HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Public Consultation on
Annual Review and Proposal for Fees – For Financial Year 2019

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

DATE <3rd October 2018>

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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.

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 2019.

2 THE OPERATING ENVIRONMENT

Following the economic crisis, there are clear signs of recovery and the Irish economy is one of the fastest growing in Europe. However, despite the projected growth in the economy, that growth is not translating into a better economic outlook for the HPRA. Regulatory activity has remained flat during the last number of years while wage inflation/wage pressure have increased. 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 have increased without a corresponding increase in income. Brexit has also had a considerable impact on the HPRA. Industry is uncertain of the future which appears to be reflected in a reduced number of new incoming regulatory submissions while the work related to Brexit has increased significantly without corresponding income.

Government policy in relation to pensions has changed and the HPRA are now being asked to make significant contributions to the pension scheme in 2019 and this has resulted in a disproportionate increase to payroll costs.

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

The impact of new legislation continues to be rolled out across the organisation. The Clinical Trials Regulation will be implemented in 2019/2020, the safety feature and the medicines repository under the Falsified Medicines Directive will commence in 2019 and the EU Medical Device Regulation will start its implementation in 2019. 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 2019. As noted in previous consultations the HPRA has absorbed the payroll cost resulting from greater regulatory complexity and additional requirements from the changing regulatory and legal environment without increasing its fees.

3 STRATEGIC DIRECTION OF THE HPRA

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).
- **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 2019 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, parts of the falsified medicines directive and changes to the supervision of ATMPs.

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

4 REVIEW OF THE 2010 TO 2018 FEES

The HPRA last increased fees significantly in 2010. In 2011 and 2012 the HPRA reduced fees and from 2013 to 2017 fees were not increased. In 2018 there was a minor cost of living increase of 2%. In the intervening period, the HPRA has increased payroll numbers from 283 to 360 without recourse to increased fees. Some of these increases relate to increased volumes but much of the staffing is to reflect the greater regulatory offerings, increased support for public health, the implementation of new Directives and Regulations (pharmacovigilance, falsified medicines and clinical trials), and the increasing complexity of the work and the development of the agency. The development of an innovation office and an international platform has brought greater oversight and global co-operation to the benefit of stakeholders and public health. The development of the agency has ensured the HPRA well placed to negotiate the impact of Brexit and the ever changing regulatory environment that we operate in but it comes at a cost. To date these staff increases have been primarily funded through supressed payroll and other costs arising out of the economic crash where all State sector salaries were significantly reduced. These reductions (Haddington Road) are being reversed and we have also seen the reintroduction of cost of living increases. HPRA and the pharmaceutical industry recruit from the same pool of candidates and it is becoming more challenging to retain staff in the light of significantly higher salaries in industry. As outlined below, HPRA will see a substantial increase in payroll costs next year and these increases are set to continue as upward pressure remains on payroll costs, particularly for technical staff.

5 PROPOSED CHANGES FOR 2019

The HPRA, as outlined above, is operating in a difficult economic environment particularly in the light of Brexit. We have committed proactively to supporting the industry and to manage its regulatory obligations in Europe following the outcome of their Brexit negotiations.

Overall income has remained flat or is decreasing for the first 8 months of 2018. Incoming new applications are down by 8% from the previous year, suggesting perhaps Brexit related caution. Product withdrawals are significantly higher compared to the same time last year which again may be a reflection of Brexit.

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 78% of total costs. Payroll costs

have increased over the last number of years but will increase particularly in 2019 for the following reasons:

- The impact of Haddington road is being reversed and as a result pay awards of nearly 3% are being awarded end 2018 and 2019.
- DPER has requested an employer contribution from fee funded agencies of up to 17% of the salary of those on the single service scheme (SSS). As HPRA have over 130 staff in that scheme, this is the single biggest increase to our payroll.
- HPRA received 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.
- Overall staff numbers and specialty resources have increased to reflect the increasingly complex regulatory environment and our role as Reference Member State and/or EU Rapporteurships and our increasing scope of responsibility.
- Brexit: the impact of Brexit is twofold, in 2018 and into 2019 we will have significant numbers of staff working on Brexit and its impact for the Irish market to process additional regulatory procedures mandated by changes in registered MAH's or supply chain elements due to Brexit. In addition we have committed to take on any of the work currently carried out by the UK. This will impact on the mix of work HPRA undertakes with a much greater emphasis on outgoing work. HPRA's fees for outgoing work are modest compared to other MSs in Europe as our numbers of outgoing work were traditionally low. But this model is not sustainable where outgoing work increases as is planned for 2019. The fees charged do not reflect the time or cost of providing this service.

For these reasons it is proposed that the fees will be increased as follows;

- General fee increase of 8%.
- Increases and alignment of new product application fees to match more closely the resource utilised in assessment.
- Increase in fees for clinical trial amendments.
- New fee for IMP fast track variation applications.

5.1 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 2018. 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.

The HPRA has been able to freeze fees in previous years with a small increase in 2018 due to the continued management of our cost base. 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 will also be required to pay significant pension contributions to DPER for the first time. 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 2019 and further amend the fees and fee structure, if required, for 2020.

6 FINANCIAL OUTURN 2018

The financial position in 2018 is as expected and HPRA expect income to cover costs for the year. However, as noted above our cost base and in particular salaries are increasing. As outlined in previous submissions we have increased headcount to reflect additional responsibilities and deliverables while absorbing these costs without additional fees. As noted above, 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 starting to lose key senior members of staff as salaries are falling below the market place.

As stated in every consultation for the last number of years, the HPRA has an unfunded pension liability which is a cost of the business, but to date has not been reflected in the fee model. 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. Although we hope to break even at year-end, we have substantial financial commitments. 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 increasingly more challenging to support. Given the importance of IT in our service delivery we started a four-year programme in 2016 to replace all the internal workflow and stakeholder facing systems to ensured continued provision of a 'best in class' service. The investment in IT and infrastructure has delivered and will continue to deliver long-term savings and efficiencies.

The HPRA will also be required to pay significant pension contributions to DPER for the first time in 2019.

7 PROPOSED FEES

As outlined above there will be a general increase of 8% in HPRA fees in 2019.

8 DETAILED CHANGES TO FEES

8.1 General change to fees

It is proposed that there will be an 8% increase applied to all fees.

8.2 Other proposed adjustments to fees - human medicines

8.2.1 New applications

It is proposed to increase the fees for applications to reflect the actual time involved in these applications. A review of the time input into new applications has shown that we cannot continue to provide a service in this area without aligning the fees with the costs of delivering the service. **Note: these increases are inclusive.**

Reduced Dossier Standard	Current Fee	Proposed Fee	Change
National Application	7,811	10,000	2,189
Mutual Recognition – CMS	5,457	7,000	1,543
Mutual Recognition Supplement - RMS	7,269	10,000	2,731
Decentralised – CMS	7,811	10,000	2,189
Decentralised – RMS	20,400	26,000	5,600

Reduced Dossier Complex	Current Fee	Proposed Fee	Change
National Application	11,556	15,000	3,444
Mutual Recognition – CMS	8,239	10,000	1,761
Mutual Recognition Supplement - RMS	11,181	15,000	3,819
Decentralised – CMS	11,556	15,000	3,444
Decentralised – RMS	30,600	40,000	9,400

Complex Dossier	Current Fee	Proposed Fee	Change
National Application	15,515	20,000	4,485
Mutual Recognition – CMS	10,860	14,000	3,140
Mutual Recognition Supplement - RMS	11,181	15,000	3,819
Decentralised – CMS	15,515	20,000	4,485
Decentralised – RMS	40,800	50,000	9,200

Related fees to each of these categories will increase proportionally as per Appendix III.

8.2.2 Clinical Trials Amendments

As noted in previous years, it was agreed to reconsider an increase in the existing fee for clinical trial amendments. It is proposed to increase the existing fee for clinical trial amendments from €100 to €400.

Amendments to clinical trials are becoming increasingly complex due to new clinical trial designs. This is particularly common in oncology where "basket" trials are used. In these trials a single treatment is trialled on different cohorts of patients; such cohorts are added after the initial trial is approved. The HPRA continues to charge no fees for academic trials, consistent with our desire to support clinical trials in Ireland.

8.2.3 Pre Submission applications

It is proposed that the existing fee of €1,000 for DCP slots will apply to pre submission Mutual Recognition Procedures. The fee is non-refundable and will be credited against the application fee when the new application is submitted.

8.2.4 Procure & Supply only" WDA holders Annual Maintenance Fee

It is proposed to re-categorise these wholesalers as general sale wholesalers (minor sites). The "procure & Supply only" category of wholesaler requires more oversight on a risk basis due to the complexity of the financial supply chains involved.

8.2.5 IMP Fast Track variation applications

It is proposed to introduce a new fee of €1,200 for expedited assessments of IMP MIA variations for Annex 3 & 4 (contract manufacturer's and contract laboratories). The scope of the expedited process is limited to the variation types described above.

8.2.6 Inspection fee

It is proposed to charge the normal HPRA inspection fees to the following:
(a) Irish Medicines Verification Organisation inspections.
(b) Desk-top assessments of 3rd Country sites.

9 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 31 October 2018. 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 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:

- 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 ensured a reduction in the number of human medicine applications overdue.

- 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.

- 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 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:
  - the new requirements of the Clinical Trials Regulation
  - the new requirements of the Medical Devices Regulations
  - the registration of traditional herbal medicinal products

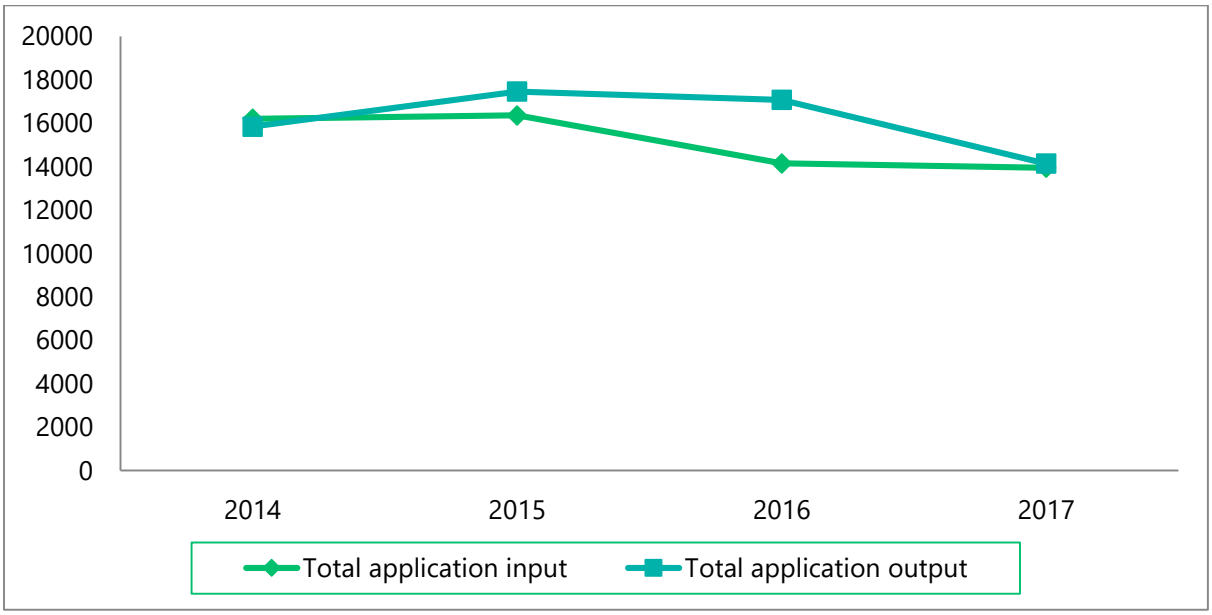
- Continued progression of a public health initiative focused on providing important online information about all medicines licensed by the HPRA. This includes maintaining publication of the summary of product characteristics document, patient information leaflets, ATC codes, interchangeable lists and 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.

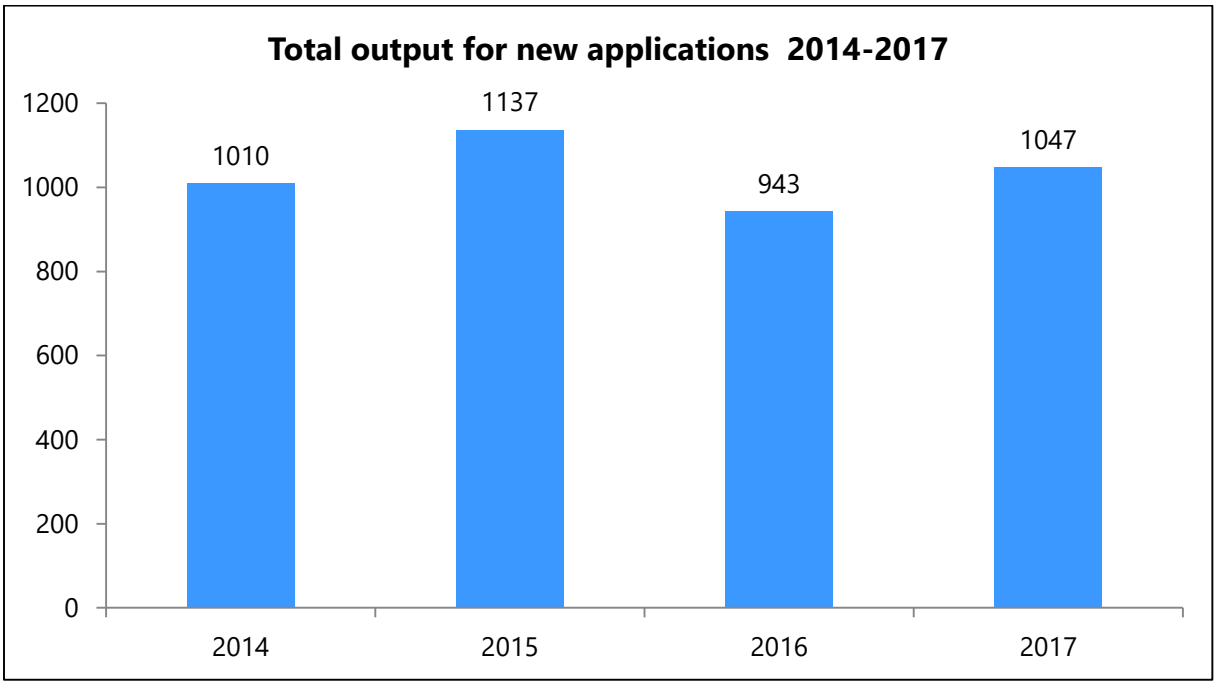
- A proactive approach to switching is ongoing. Following a review of policies in this area, and after liaison with the Department of Health, the HSE Health and Wellbeing Directorate and healthcare professionals, the HPRA has taken a proactive approach to the reclassification of medicines since 2014. 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 2017.




Total output for new applications 2014-2017
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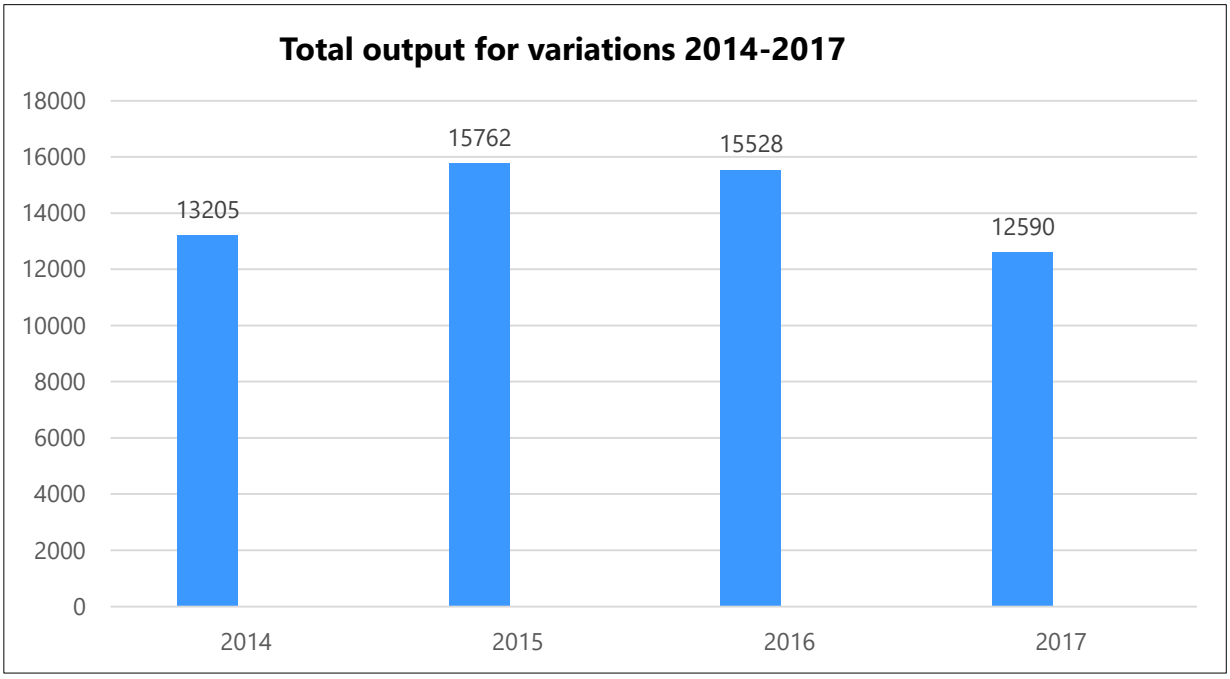
1000
800
600
400
200
0
1010
1137
943
1047
2014
2015
2016
2017


Total output for variations 2014-2017
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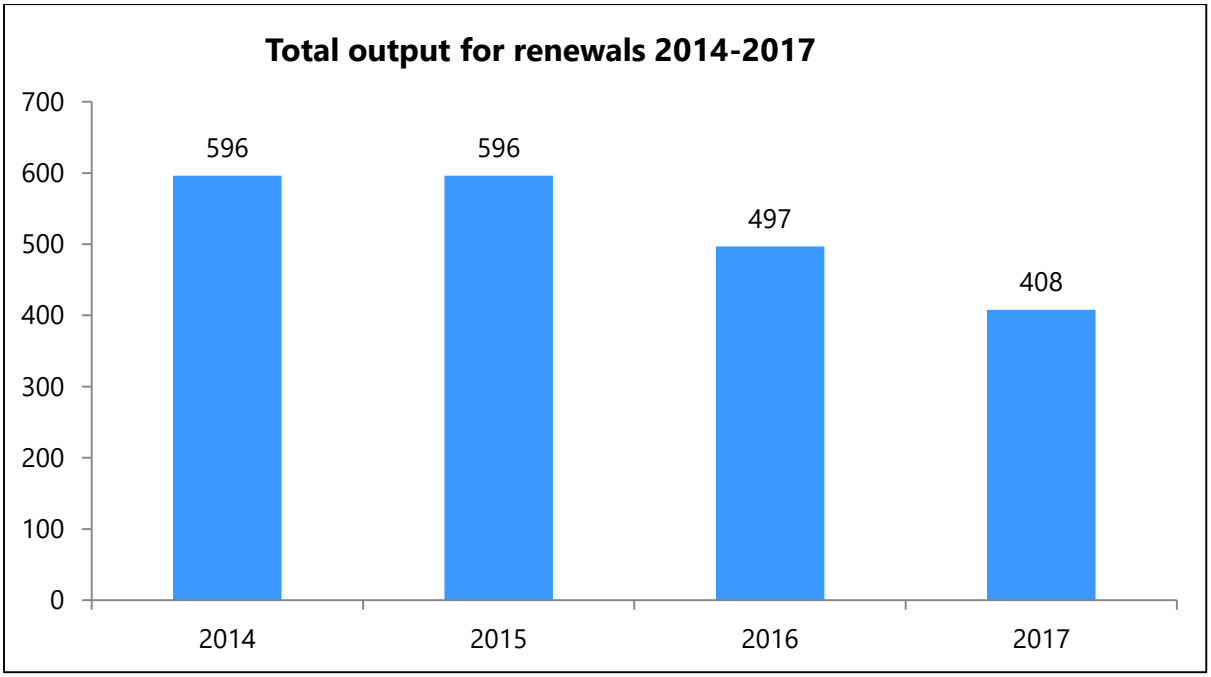
16000
14000
12000
10000
8000
6000
4000
2000
0
13205
15762
15528
12590
2014
2015
2016
2017


Total output for renewals 2014-2017
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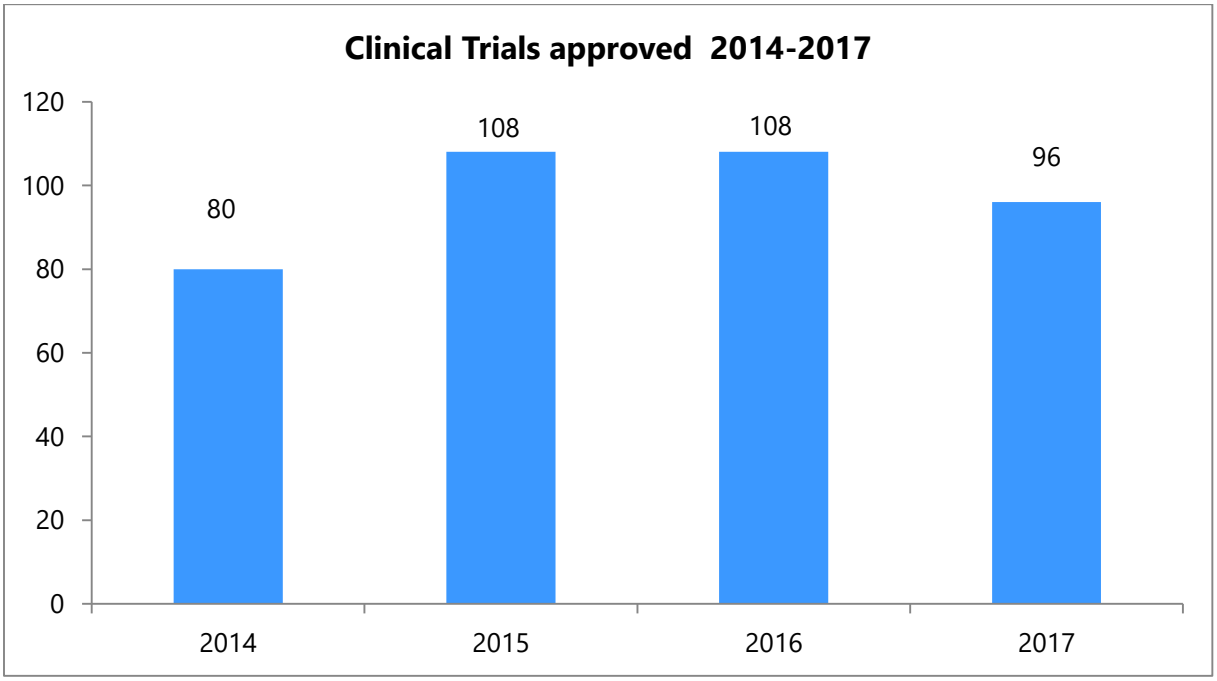
600
500
400
300
200
100
0
596
596
497
408
2014
2015
2016
2017


Clinical Trials approved 2014-2017
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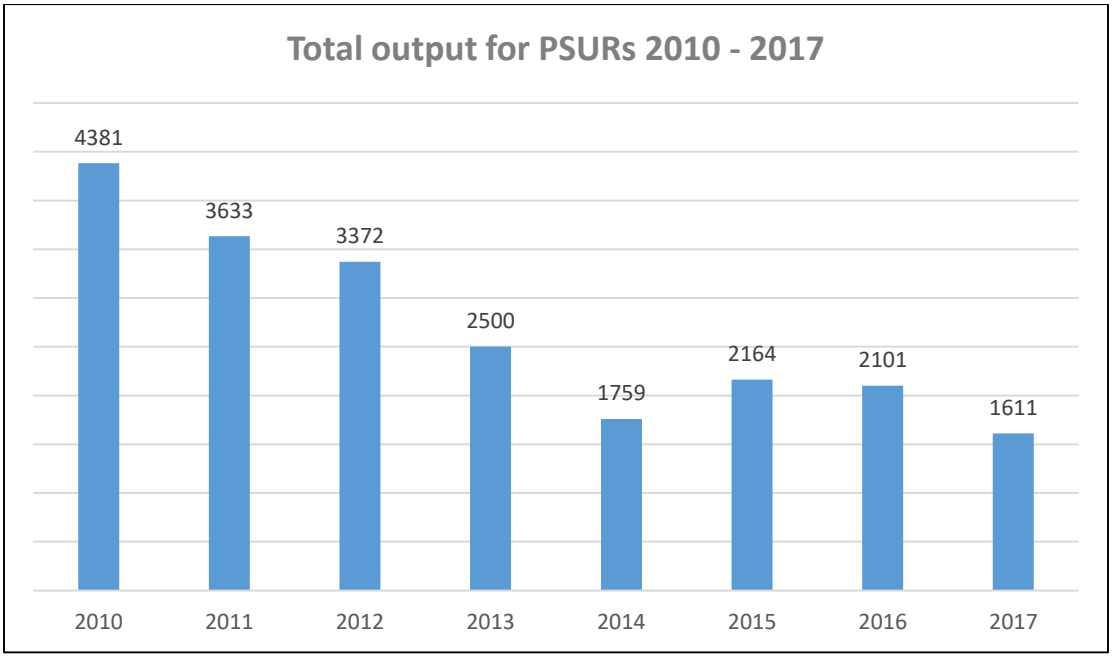
100
80
60
40
20
0
80
108
108
96
2014
2015
2016
2017


Total output for PSURs 2010 - 2017
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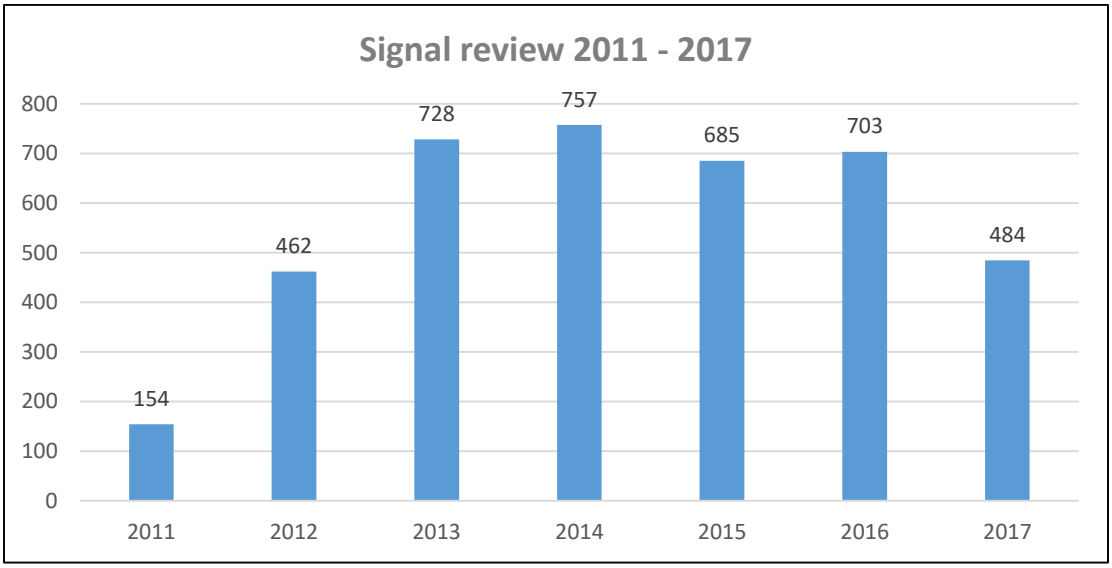
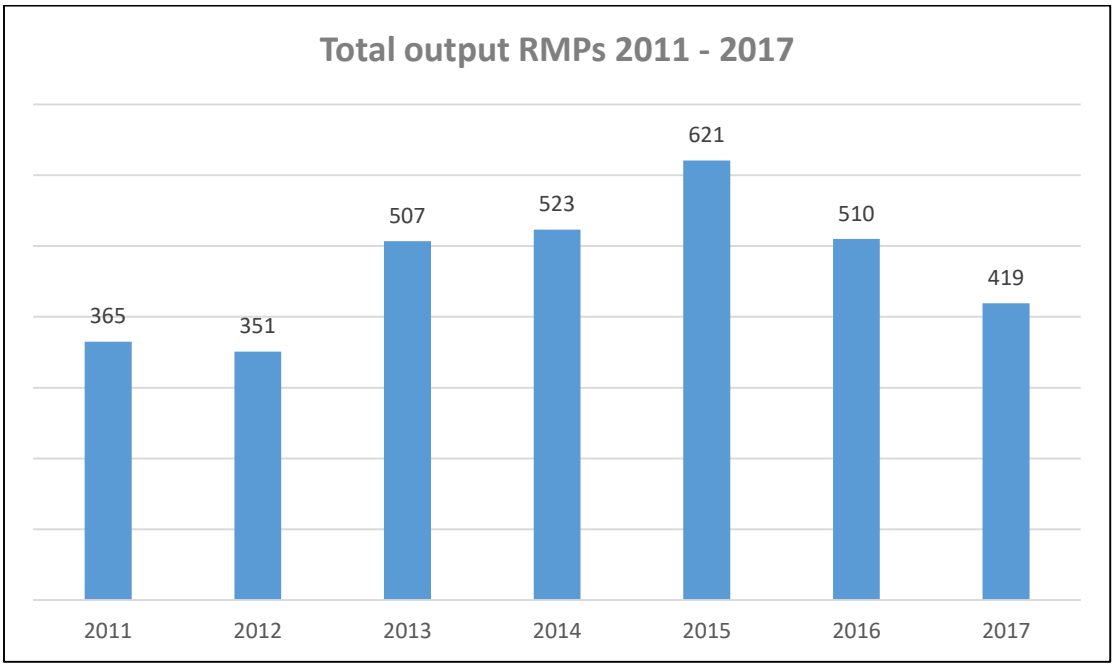
3633
3372
2500
1759
2164
2101
1611
2010
2011
2012
2013
2014
2015
2016
2017


Signal review 2011 - 2017
800
700
600
500
400
300
200
100
0
154
462
728
757
685
703
484
2011
2012
2013
2014
2015
2016
2017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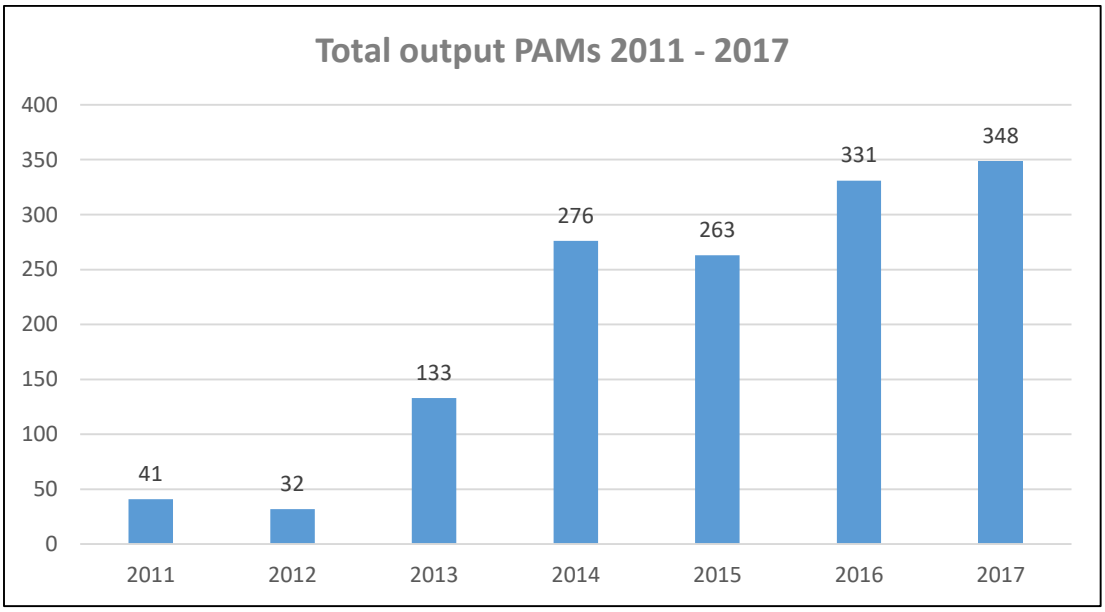
507
523
621
510
419
2011
2012
2013
2014
2015
2016
2017


Total output PAMs 2011 - 2017
400
350
300
250
200
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100
50
0
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133
276
263
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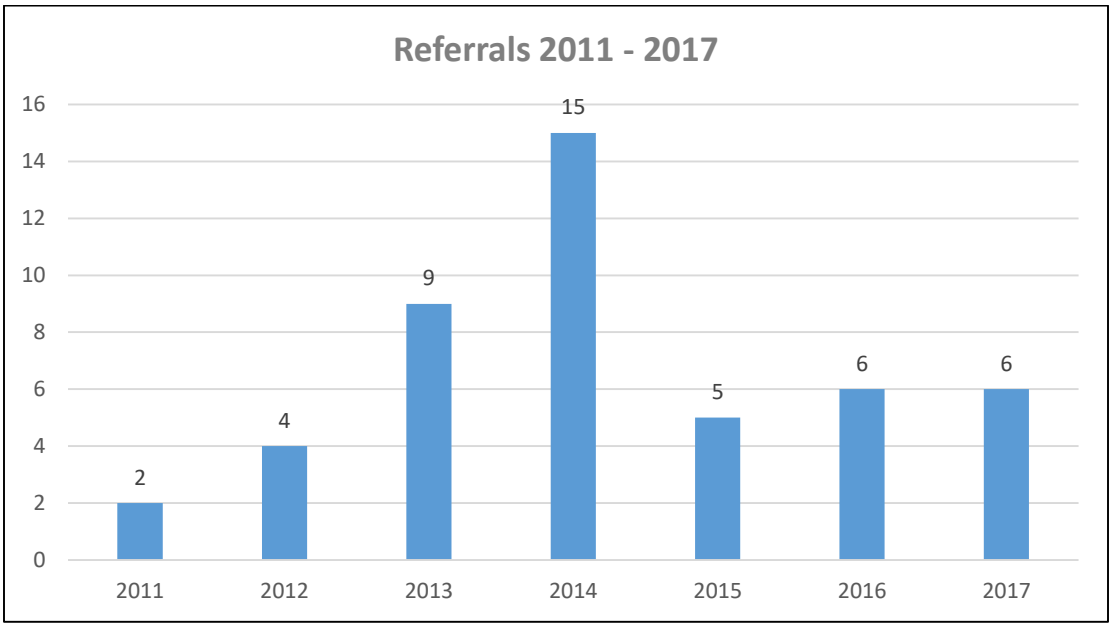
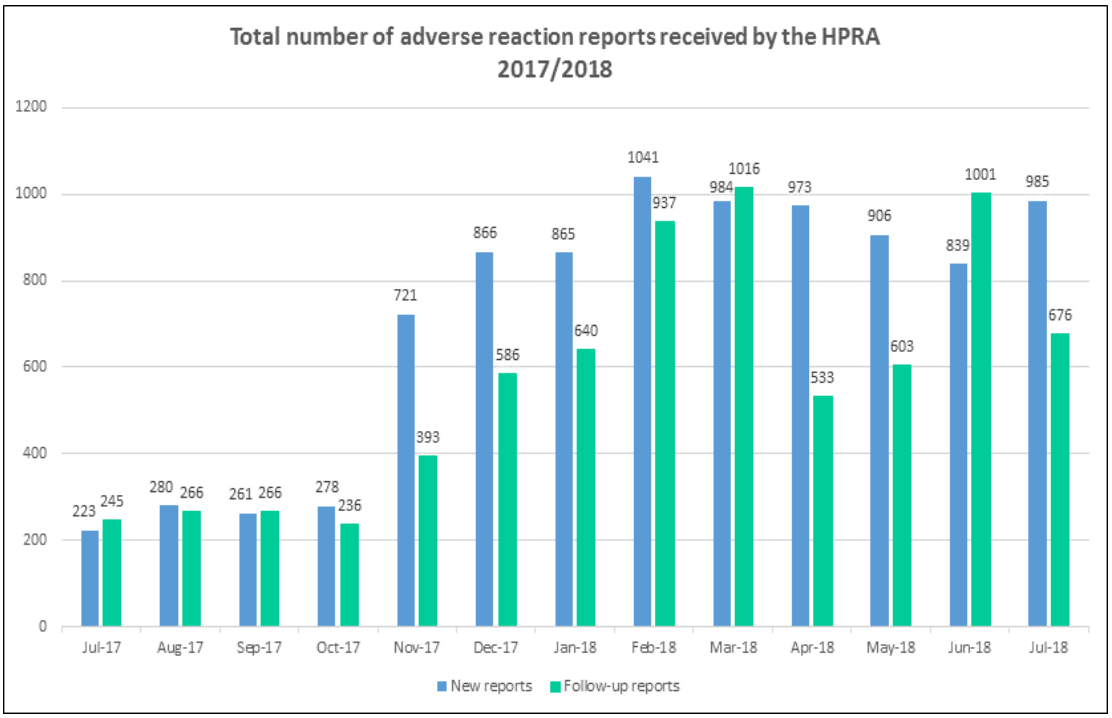
2011
2012
2013
2014
2015
2016
2017


Referrals 2011 - 2017
16
14
12
10
8
6
4
2
0
2
4
9
15
5
6
6
2011
2012
2013
2014
2015
2016
2017


Total number of adverse reaction reports received by the HPRA
2017/2018
1200
1000
800
600
400
200
0
223 245
280 266
261 266
278 236
721 393
866 586
865 640
1041 937
984 1016
973 533
906 603
839 1001
985 676
Jul-17
Aug-17
Sep-17
Oct-17
Nov-17
Dec-17
Jan-18
Feb-18
Mar-18
Apr-18
May-18
Jun-18
Jul-18
New reports
Follow-up reports

APPENDIX II SERVICE LEVELS – COMPLIANCE DEPARTMENT

Compliance Department General Activities

Initiatives undertaken / further developed in 2017/2018 included:

- Preparations for Brexit, in conjunction with other departments across the organisation, have included:
  - Participation in a stakeholder meeting in August 2017. Following on from that, guidance on Brexit was published on our website and has been updated since.
  - 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.
  - Meetings with industry bodies, and attendance at workshops organised by one of those bodies, in order to consider and clarify Brexit related questions.
  - Advising potential applicants for authorisations and licences of the requirements and processing of a number of new applications.
  - Provision of support to the Departments of Health and Agriculture, Food & the Marine.
  - Liaison with other agencies, including Revenue's Customs Service, on issues of mutual interest.
- On 1st 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. This means that, in the short to medium term, the number of FDA inspections of sites in Ireland manufacturing active substances and human medicines for supply to the US will reduce considerably.
- 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 2017 and 2018.
- 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 is due for implementation by relevant marketing authorisation holders and manufacturers by the 9th 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 includes 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 IMVO, we will continue to liaise closely with it.
We will 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.

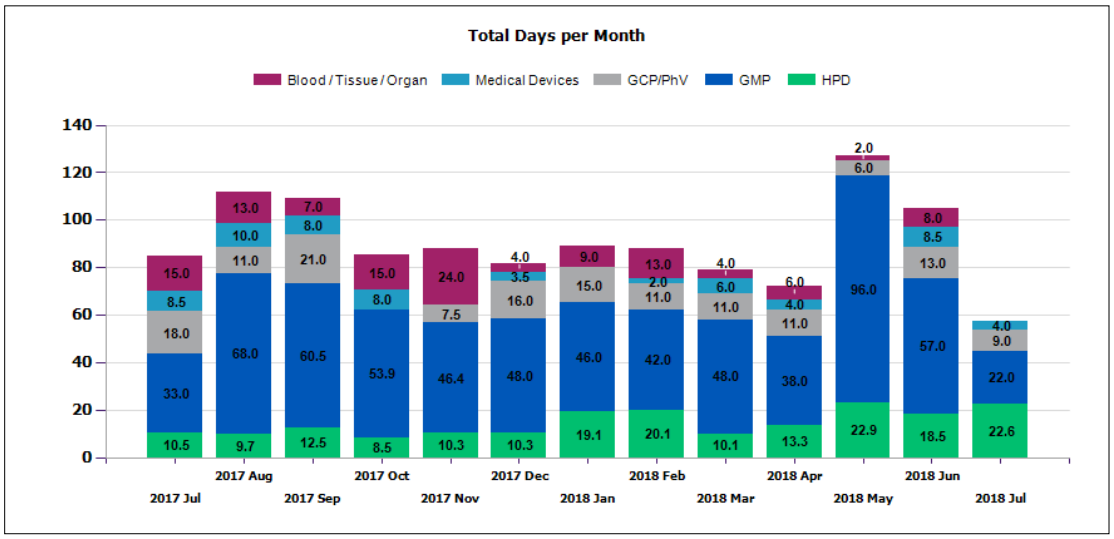
- Continued upload of post-inspection good distribution practice (GDP) certificates to the EudraGMDP database. All existing Wholesale Distribution Authorisations (WDAs) had already been uploaded to the database and upload of new or varied WDAs continued.
- Continued upload of Manufacturers' / Importers' 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, has commenced in 2018.
- 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 (Misuse of Drugs Regulations 2017).
- Provision of support to the Department of Health in the development of an access programme for cannabis for medical use.
- Continued liaison with wholesalers on the implementation of revised EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use.
- 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 which were published and made available to Competent Authorities in October 2017.
- 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.
- 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 developing a new risk-based approach to the sampling and analysis of mutual recognition, decentralised and centralised medicines which was finalised during 2018.
- The HPRA led on a complete modernisation of the processes used by EEA medicines Competent Authorities for the management of quality defects, recalls and rapid alerts. This work was completed and revised (more risk-based) versions of the relevant EEA procedures in these areas were agreed in mid-2018.
- 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.
- 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.

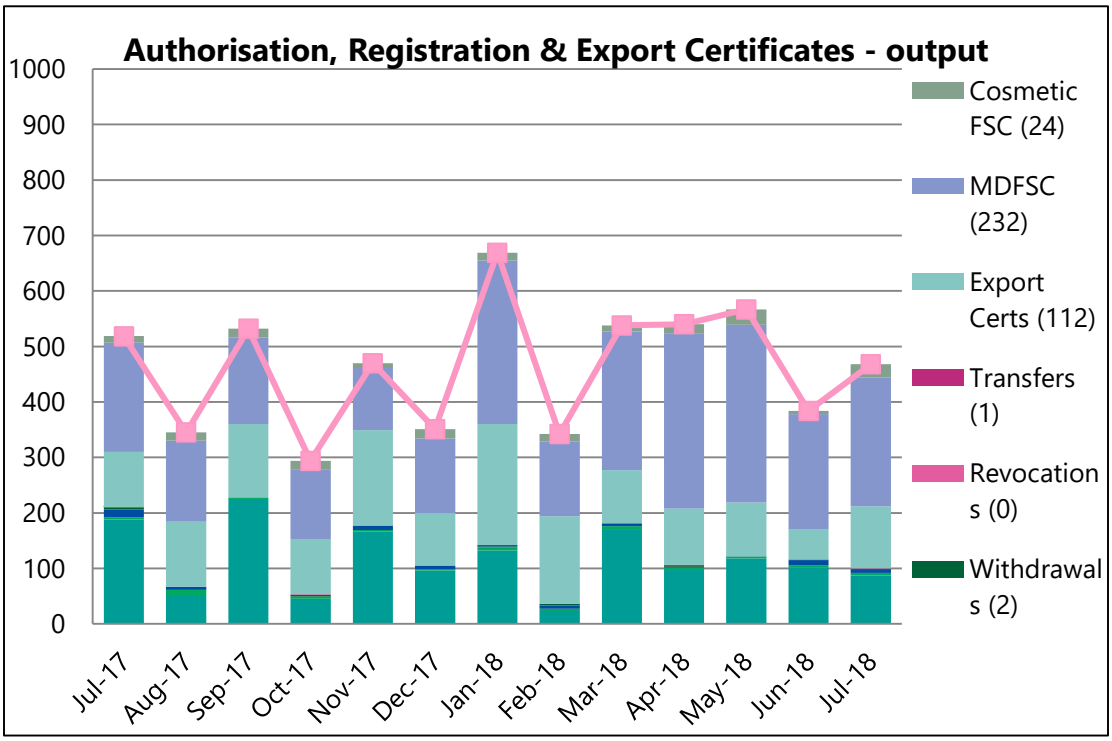
Other activities included:

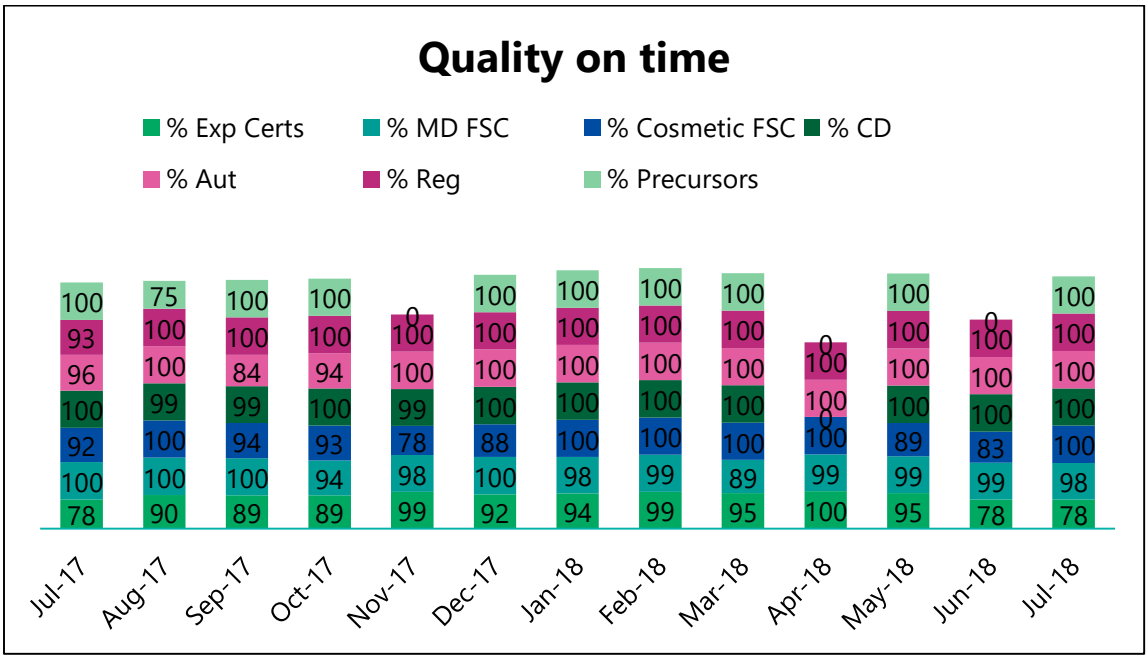
- Continued interaction and communication with stakeholders, including industry and other representative groups. These included meetings with industry representative bodies and individual companies.
- Continued management of the controlled drugs function on behalf of the Department of Health.
- Continued management and use of the Exempt Medicinal Products importation/supply data that are notified to the HPRA. These data 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 and controlled drugs licences.
- Introduction of a process that supports expedited assessment and approval of variations of certain annexes to investigational medicinal product manufacturer's authorisations.
- 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, 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 2017 to month-end July 2018.

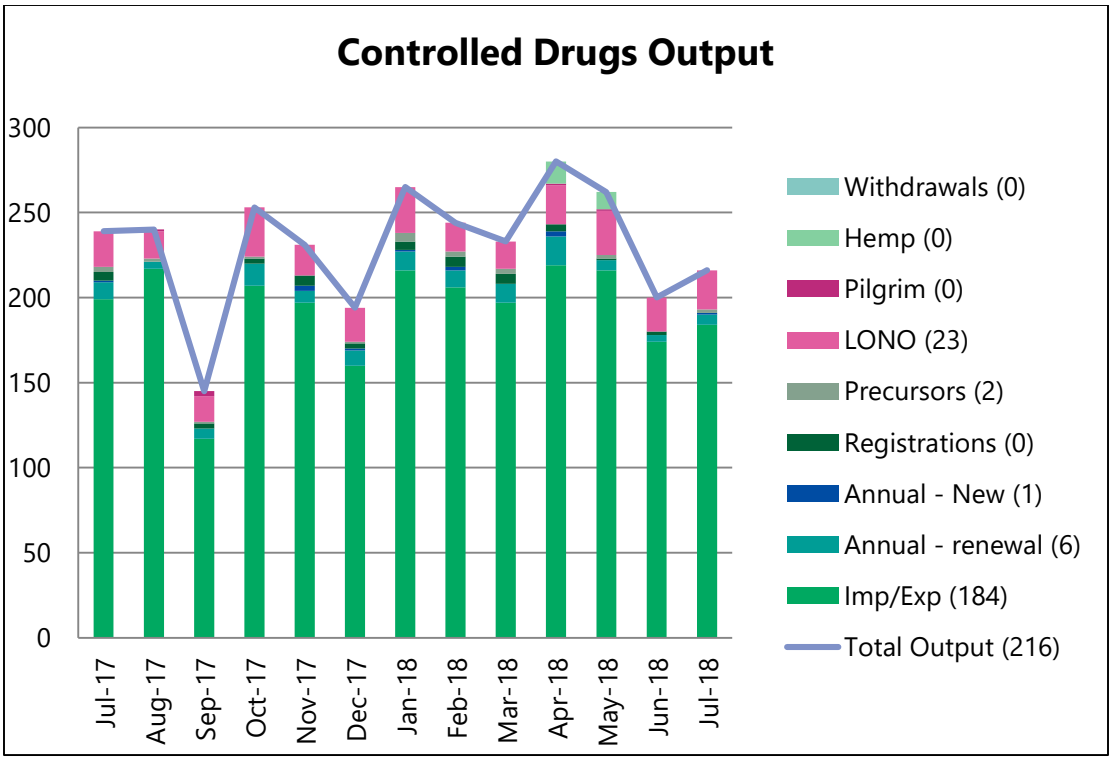


The following graphs show the numbers issued and the percentages issued on time, for export certificates, controlled drugs licences and GDP, GMP and IMP licences, over the period July 2017 to July 2018, inclusive.

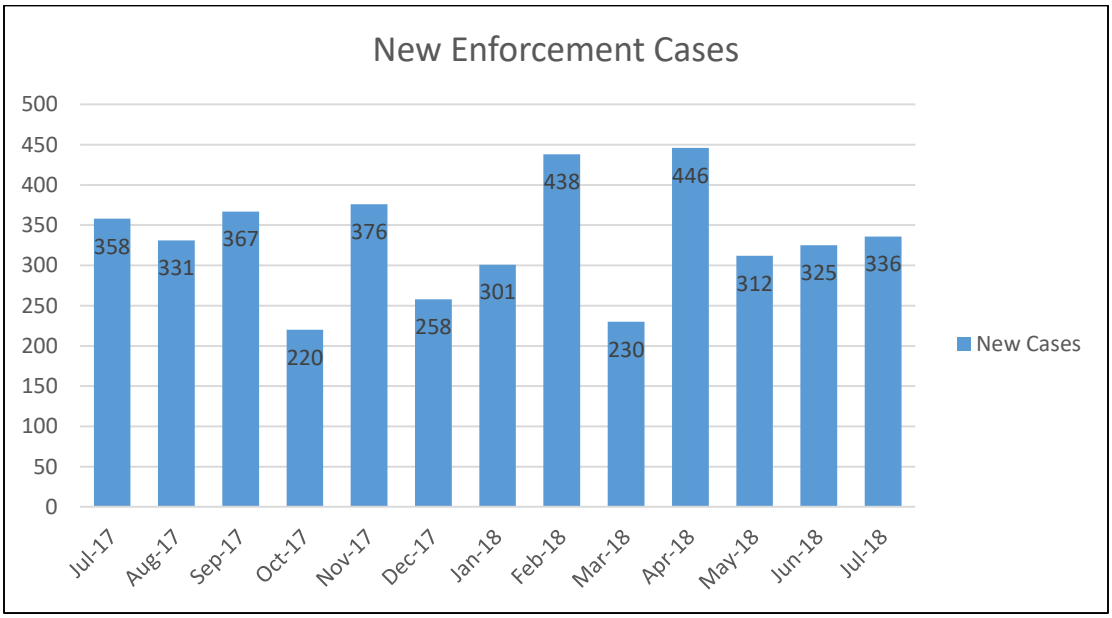




The graph below shows the output of licensing of controlled drugs, by category of licence.



The graph below shows the number of enforcement cases for the period July 2017 – July 2018 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 2017 to 2018 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 2017 and 2018, 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 tissue 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 Tissue & Cell 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. 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 2017 and 2018, 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.

APPENDIX III NEW APPLICATION FEES

Reduced Standard Dossier	Current Fee	Proposed Fee	Change
National Application – each additional form	5,192	7,000	1,808
National Application – each additional strength	669	1,000	331
Mutual Recognition CMS- each additional form	2,916	4,000	1,084
Mutual Recognition CMS- each additional strength	669	1,000	331
Decentralised – each additional form	5,192	7,000	1,808
Decentralised – each additional strength	669	1,000	331
Decentralised/MR – RMS supplement 15<CMS countries	1,020	1,500	480
Additional DMF submitted	3,316	4,000	684

Reduced Complex Dossier	Current Fee	Proposed Fee	Change
National Application – each additional form	5,192	7,000	1,808
National Application – each additional strength	669	1,000	331
Mutual Recognition CMS- each additional form	3,316	5,000	1,684
Mutual Recognition CMS- each additional strength	669	1,000	331
Decentralised – each additional form	5,192	7,000	1,808
Decentralised – each additional strength	669	1,000	331
Decentralised/MR – RMS supplement 15<CMS countries	1,020	1,500	480
Additional DMF submitted	3,316	4,000	684

Complex Dossier	Current Fee	Proposed Fee	Change
National Application – each additional form	5,192	7,000	1,808
National Application – each additional strength	669	1,000	331
Mutual Recognition CMS- each additional form	3,733	5,000	1,267
Mutual Recognition CMS- each additional strength	669	1,000	331

Decentralised – each additional form	5,192	7,000	1,808
Decentralised – each additional strength	669	1,000	331
Decentralised/MR – RMS supplement 15<CMS countries	1,020	1,500	480
Additional DMF submitted	3,316	4,000	684

Subsequent Extensions	**Current Fee**	**Proposed Fee**	**Change**
National Application – first additional form	7,811	10,000	2,189
National Application – each additional form	5,192	7,000	1,808
National Application – first additional strength	2,811	3,000	189
National Application – each additional strength	669	1,000	331
Mutual Recognition CMS- first additional form	5,457	7,000	1,543
Mutual Recognition CMS- first additional strength	1,968	2,000	32
Mutual Recognition CMS- each additional strength	669	1,000	331
Mutual Recognition RMS- each additional form	2,916	3,000	84
Mutual Recognition RMS- each additional strength	669	1,000	331
Decentralised CMS - first additional form	7,811	10,000	2,189
Decentralised RMS – first additional form	20,400	26,000	5,600
Decentralised – each additional form	5,192	7,000	1,808
Decentralised – first additional strength	2,811	3,000	189
Decentralised – each additional strength	669	1,000	331
Decentralised/MR – RMS supplement 15<CMS countries	1,020	1,500	480
Additional DMF submitted	3,316	4,000	684

Other	**Current Fee**	**Proposed Fee**	**Change**
Switching application	5,100	5,100	0