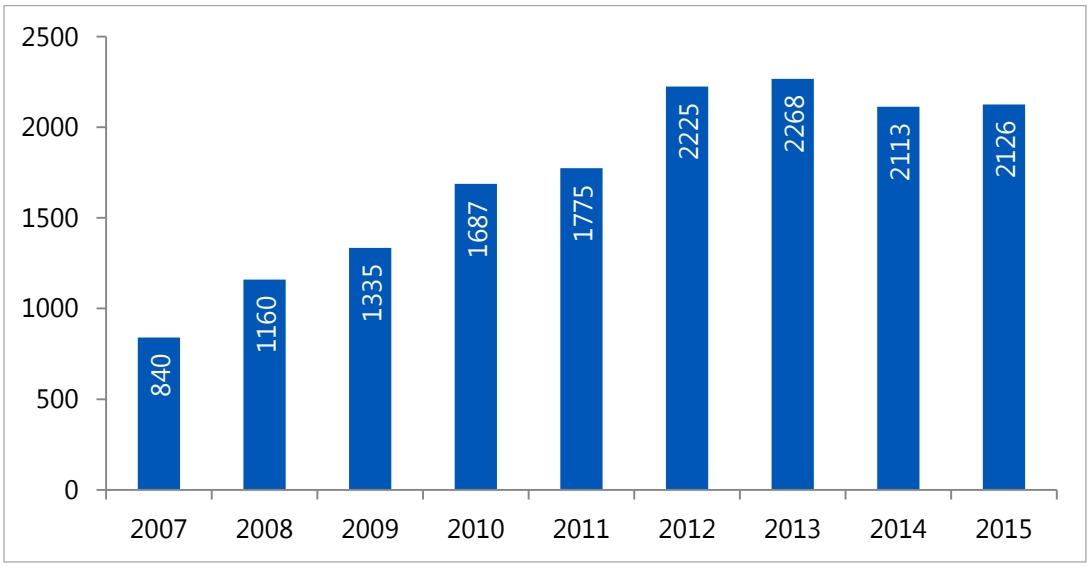
Vigilance & Compliance

Several significant medical devices issues resulted in significant workload over the period 2013 to 2016. These include issues with intraocular lenses, metal on metal hip implants, infusion pumps both implanted (for example for diabetes and pain management) and hospital pumps and defibrillators (AEDs and professional). There has been significant ongoing work with the HSE in various National Incident Management Teams.

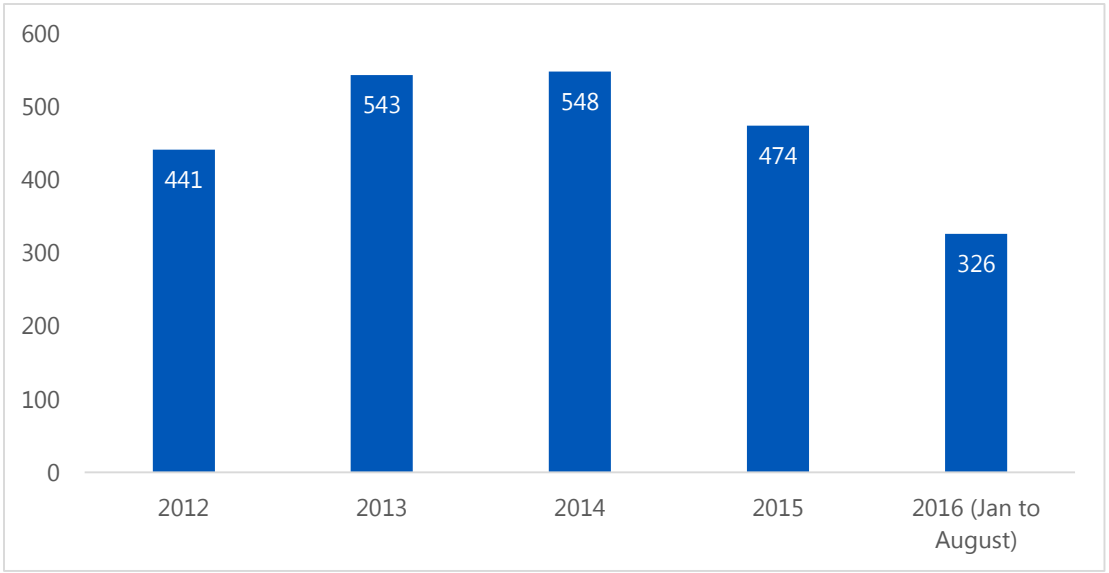
To date in 2016 the vigilance workload continues at consistent levels, with an increase in complexity in relation to vigilance cases. Year to date (January to end August) 1509 vigilance cases were opened and reviewed. Also in this period, among other communications, 25 HPRA safety notices and 61 NCAR's were issued nationally, across Europe and internationally. The HPRA continues to be very active at a European level in the area of vigilance. It is ranked fifth in the EU for the total number of NCARs circulated in 2014.

In 2015 and 2016 work has been undertaken 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 2015)



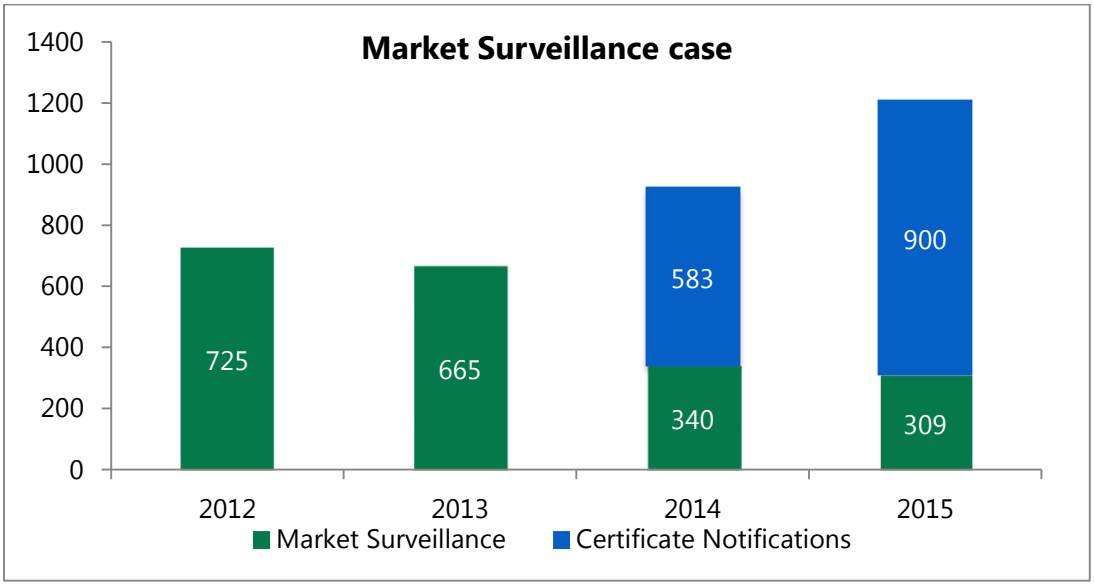
Graph 2: Number of Field actions affecting Irish Market (2012 to 2016 end August)

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 2015, the HPRA continued to develop its lifecycle approach to market surveillance and investigated 309 market surveillance cases.



Graph 3: Number of Market Surveillance Cases 2012-2015

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 – 2015.

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 or devices or issues identified through the review of scientific data and literature.

Other market surveillance activities conducted in 2015 include:
- The development of the system and procedure guidance pack;
- The development of a Medical Device Information Notice for communicating market surveillance issues;
- Review of food intolerance products available on the Irish market;
- Review of the standalone software on the HPRA register;
- Proactive reviews of respiratory and ophthalmic manufacturers based in Ireland;
- Review of bio resonance products;
- Reviews of clinical data presented as part of clinical evaluations of high risk medical devices.

The HPRA also initiated a program of sampling and analysis in 2015 which included testing of several types of implants.

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 programme of audits of class I and custom-made manufacturers along with a series of reactive/for cause audits of medical device manufacturers based in Ireland is in progress. In addition, a significant number of queries for advice on regulatory issues have been processed. In 2015, we conducted 16 audits relating to medical devices. These were comprised of two observed audits of NSAI (notified body) auditors, two notified body assessments and twelve audits at medical device manufacturers' facilities. All of these were general medical devices manufacturers.

Certificate notifications

The HPRA was notified of 959 notified body certificate refusals, restrictions, suspensions and withdrawals in 2015. The number of notifications increased significantly over that for the previous year. The increased number of notifications received highlights the impact of the joint assessment process for notified bodies which may affect the scope of activities and, potentially, the ongoing validity of certificates previously issued by some notified bodies. Those with implications for the Irish market and those resulting from reduction of designation of notified bodies were investigated.

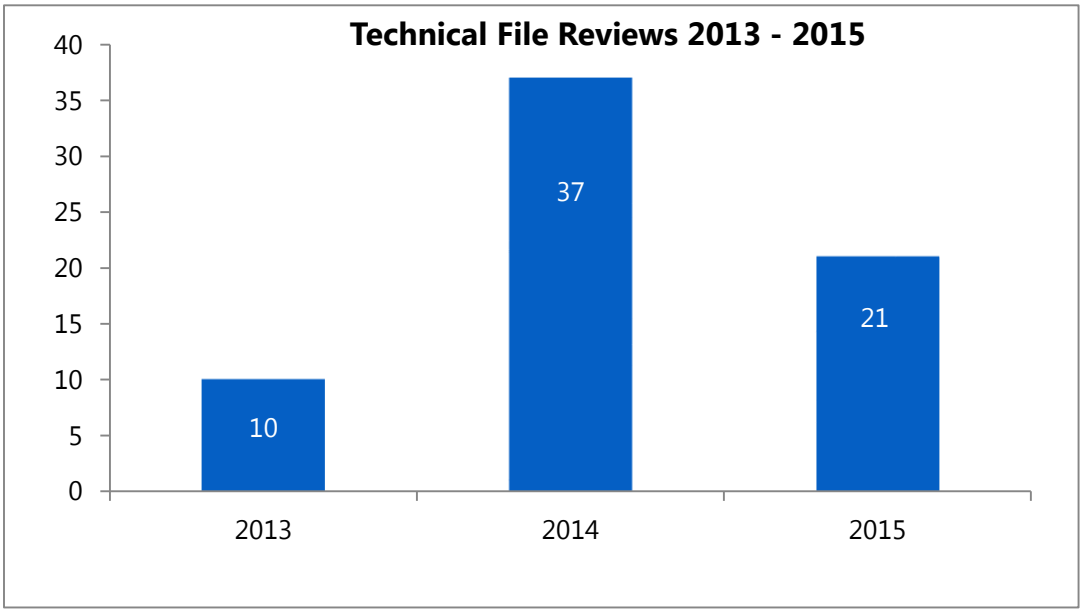
Technical file reviews

In 2015, the HPRA joined the first European Joint Action on Market Surveillance on instructions for use of re-sterilisable medical devices sponsored by CHAFEA.

A total of 21 technical file reviews were initiated in 2015. These related to proactive surveillance of manufacturers in the areas of IVDs, ophthalmic and software devices. 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. In the latter half of 2015 a number of reactive cases related to implanted devices, which required a significant level of resource and impacted significantly on some of the proactive activity scheduled for that time.

Clinical Evaluation Review

During 2015, the HPRA increased its activities further in the assessment of clinical data presented by manufacturers to support the safety and performance of their device. A total of 32 clinical evaluation reviews were conducted. This 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 3: Number of Technical File Review Cases created (2013 – 2015)

Product registrations

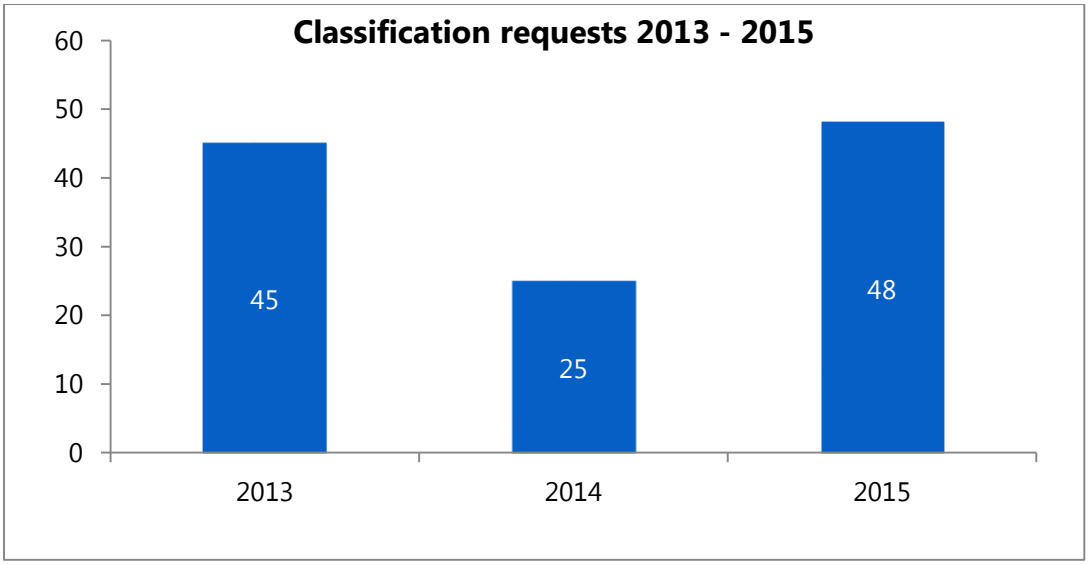
In 2015 the HPRA received 371 notifications of new medical devices to the medical device register. In addition, 43 new organisations as Irish-based manufacturers or authorised representatives for class I, custom-made, *in-vitro* diagnostic medical devices, as manufacturers of system or procedure packs, or as sterilisers of medical devices, have been notified. These relate to class I, *in-vitro* diagnostic, custom-made medical devices and to system and procedure packs. 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 48 applications for classification of medical devices or products queried as medical devices in 2015. 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 2013-2015

Clinical Investigation Applications

The HPRA received ten applications for clinical investigations of a medical device to be conducted in Ireland in 2015. The investigations involved areas such as closure devices, ophthalmology, general surgery, cardiac and software medical devices.

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

Queries

During 2015, the HPAR medical devices team received 459 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.

It is expected that, with the advent of the new Medical Device legislation, the numbers of queries relating to medical devices will increase further over the coming years.