Annual Report 2018

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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18th

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100

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1,800

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4,009

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28

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10,398

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394

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2,358

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1,604

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202

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116

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379

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619,213

Dosage units of fake (falsified) and other illegal medicines detained

500,000+

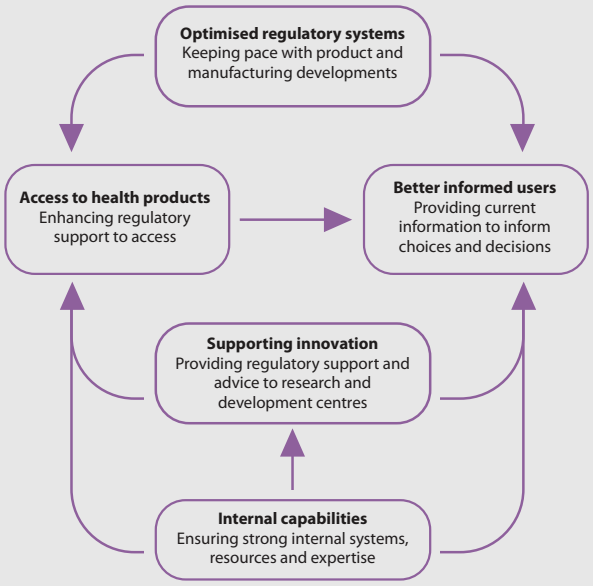
Unique visitors to our website – our highest ever annual figure

Chairperson's Statement

As I present the 2018 Annual Report, now in my fourth year as Chair, I continue to be incredibly proud of my association with the Health Products Regulatory Authority (HPRA).

The HPRA's five-year Strategic Plan (2016-2020), which sets the direction for the agency, reached its mid-way point in 2018. The Authority invested time in the midterm review of the plan and began discussions on proposals for the next iteration of the Strategic Plan, for which development will begin in 2019. As an Authority, we are very much looking forward to working with the management team and staff to set the future direction, with input from our stakeholders and key health sector representatives.

HPRA Strategic Goals 2016-2020



The primary focus and work of the HPRA in 2018, as in previous years, was the protection of public and animal health and Dr Lorraine Nolan, Chief Executive, elaborates on this in her report.

I would like to highlight and acknowledge the early action and cohesive, strategic approach taken by the agency in response to the UK's decision to leave the EU. The work at national and EU level has been stellar and relentless. I and my fellow Authority members are invested in the steps taken to develop the HPRA's strategic response to this issue to ensure the best possible outcome is achieved for the protection of public and animal health in Ireland.

The composition of the Authority changed in 2018, with the retirement of Professor Mary Horgan. Professor Horgan was also Chair of the Advisory Committee on Human Medicines and contributed greatly to the organisation since 2003. Her professional approach and technical acumen was valued by colleagues across the organisation. In 2018, in light of upcoming changes to the Authority, I progressed an initiative in respect of succession planning and am pleased to say we have developed a robust framework which will ensure the skills, competencies and technical requirements will be met by the Authority of the HPRA into the future.

2018 also brought some changes to the executive team at the HPRA, with the appointment of Dr Niall MacAleenan as Deputy Director and Head of the Medical Devices department and Grainne Power as Director of the Human Products Authorisation and Registration department. Both made immediate and important contributions in 2018. I acknowledge the excellence of all the HPRA staff, led by our Chief Executive and the members of the Management Committee. The year in review presented challenges but the significant progress and results achieved by the organisation in spite of those challenges are clearly reflected throughout this annual report.

On behalf of the Authority, I would like to thank the Minister for Health, the Minister for Agriculture, Food and the Marine, their advisors and the staff of their departments for their ongoing support of the HPRA and its activities.

On a personal note, as Chair, I would like to express my gratitude to the members of the Authority, the Chairs and the members of the HPRA advisory committees and sub-committees for their expert input and support throughout 2018. The contribution of the independent experts who share their valued opinions and time is of immense benefit to our organisation and our public health remit.

In conclusion, the HPRA continues to be highly effective in addressing the public and animal health challenges it faces while at the same time evolving and enhancing its regulatory approach. As national competent authority, it must remain flexible and adaptable to the constant changes in its operating environment to meet the needs of patients, the wider public, health professionals and all those who use health products.

Ms. Ann Horan
Chairperson

Authority Members

The Authority of the HPRA is appointed by the Minister for Health in accordance with the powers conferred by subsection 2 of section 7 of the Irish Medicines Board Act, 1995. The members of the Authority during 2018 were:

Ms. Ann Horan
(Chairperson)

Mr. Pat Brangan

Mr. Wilfred J. Higgins

Mr. David Holohan

Prof. Mary Horgan
Resigned July 2018

Mr. Brian Jones

Prof. Elizabeth Keane

Prof. Caitriona O'Driscoll

Dr. Diarmuid Quinlan

Management Committee

The members of the Management Committee during 2018 were:

Dr. Lorraine Nolan
Chief Executive

Ms. Rita Purcell
Deputy
Chief Executive

Dr. J.G. Beechinor
Director of
Veterinary Sciences

Dr. Caitríona Fisher
Director of Quality,
Scientific Affairs and
Communications

Dr. Joan Gilvarry
Director of Human
Products Monitoring

Mr. Kevin Horan
Director of ICT and
Business Services

Mr. John Lynch
Director of Compliance

Dr. Niall MacAleenan
Deputy Director of Medical
Devices
Appointed February 2018

Ms. Lynsey Perdisatt
Director of Human
Resources and Change

Ms. Grainne Power
Director of Human
Products Authorisation
and Registration
Appointed July 2018

Chief Executive's Report

This is my fourth foreword to our Annual Report, and I continue to be immensely proud of the HPRA, our people and all those who contribute to making it the effective, efficient engine that it is.

To enable our continued success in protecting and enhancing public and animal health, our organisation has to continuously develop and evolve to deliver on its public service role. The year under review, 2018, was an exciting period in terms of our ongoing development. A number of key projects and focus areas for the organisation have come to fruition or made critical progress. I have full confidence that the investment we have made in these over the past year and beyond will serve to strongly position the organisation and its staff for the future through enhanced capabilities, expertise and systems, and a more fulfilling workplace. All of these enhancements will enable the HPRA to continue to deliver in its role as a regulator of health products both used and manufactured in Ireland. I am confident that as an organisation consistently focused on change and enhancement, we are well positioned for the opportunities that 2019 and future years bring.

Health and Wellbeing

To be truly successful, an organisation must be healthy from the inside out. I am incredibly proud that 2018 saw the HPRA being awarded the IBEC KeepWell Mark health and wellbeing accreditation. The HPRA was the first public sector body to be awarded the national workplace wellbeing accreditation which demonstrates the HPRA's commitment to improving the health and wellbeing of employees in the organisation. I am very proud of the HR and Change team who initiated this programme and colleagues across the organisation who contributed to its success. We will continue to work on our development across all areas of the KeepWell Mark throughout 2019 and beyond.

Brexit

2018 was an incredibly busy year, a year which saw our planning and preparedness strategy continue for the UK's exit from Europe and the European regulatory network. Given the UK has been a major contributor to the network and of course as a close neighbour, this was difficult and complex on many levels. However, our core remit of protecting public and animal health remained the key driver to our approach. We engaged early with our stakeholders, with the national action plan and with the European system. Regardless of the UK's exit from Europe, we are confident that our focus on preparedness will help us to effectively manage the potential impact on health product supply and availability.

Change

Throughout the year we have said goodbye to staff and members of our Authority and advisory committees, as well as welcoming new colleagues. Of specific mention, we have had two new members join our executive Management Committee. Grainne Power was appointed Director of Human Products Authorisation and Registration with oversight of the pre-marketing management of human medicines. Strategically, within this department, our operational focus was on increasing our footprint in terms of human medicines assessment capacity. In 2018, we made great progress on that goal. Our contribution to European assessments grew steadily throughout the year and we look forward to further progress in this area.

The Medical Devices department underwent significant change in 2018, under the leadership of newly appointed Head of Medical Devices, Dr Niall MacAleenan. Through a change programme, we identified a new structure comprised of technical teams designed to deliver a more flexible and agile approach to regulation. This revised model will ultimately better serve the public and our health system in the area of medical devices. This includes strengthened skills and capabilities in terms of embracing the opportunities presented by the highly innovative medtech sector as well as implementing the new regulatory framework for medical devices and in-vitro diagnostics within Europe during the coming years. As a responsive and adaptive organisation, I believe we are well equipped to grow and respond to the innovation and emerging technologies in all the sectors that we regulate.

Contribution and Collaboration

The HPRA continues to be very busy internationally with a wide range of work, which includes the quarterly cycle of meetings at the European Heads of Medicines Agencies (HMA). We continue to work very closely with our regulatory counterparts through a wide range of committees and working groups at the European Medicines Agency (EMA) and within the HMA network, as well as at a bilateral level. As Chief Executive, I joined the HMA Management Group and also took on the position of Co-Chair of the HMA/CAMD joint task force in 2018, both of which will ensure the Irish perspective is presented and considered in these fora. The CAMD refers to the EU Competent Authorities for Medical Devices.

In the ever-changing regulatory landscape, the development of new products, technologies, and production models are constantly challenging existing regulatory frameworks. Collaboration with other regulators is essential to achieve harmonised approaches and the comprehensive regulatory oversight required to facilitate the timely approval of new medicines and technologies while at the same time protecting public health. As part of our work within the International Coalition of Medicines Regulatory Authorities (ICMRA), the HPRA joined with a number of global authorities both to review and enhance existing regulatory approaches and to identify new regulatory tools to ensure safe and timely access to innovative health products. The ICMRA innovation project saw the HPRA co-lead one of three work-streams with the EMA focused on leveraging the outcomes of horizon scanning. This seeks to identify products and technologies where new regulatory science tools and expertise are required and will be of benefit, and to make use of the findings in terms of the regulatory enhancement. The network will aim to explore further innovative challenges and harmonised solutions on a global level.

Towards the end of the year, we hosted the 18th International Conference of Drug Regulatory Authorities (ICDRA) on behalf of the World Health Organization (WHO). The conference brought together WHO Member States to strengthen collaboration and develop international consensus on regulatory priorities. The conference covered topics under the theme 'Smart Safety Surveillance: A life-cycle approach to promoting safety of medical products' and resulted in a number of key recommendations.

We are both proud of and energised by our significant involvement at European and international levels. This participation affords us the opportunity to observe and contribute to international best practice and bring this home for the benefit of Irish patients.

Inspection, Surveillance and Enforcement

Inspection, surveillance and enforcement activities are key components of our role as regulator. In June 2018, the US FDA concluded its assessment of the HPRA and confirmed that our agency has the capability, capacity and procedures to carry out GMP inspections at an equivalent level. Attaining a position on the EU / US Mutual Recognition Agreement list of recognised member states, reflects international recognition of the very high standards of our inspection expertise and processes.

The past year has seen the HPRA make a significant contribution to the fight against counterfeit and falsified medicines and medical devices. The outcome of the most recent Interpol co-ordinated Operation Pangea was announced in October. The HPRA, in partnership with Revenue's Customs Service and An Garda Síochána, confirmed the detention of almost 90,000 dosage units of illegal prescription medicines, valued at over €375,000. The international week of action targeting the online sale of falsified and illegal medicines saw Irish authorities join representatives from 61 other countries to target criminal networks behind the sale of falsified and illegal medicines via illicit online suppliers and online e-commerce platforms.

Zero Gains Information Campaign

The use of falsified / fake and illegal medicines is an area of concern and focus. We entered somewhat uncharted territory with the launch of our public information campaign to raise awareness of the potentially serious side effects and health risks of non-medical use of anabolic steroids. The campaign entitled 'Zero Gains' incorporated online search, social and digital media in addition to outdoor and in-gym adverts. It targeted young Irish men and was developed in light of growing evidence of an increased use of anabolic steroids for body enhancement as well as new research showing a significant lack of awareness of the serious health complications posed by these products.

Going Forward

Despite continued challenges and the ever changing and evolving environment in which we operate, there are many exciting opportunities ahead of us. We will continue to prioritise better regulation to best serve the Irish public, to be leaders in the regulatory space, to ensure appropriate access to medicines, medical devices and other healthcare products, and to deliver on our remit to protect and enhance public and animal health.

Acknowledgements

I wish to acknowledge and thank the Ministers and staff of the Department of Health and of the Department of Agriculture, Food and the Marine for their continued support.

On behalf of the Management Committee and all our colleagues, I wish also to acknowledge the significant contribution and commitment of the members of the HPRA Authority and advisory committees. Their knowledge and advice is of great value to our agency and is much appreciated.

My particular gratitude to the Authority Chairperson, Ann Horan, for her support and counsel throughout the year.

Finally, to all my colleagues in the HPRA, you deserve huge credit for all the progress and achievements outlined in this report. I look forward to working with you all in the coming years as we continue to focus our efforts on delivering on our critical public and animal health remit.

Dr. Lorraine Nolan

Chief Executive

Planning for Brexit – Annual Update on Progress

The UK is due to leave the European Union. While the how and when they leave is not yet certain, any kind of Brexit will result in changes to the European health products sector and regulatory network as a whole. The UK withdrawal from the EU has potentially significant implications for Ireland in particular given our shared marketplace and the fact that many health products are manufactured in or moved through the UK to get to Ireland. Consequently, the HPRA has been actively contributing to a whole-of-Government response to Brexit which includes a range of measures to ensure the continuity of supply of health products in the event of a no-deal Brexit.

HPRA Response to Brexit

Once Article 50 was invoked by the UK on 29 March 2017, the HPRA commenced our Brexit preparedness planning. The protection of public health by supporting the continued supply of health products after Brexit was identified as our key strategic objective while also optimising our role within the European regulatory network.

Adopting an organisation wide approach, an internal task force was established to inform internal and external planning as well as our communications and engagement activities. As part of this approach, we developed the five key pillars to support delivery of our strategic objective and high level outputs:

Stakeholder Engagement / Communications	Stakeholder meetings, Q&As published, website content, one-to-one meetings with impacted stakeholders, presentations to industry meetings, media engagement.
Existing work where the UK is lead Member State	Committed to taking on all work where UK is the RMS and Ireland a CMS. Seeking newly available work under centralised system. Encouraging UK notified bodies to relocate to Ireland. Purpose: To maintain product on the market.
Future work to be allocated	Developing our capacity to bid for centralised and decentralised work to increase our European footprint and enhance our position as a leading EU regulator.
Leadership / Public Health / Advocacy	Ensuring the views of the Irish regulator are represented and understood at a European level. Proactively contributing to all EU Brexit meetings and engaging F2F with the Commission and the ENVI committee.
Internal Capability	Reviewing HPRA capacity to deliver on Brexit commitments. Staffing plan submitted to the Department of Health.

Key Brexit Pillars – Activities carried out in 2018

Building on progress achieved during 2017, the following details the main activities and work streams delivered during 2018 in respect of our five Brexit pillars:

- **Stakeholder Engagement / Communications**
  - There was continued implementation of our programme of communications and outreach including regular and sustained contact with individual manufacturers, industry, wholesalers and distributors, in addition to their representative bodies. Specifically we (1) contacted all MAHs to ensure Brexit preparedness, supply chain and regulatory compliance, and (2) engaged with wholesalers to understand critical products, potential supply issues and capacity for "buffer" stocks.
  - Our detailed Brexit guidance document and website content were both updated to reflect queries received from stakeholders and emerging information from the European Commission, the EMA and the HMA. Updates were also made to the medical devices and cosmetic products section of the HPRA website to highlight potential impacts of Brexit.
  - We presented at a number of industry seminars on the impact of Brexit and commenced planning for a second HPRA stakeholder information day in February 2019.
  - There was regular staff communications in respect of Brexit planning.
- **Existing Work where the UK is Lead Member State**
  - We engaged with companies to encourage the transfer of the RMS to the HPRA.
  - We reviewed product exposure to the UK from a regulatory perspective and contacted companies to request that they transfer necessary regulatory functions to the EU.
  - We contacted companies who have a large portfolio of products on the Irish market to understand any future barriers to supply and we responded to any potential supply issue identified.
  - We provided updates in respect of joint labelling with the UK and met with other EU agencies to assess the possibility of multilingual labelling.
  - We concluded an agreement with the UK's Veterinary Medicines Directorate for a work-sharing arrangement post Brexit.
- **Future Work to be Allocated**
  - 502 RMS transfers to Ireland were accepted in 2018 (346 for human medicines and 156 for veterinary medicines).
  - As RMS, we progressed 25 new outgoing MRP/DCP applications for human medicines. We also progressed 25 new MRP/DCP veterinary product applications.
  - We were appointed rapporteur / co rapporteur for 12 centralised human medicines while also being appointed rapporteur for 6 centralised veterinary products.
  - We acted as co-ordinator for 78 EMA scientific advice procedures for human medicines and three for veterinary medicines.
  - Support was provided to UK based notified bodies assessing their regulatory requirements as a result of Brexit and we received an application from one notified body for designation in Ireland.

- **Leadership / Public Health / Advocacy**
  - We participated in all Commission seminars and other EU meetings to advocate and promote greater understanding of the potential impact of Brexit for Ireland.
  - We led discussions at an EU level for the acceptance of dual labelling and for a pragmatic approach to contingency planning.
  - There was regular engagement with officials at the Department of Health and the Department of Foreign Affairs and Trade.
  - We engaged at a national level with the Revenue Commissioners with a view to minimising potential customs impact.
  - We liaised with IDA Ireland, IBEC and industry representative bodies, and other stakeholders as appropriate.
- **Internal Capability**
  - Our Brexit planning includes due consideration of potential staffing requirements and we continued to work closely with the Department of Health on this matter.
  - We are committed to ensuring that we have sufficient staff levels to manage the implications of Brexit and throughout 2018 we devoted expert staff resources to this important area through a combination of allocating existing staff as well as some new staff.

Contingency Planning for No-Deal Brexit

During the course of 2018, our Brexit planning was based on a no-deal outcome as of 29 March 2019 without a transition period. Consequently, all our advice and direction to industry stakeholders was that they must carry out all their regulatory changes before that key date.

From late 2018, the HPRA moved from operational planning to Brexit contingency planning under the following headings:

- Regulatory compliance of medicines and clinical trials authorised on the Irish market;
- Supply chain management and stock levels;
- Exempt medicinal products;
- Shortages protocol;
- Development of a list of essential medicines;
- Communications with stakeholders;
- Medical devices with UK CE marks;
- Veterinary medicines and engagement with the Department of Agriculture, Food and the Marine;
- Engagement within the European network.

While the European Council subsequently agreed to an extension of the Article 50 process until 31 October 2019, with the possibility that the UK will exit prior to that date if its Parliament ratifies the "Withdrawal Agreement", the risk of no deal has not been eliminated. For that reason, our Brexit contingency planning will continue throughout 2019 for as long as it is deemed necessary. We will report fully on progress and achievements in our 2019 Annual Report.

Human Medicines

The HPRA grants licences for medicines subject to a review of their safety, quality and effectiveness and continuously monitors their use once they become available on the Irish market. We also approve and monitor clinical trials, inspect and license manufacturing sites and wholesalers, and investigate activities associated with the illegal supply, manufacture or advertising of medicines.

Authorisation and Registration

- Prior to a new medicine being placed on the Irish market, it must be assessed and authorised (licensed) by the HPRA or by the European Medicines Agency (EMA) in conjunction with the European Commission. The assessment involves establishing that a medicine's health benefits outweigh its known risks. Where this is the case, it may be granted a marketing authorisation.

  There are a number of routes through which a product can be authorised by the HPRA. These include the national procedure, the mutual recognition procedure (MRP) and the decentralised procedure (DCP). Both MRP and DCP involve the simultaneous submission of applications in a number of EU Member States.

  The centralised route is coordinated by the EMA and results in an authorisation which is granted by the European Commission and is valid across Europe. The assessment is carried out by Member States appointed as lead assessor (rapporteur), joint lead assessor (co-rapporteur) and peer reviewer, with input also from all other Member States.

  During the year in review, the total number of new medicines authorised in Ireland was 376. The 2018 figure incorporates:

  – 66 new national applications which includes 60 parallel import applications;

  – 35 applications made under the MRP and 168 applications made under DCP. The HPRA acted as reference (lead) Member State for the assessment of 18 of the DCPs;

  – 5 rapporteurships and 11 co-rapporteurships under the centralised route;

  – An additional 91 medicines authorised through the centralised route where the HPRA was neither rapporteur nor co-rapporteur.

- The EMA operates a scientific advice and protocol assistance procedure system to applicants on the appropriate tests and studies in the development of a medicine. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines for the benefit of patients. During 2018, the HPRA acted as co-ordinator for 78 EMA scientific advice requests across a broad range of conditions.

  Our national scientific and regulatory advice procedure functions in a similar way and assists commercial and non-commercial entities making applications for clinical trial authorisation or marketing authorisations. This service complements advice which we provide on earlier stage product development through the Innovation Office. During the year, we completed 10 requests under this procedure.

- Participation in clinical trials can enable patients to benefit from new and promising therapies. During 2018, we issued 100 new clinical trial applications. Of these, 22 applications were voluntary harmonisation procedures for clinical trials with the HPRA acting as lead Member State for one of these co-ordinated work-sharing assessments for multinational clinical trials.

- Reclassification of the legal status of medicines aims to increase the number of medicines available to patients without prescription where it is safe to do so. This year:
  - Medicines for the treatment of hay fever and fungal skin infections were authorised for non-prescription, pharmacy-only sale.
  - A medicine containing folic acid and seven medicines for the treatment of skin conditions were authorised for sale in pharmacies and non-pharmacy outlets (general sale).

- In 2013, the HPRA commenced publication of a list of interchangeable medicines to facilitate generic substitution by pharmacists and to allow for reference pricing by the Health Service Executive (HSE). By year end, the interchangeable medicines list included 63 active substances.

- Medicine shortages have been an ongoing concern globally and in Ireland for some years. In September, we launched a new national initiative to better manage medicines shortages and their impact on Irish patients. The Medicine Shortages Framework is a collaborative initiative that brings together key players in the health sector with the aim of developing strategies to mitigate the effect of shortages in Ireland so that patient health is protected. See page 42 for further information on how the introduction of the framework is helping to manage shortages.

  In addition to the framework, and in the context also of potential shortages arising from the response of companies to the exit of the UK from the EU, we are progressing the option for marketing authorisation holders (MAHs) to utilise multilingual labelling. During 2018, we published an updated version of our 'Guide to Labels and Leaflets' and developed a procedure (which will be introduced in early 2019) to assist MAHs develop multilingual labelling with other Member States and to maintain joint labelling with the UK.

  An additional mechanism used by the HPRA to aid continuity of supply to the market place in the event of a medicine shortage includes the granting of a temporary authorisation for a batch of a medicine known as a 'batch specific request'. In 2018, there were 100 requests received.

- We continued to monitor the numbers of unauthorised products notified to us through the exempt medicinal product scheme. One aspect of our approach to reducing the risks to patients is to actively seek new marketing authorisation applications for high-volume products currently being imported through this scheme. Two such authorisations were issued in 2018.

  While various factors can lead to changes in the volume of packs notified to the HPRA on an annual basis, it is likely that market shortages were a contributory factor in the annual increase recorded in 2018.

Authorisation and registration: Key figures

	2016	2017	2018
Classification queries / reviews	130	152	93
Scientific advice			
Lead in EMA scientific advice:	51	47	78
National scientific advice (commenced in 2016)	13	6	10
Clinical trial applications	108	96	100
Voluntary Harmonisation Procedures (multinational clinical trials)			
Lead	8	5	1
Participating member state	22	14	22
New medicines applications for marketing authorisations			
National (including new parallel imports)	71	104	66
Mutual recognition and decentralised RMS	12	10	25
Mutual recognition and decentralised CMS	365	370	178
Centralised Rapp/Co-Rapp/Peer reviewer	20	12	19
Traditional herbal medicinal products under the simplified registration scheme	9	4	4
Homeopathic medicines under the simplified rules scheme	1	2	3
Variations to marketing authorisations (Type IA, IB, II)	13,837	11,600	10,077
Articles 45 and 46 - Variations to Update Product Information	1	2	1
Renewals of marketing authorisations	351	248	597
Transfer of marketing authorisation holder	209	208	801
Manufacturers	103	111	127
Manufacturers of investigational medicinal products	55	52	63
Wholesalers	318	348	358
Registrations for active pharmaceuticals ingredients			
Manufacturers	21	28	29
Importers	41	59	67
Distributors	49	81	87
Brokers	3	9	8
Export certificates	1,274	1,375	1,319
Exempt medicines programme for notification of unauthorised medicine import	1,827,047 packs	1,961,541 packs	3,209,365 packs

Safety and Quality

- Under the SCOPE project (Strengthening Collaboration for Operating Pharmacovigilance in Europe) created to support pharmacovigilance in the EU following legislative requirements that came into effect in June 2012:
  - There was continued collaboration with stakeholders concerning the distribution of joint communications to healthcare professionals.
  - We engaged with IPPOSI, as part of its pilot Patient Education Programme specifically tailored for Irish patient communities, to provide medicines safety input for patient training materials. Colleagues also provided support for future planning for the next iteration of the IPPOSI programme.
  - The HPRA's online ADR reporting platform was utilised to facilitate practical student learning as part of EUPATI face to face training.

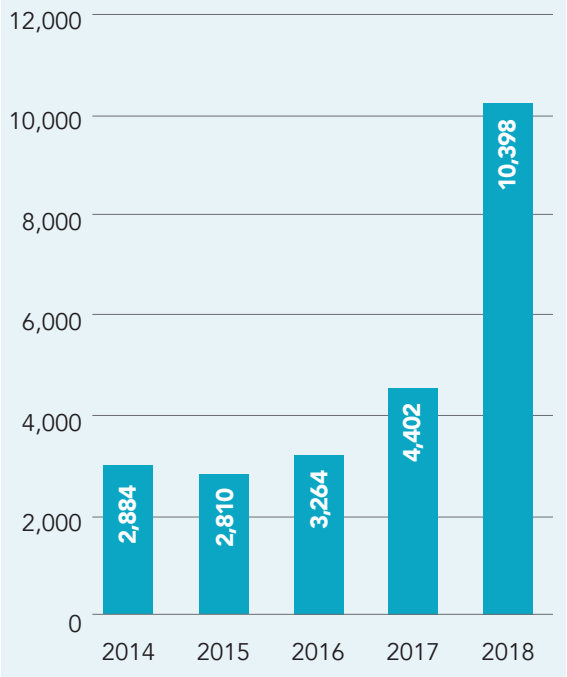
- Following the introduction of changed reporting rules for the EU's Eudravigilance database of adverse reactions in late 2017, and the simultaneous update of the HPRA's adverse reaction database, we continued to refine our processes to manage the increased volume of reports and report reconciliation activities.

- Adverse reactions reports assist the HPRA, in co-operation with pharmacovigilance professionals in Europe and further afield, to look for new types of reactions or changing trends in reporting. Reports submitted to the HPRA in many instances arise

from concerns occurring during observation of an unexpected and / or unwanted event, in the context of use of a medicine. They also include known adverse reactions, such as those described in the product information. This year:

– 10,398 adverse reactions reports were received associated with the use of human medicines. This represents a 138% increase in overall reporting rates compared with 2017. The legal obligation for MAHs to report all serious adverse reaction reports of which they become aware was extended in November 2017, to include non-serious reports. This change to reporting requirements largely accounts for the increase in the volume of reports received. However, additional complexities associated with reporting through the EudraVigilance system also impacted significantly on workload and interactions necessary to support case processing, management of duplicate reports and data quality.

Adverse Reaction Reports



– In the context of the changed reporting requirements, 92% of all adverse reaction reports received by the HPRA in 2018 were reported by MAHs, with a further 0.5% reported in the context of ongoing clinical trials. It is important to note that these reports will have initially been notified to companies by healthcare professionals, patients or consumers.

– Medicines subject to additional monitoring accounted for 24% of the reports submitted.

– The medicines most frequently included in reports to the HPRA accounted for 81% of the adverse reaction reports received in 2018 (see table). It is important to note that the place of a medicine on this list cannot be taken as an indicator of safety or risk. The number of reports received cannot be used as a basis for determining the incidence of a reaction as neither the total number of reactions occurring, nor the number of patients using a medicine, is known.

Suspect Medicine(s) / Class of Medicines	Number of Reports*
Antineoplastics, including immunomodulating medicines, monoclonal antibodies and endocrine medicines	5,302
Psycholeptic medicines	646
Anti-infective medicines, including antibacterials, antimycotics, antivirals and immunoglobulins	497
Medicines for the treatment of bone disease	355
Medicines for the treatment of Parkinson's disease	353
Cardiovascular medicines, including antihypertensives and lipid lowering agents	346
Vaccines	295
Medicines for the treatment of epilepsy and neuropathic pain	248
Antithrombotic medicines, including anticoagulant and anti-platelet medicines	248
Medicines regulating parathyroid hormone levels	227

– Of the new adverse reaction reports received by the HPRA in 2018, 252 patients were reported to have died while on treatment. The table below outlines the medicines or class of medicines associated with the highest number of reports. In many of these cases, the patients had significant underlying illness and were treated with multiple medicines and/or surgery which may also have contributed to the outcome. In addition, many of these cases were influenced by disease progression or other complications unrelated to the medicine. The majority were associated with medicines subject to close monitoring, those used in the management of severe underlying medical conditions, in patient support programmes and special patient monitoring programmes.

Suspect Medicine(s) / Class of Medicines	Number of Reports*
Antineoplastics, including immunomodulating medicines, monoclonal antibodies and endocrine medicines	109
Psycholeptic medicines	44
Anti-infective medicines, including antibacterials, antimycotics, antivirals and immunoglobulins	24
Antithrombotic medicines, including anti-coagulant and anti-platelet medicines	22
Medicines for the treatment of epilepsy and neuropathic pain	12
Medicines for the treatment of depression	10
Cardiovascular medicines, including antihypertensives, anti-arrhythmic and lipid lowering agents	9
Anaesthetic, opioid and anti-migraine medicines	8
Medicines for the treatment of gastrointestinal conditions	6
Systemic corticosteroid medicines	5

* Please note that in some cases treatment may have involved more than one medicine from the groups listed.

- The HPRA also plays a key role in monitoring the safety of medicines on the Irish market via our vigilance assessment and risk management activities. This incorporates our contribution to the work of the Pharmacovigilance Risk Assessment Committee (PRAC) at the EMA. During 2018, the HPRA:
  - Continued our involvement in the work-sharing initiative for signal detection within the EU acting as lead Member State for the monitoring of 53 nationally-authorised active substances. Serving as PRAC rapporteur, we were also responsible for the further management of any signals detected in relation to 46 centrally authorised medicines (containing 32 active substances / combination of active substances).
  - Participated in the EU periodic safety update report (PSUR) single assessment procedure, contributing to the evaluation of 900 PSURs and leading the single EU assessment for 28 of these procedures.
  - Participated as a concerned Member State in nine ongoing safety referrals, eight of which reached a conclusion during the year.
  - Contributed to the review of 253 risk management plans (newly approved or updated) submitted via national, mutual recognition, decentralised and centralised procedures. We also provided assessment input to 518 post authorisation safety procedures (safety study protocols, reports and other post authorisation safety-related measures).

- The HPRA continues to engage with multi-stakeholder groups, including patient and clinical practice representatives, to facilitate clinical readiness at national level for new recommendations on the safe and rational use of medicines following major EU benefit-risk reviews. During 2018, this included both (1) the ongoing implementation of valproate key risk minimisation recommendations and (2) the introduction of fluoroquinolone key risk minimisation recommendations into clinical practice.

- Also during 2018, the HPRA, in collaboration with researchers from the RCSI, successfully secured a HRB Applied Partnership Award, bringing together the HPRA as knowledge user and RCSI as academic researcher, to fund research into optimising effectiveness of risk minimisation measures to prevent harms from teratogenic medicines.

- The inspections and audits programme focuses on ensuring industry compliance with relevant standards and legislation. This year, there were:
  - 104 good manufacturing practice (GMP) inspections were conducted at sites that produce human medicines or active substances.
  - 183 good distribution practice (GDP) inspections at wholesalers and distributors;
  - 10 good clinical practice inspections at investigator or sponsor sites;
  - 7 pharmacovigilance inspections;
  - 4 bioanalytical inspections;
  - 3 regulatory compliance inspections were conducted at the premises of marketing authorisation holders to determine the level of compliance with the legal requirements for the marketing and advertising of medicines.

- The risk based sampling and analysis programme is part of our monitoring of the quality and safety of medicines on the Irish market or which are manufactured in Ireland for export. It involves the analytical testing of products and / or examination of their packaging and labelling. 358 samples were taken under the programme in 2018. This included:
  - Examination of the packaging and labelling of 126 medicines and other products available on the Irish market. 15 non-compliances were identified including Braille-related issues, non-compliant packaging and labelling, and the absence of updated safety information. Appropriate follow-up actions were taken in each case.
  - Additionally, 205 medicines and other product samples for human use were sent for analytical testing during the past year. Although the majority were found to be compliant with their specifications, a number of out of specification results were also obtained. The most frequent of these related to product appearance not being in accordance with the registered specification, and nitrosamine impurity levels in sartan-containing medicines being above the required limits. Again, appropriate follow-up actions were taken in each case.
  - Testing of a small number of investigational medicinal products was carried out and, where required, related follow up was initiated.

- The quality defect and recall programme investigates, on a risk basis, reports of suspected quality defects in medicines and in their related active substances. It also co-ordinates recalls from the Irish market. Quality defects pertaining to 925 medicines for human use were reported or identified in 2018. The risk classifications that were assigned, along with the corresponding figures for the previous two years, are outlined in the accompanying table.

Year	2016	2017	2018
Critical quality defects	119	124	325
Major quality defects	331	196	280
Minor quality defects	382	327	308
Number of reports not justified	3	3	12
Total Number Quality Defects	**835**	**650**	**925**

As in previous years, companies (52%), including manufacturers, distributors and/or authorisation holders, and other competent authorities (41%) were the primary sources of reports received.

- In certain cases, it may be deemed necessary to withdraw, or recall, medicines from the Irish market in order to protect public health. During the year, 196 medicine recalls occurred representing a 73% increase when compared to 2017. Overall, the most common causes of recalls were:

Cause of Recall	Number of Recalls
Lack of sterility assurance	80
Contamination issues	55
Erroneous distribution activities	22
Stability issues	11
Adverse reactions or changes in benefit/ risk ratio	6
Primary/secondary packaging component issues	6

- The HPRA monitors the sale of certain consumer health products in outlets such as grocery shops, health food shops and, where necessary, pharmacies. There were 11 cases investigated, some of which involved multiple products. Of these,
  - nine cases related to the sale of medicines that did not carry a valid registration number or authorisation number for the Irish market resulting in 18 medicines being removed from sale and necessary follow-up actions being taken;
  - two cases related to the classification status of the products.

  In addition, 80 queries linked to the sale of health products in Ireland were addressed.

- The advertising compliance programme monitors and reviews advertising and promotion activities carried out by the industry in relation to human medicines for compliance with the legislation. In total, 310 advertisements were reviewed, and non-compliances, including both major and minor issues, were identified in 37 of these. In addition, four other minor deficiencies related to advertising activities were identified during inspections of marketing authorisation holders. In all cases, we oversaw the necessary corrective and/or preventative

actions, where relevant. (The HPRA has published a standalone report available from our website that provides an overview of the main elements of the advertising compliance programme for 2018).

- Under our enforcement programme:
  - The HPRA detained 619,213 dosage units (including tablets, capsules and vials) of falsified and other illegal medicines in 2018, compared to 948,915 units in 2017. The products detained included sedatives (36%), erectile dysfunction medicines (18%) and anabolic steroids (16%). There were 4,532 enforcement cases initiated, compared to 3,866 in the previous year.
  - Several HPRA operations took place in conjunction with An Garda Síochána, Revenue Customs Service and the Food Safety Authority of Ireland. These operations resulted in the detention of over 40,000 capsules, tablets and vials containing anabolic steroids in the Dublin area.
  - We initiated 10 prosecution cases and issued 14 voluntary formal cautions. Prosecutions are taken where the HPRA considers that there is a significant risk to public health or where there are persistent non compliances. The prosecutions related to the unauthorised supply of prescription medicines, including falsified anabolic steroids, erectile dysfunction products and sibutramine containing medicines. We also support prosecutions brought by the Director of Public Prosecutions in relation to the illegal supply of medicines.
  - The HPRA, in conjunction with Revenue's Customs Service and An Garda Síochána, detained over 90,000 units of unauthorised and falsified medicines in Ireland, valued at over €375,000, as part of the Interpol-coordinated Operation Pangea XI. The products detained included significant volumes of anabolic steroids, sedatives, analgesics and erectile dysfunction medicines. Nationally, the operation also resulted in the investigation of 56 websites, with 10 e-commerce advertisements and 14 social media pages being taken offline. Operation Pangea XI was an international week of action across 61 countries to tackle the online sale of counterfeit and illicit medicines and to highlight the dangers of buying medicines online.

Legislation and Regulation

- The new Clinical Trial Legislation, Regulation EU No 536/2014, is planned to be implemented during 2020, when the development of the Clinical Trial Information System (CTIS) has been completed by the EMA.

  The following national activities were progressed during 2018:
  - We engaged with the Department of Health regarding the implementation of the Regulation and the development of national legislation;
  - We commenced a pilot project for simultaneous submission of applications to both the HPRA and ethics committee which enables preparation for implementation of the Regulation. Guidance and templates for sponsors are available on the website;
  - We actively participated in the European voluntary harmonisation project which is similar to the approval process for clinical trials under the planned new legislation (see page 15).

- As of 9 February 2019, under the Falsified Medicines Directive, the majority of prescription medicines must carry special safety features in the form of an anti-tamper device and a barcode containing 'unique identifiers' (including a serial number) to enable the authenticity of the pack to be checked prior to dispensing. In 2018:
  - Work towards national implementation and introduction of these measures continued. This was led on behalf of the industry and pharmacy sector by the Irish Medicines Verification Organisation (IMVO). We met regularly with the IMVO for updates on implementation of the necessary repository and software systems;
  - We contributed to a Department of Health led group of stakeholders which met regularly to monitor progress on implementation both nationally and across the EU;
  - The EU working group on supervision of the national repositories of unique identifiers, led by the HPRA, continued to work through its plan for the project.

Stakeholders and Partners

- In April, the HPRA appeared before the Joint Committee on Health which was discussing foetal anti-convulsant syndrome. The HPRA's Director of Human Products Monitoring and our Pharmacovigilance and Risk Management Lead were in attendance along with representatives from the Foetal Anti-Convulsant Syndrome (FACS) Forum and the HSE. The HPRA provided an update on the regulatory aspects of the medicine valproate (Epilim). This included details of the most recent European safety review and our collaboration at a national level with representatives from the FACS Forum, the Department of Health, the HSE and the Pharmaceutical Society of Ireland to facilitate timely and effective implementation of the new recommendations arising from the review. The HPRA also provided responses to a number of queries from the Committee members.

  In September, the HPRA's Clinical Assessment Manager, accompanied by our Director of Compliance, appeared before the Committee to address the matter of the authorisation of medicines in the context of the planned introduction of the termination of pregnancy legislation in late 2018. The HPRA representatives provided an update to the members and responded to a number of queries linked to this matter.

- As in recent years, the HPRA delivered a programme of presentations and talks at external stakeholder events such as meetings, seminars, conferences and training courses. Such presentations provide stakeholders such as healthcare professionals and regulatory professionals with access to relevant, up-to-date information. In addition, a programme of presentations was delivered to undergraduate and postgraduate students studying courses related to the role of the HPRA. A full list of all presentations delivered during 2018 relevant to human medicines is provided in Appendix 2.

- Publications and Information
  - The Drug Safety Newsletter provides important safety information to healthcare professionals with hyperlinks to product information and other relevant documents on the HPRA and EMA websites. Six issues of the newsletter were published and distributed to registered healthcare professionals, all of which are accessible from the HPRA website. A full index of topics covered during the past year is included in Appendix 3.
  - Risk communications:
    - During 2018, 90 new or updated educational materials were approved by the HPRA in addition to 28 direct healthcare professional communications.
    - The PRAC monthly agendas, minutes, meeting highlights, notifications of safety reviews and signals were also made available via our website.
  - There were a number of articles provided for inclusion in the monthly MIMS (Ireland) publication in addition to articles for the Irish Medicines Formulary. The full list of topics covered in these articles is included in Appendix 3.
  - The Medicinal Products Newsletter provides regulatory news and updates for those working in the pharmaceutical industry. Three editions were published on our website in 2018 and are available to download from the 'Publications' section.
  - Two new guidance documents relevant to human medicines were published in 2018 and are available to download from our website:
    - Guide to the sale of paracetamol-containing medicines by non-pharmacy retailers;
    - Guide to new applications and variations to wholesale distribution authorisations.
  - The Medicines Shortages Framework document was published online in September (see page 42).

- HPRA information seminars and training events provide regulatory guidance and updates to a range of stakeholders. Our programme of events in 2018 included an information day on good clinical practice (GCP) for investigational medicinal product trials. This event, which was attended by over 130 delegates, was held in Dublin in October.

- Following on from related activities in 2017, we published a research paper entitled 'Knowledge of adverse drug reaction reporting and the pharmacovigilance of biological medicines: A survey of healthcare professionals in Ireland' in the online journal Biodrugs. A poster of the same title was presented at the annual Prescribing and Research in Medicine Management meeting in London. Additionally, we published a review entitled 'Regulation of biosimilar medicines and current perspectives on interchangeability and policy' in the European Journal of Clinical Pharmacology.

25 Years of Medicines Safety Monitoring

Dr Joan Gilvarry,
Director of Human Products Monitoring

In May 2019, Dr Joan Gilvarry retired from the HPRA following an eminent career in medicines regulation, which first started when she crossed the threshold of the National Drugs Advisory Board (NDAB) in 1993. During her 26 year career, she has been a driver of and witness to the many advances that have taken place in national and European medicines regulation – most notably in the pharmacovigilance and safety monitoring of medicines.

When Dr Gilvarry joined the NDAB there were around 50 employees with a role to assess human and veterinary medicine applications and to provide advice to the Minister for Health. The Minister, who had the legislative remit to license medicines at that time, would consider the advice and then make the decision to authorise the medicine or not. In 1996, the NDAB was replaced by the Irish Medicines Board (IMB), which was established in legislation with the statutory powers to regulate and licence both human and veterinary medicines. Over the following decade, the IMB's regulatory remit expanded to include a wide range of other health products. It would ultimately become the Health Products Regulatory Authority in 2014 which today employs some 350 people.

In parallel, Dr Gilvarry's career progressed. From being one of just four medical assessors in 1993, she was appointed Medical Director in 2000. She recalls the vast changes in medicines regulation that have brought tremendous benefit to patient safety during her lengthy career. When she joined the NDAB, all the applications were assessed in hard copy format and fax machines were the fastest means of communication. 'Essentially, it was a lot of big, big boxes and folders of data arriving with new medicine applications that required quality, safety and efficacy assessments. There is no doubt that the evolution of technology, and the innovations brought about by a connected IT infrastructure, revolutionised our way of working and brought immense efficiencies to the assessment process,' she says.

'At that time, the organisation consisted of the human medicines team, veterinary medicines team, pharmaceutical assessors and the all-important support staff for these areas. There were just two people - including my colleague Niamh Arthur who I have worked with and who has supported me throughout my 26 years here - dedicated to adverse reactions and assessing safety reports. Adverse reactions were reported through a yellow card freepost system. The technology to support case report processing was first introduced around 1996, with electronic reporting then established in 2005.'

In 1996, when the NDAB became the IMB, Dr Gilvarry says this 'marked a significant change in medicines regulation' in Ireland and across Europe. This coincided with changes to the European legislative framework to enhance and develop common and harmonised assessment procedures while maintaining a reactive approach to the safety monitoring. In comparison, 'the risk/benefit monitoring is now significantly integrated into the product life cycle and there is substantive sharing of information and data.'

With the establishment of the European Medicines Agency in 1995, there began greater sharing of expertise and information between regulators across all Member States.

It ultimately brought about significant changes in pharmacovigilance between 2003 and 2004 and Ireland got the opportunity to play a more proactive role with an approach that enabled EU wide licensing of and monitoring of medicines. The positive benefit of EU participation was advanced further with more knowledge sharing platforms for establishing and monitoring the safety of medicines. The EU Commission also reviewed the conduct of pharmacovigilance across Europe and after a consultation process published new legislative requirements in 2010 which were implemented in July 2012. This Dr Gilvarry says was a 'sea-change' in the safety monitoring of medicines in Ireland and across the EU with probably the most significant change being the establishment of a new committee - the Pharmacovigilance Risk Assessment Committee (PRAC). This resulted in structures for formalised pan-European assessments and monitoring of medicines, and recommendations that were legally binding.

The HPRA has been a very active contributor to the enhanced process, leading and supporting EU wide medicine reviews as well as providing expert staff to all appropriate EU working groups. Here Dr Gilvarry pays tribute to her colleague Dr Almath Spooner, the Pharmacovigilance and Risk Management Lead at the HPRA for her very strong voice as Vice-Chair of the PRAC for some six years and advocating strongly for Irish patients. Fundamentally, the PRAC 'enabled a progressive shift from reactive safety medicine monitoring to a much more proactive model.'

Many safety reviews (referrals) have been conducted across the EU over the past years with the HPRA playing a significant role in their outcome in the interests of public health and Irish patients. These include reviews of fluoroquinolone antibiotics, valproate containing medicines, oral contraceptives and gadolinium contrast agents to name but a few.

Of particular note, the referral process for fluoroquinolones included the PRAC's second ever public hearing, which was hosted at the EMA in June 2018. These public hearings enable regulators to engage EU citizens in the oversight of medicines and to listen and learn from their views and experiences. The patient input was a key element for the PRAC as it carried outs its review and resulted in a fully informed assessment based on the scientific and clinical data in addition to direct patient testimonies. The PRAC's considered decision, published in October 2018, was that fluoroquinolone antibiotic use should be further restricted and the information provided to patients on potential adverse reactions should be expanded to emphasise, in particular, the possibility of persisting effects. The HPRA immediately moved to implement the PRAC recommendations at a national level here with a multi-stakeholder meeting held in December with relevant healthcare professionals and representatives from the health service and patient organisations.

Dr Gilvarry also cites Valproate as another medicine where the voice of EU citizens – including patients, carers, healthcare professionals and academia – was critical in the PRAC evaluation of the medicine and clearly supplemented the available scientific evidence. First reviewed by the PRAC in 2013, a further European-wide review commenced in 2017, to assess the measures taken to increase awareness and reduce exposure to valproate use during pregnancy. This review featured the first ever EMA public hearing held in autumn 2017, with contributions from patients and carers from across Europe including representatives from Ireland. The subsequent recommendations and measures were announced by the PRAC in early 2018 and included the introduction of important new contraindications, strengthened warnings and further measures to prevent valproate exposure during pregnancy, including a new pregnancy prevention programme. Throughout 2018, the HPRA worked with the HSE, clinical leads, the Pharmaceutical Society of Ireland (PSI) and the Department of Health to facilitate the timely and effective implementation of the new recommendations nationally and, crucially, to support their successful introduction into everyday clinical practice.

Speaking on leaving her role where she has overseen the introduction and development of a more inclusive and sophisticated pharmacovigilance model, Dr Gilvarry states that there are more opportunities to enhance the safety monitoring of medicines with new innovations in technology and new ways to optimise communication and to enhance and coordinate the vigilance frameworks across the EU. This combined with strong legislation and appropriate regulation augers well for the future.

According to Dr Gilvarry, the EU (EMA) and the committee structures enable such positive developments but explains, "the EMA is the machine behind us, they co-ordinate and give guidance and support on issues but the scientific assessments and national expertise comes from the member states." In this regard, she states that the HPRA has 'punched above our weight at an EU level' over many years.

'The decisions taken are science driven and always in the public health interest. With advancements in communication methods over the years we can now quickly implement new prescribing advice, make instant contact with the medical and pharmacy professionals that prescribe and dispense the medicines, very importantly, the patients taking the medicines and their organisations.

'There have been many milestones over the years and some difficult and challenging safety issues. Our focus, however, must always be on ensuring the best possible health outcomes and it is incumbent on regulators to act decisively and in a timely manner on all information that is available to protect patients. This will continue to be the central driving force of medicine safety monitoring and regulatory action and I'm leaving a fantastic team behind me who can bring pharmacovigilance onwards and upwards over the coming years.'

Medical Devices

As the national competent authority for medical devices, the HPRA carries out a range of registration, surveillance, monitoring and compliance activities. Our aim is to ensure that these health products perform as intended and do not compromise the health and safety of the patient or the person using them.

Authorisation and Registration

- The HPRA is focused on ensuring effective and consistent designation and oversight of notified bodies at national and European level. In 2018, we:
  - Assessed a number of applications from organisations seeking to be designated as notified bodies in Ireland under both the new Regulations and the existing Directives;
  - Continued our schedule of oversight of the notified body in Ireland based on ongoing assessment, surveillance and observed audits;
  - Provided expert assessors to participate in five EU joint assessments of notified bodies based in other European countries;
  - Continued to provide leadership and support development of EU coordination of notified body designation and oversight by acting as the deputy chair for the EU Notified Body Operations Group (NBOG);
  - Identified and prioritised development of systems and resources at national and EU level to allow timely and effective designation of notified bodies required under the new EU Device Regulations (EUDR).
- Supporting innovation and research of new technologies is a key strategic priority for the HPRA devices team. In 2018, this involved:
  - The review of applications to conduct clinical investigations of medical devices in Ireland. The number of clinical investigations remained stable with nine new applications and 15 amendments to ongoing investigations received in 2018. HPRA anticipate that numbers will increase when the new EU Regulations are implemented;
  - The HPRA continue to focus on this area to ensure regulatory requirements and processes are clear and accessible to potential applicants;
  - Encouraging engagement during product development and innovation of medical technologies. We met with 18 groups of innovators (13 preliminary and five pre-submission meetings);
  - Supporting the work of the HPRA Innovation Office on medical devices queries received.
  - Presenting and participating in innovation sessions at a variety of conferences and workshops including the Euro PCR conference in Paris.

- Manufacturers of certain medical devices and in vitro diagnostics are required to register with the HPRA. In 2018, the HPRA received 50 registrations of new organisations manufacturing these products in Ireland. A total of 831 medical devices were also registered. HPRA anticipate increased numbers of organisations and devices will be registered in the run up to the UK exit from the European Union.

Safety and Quality

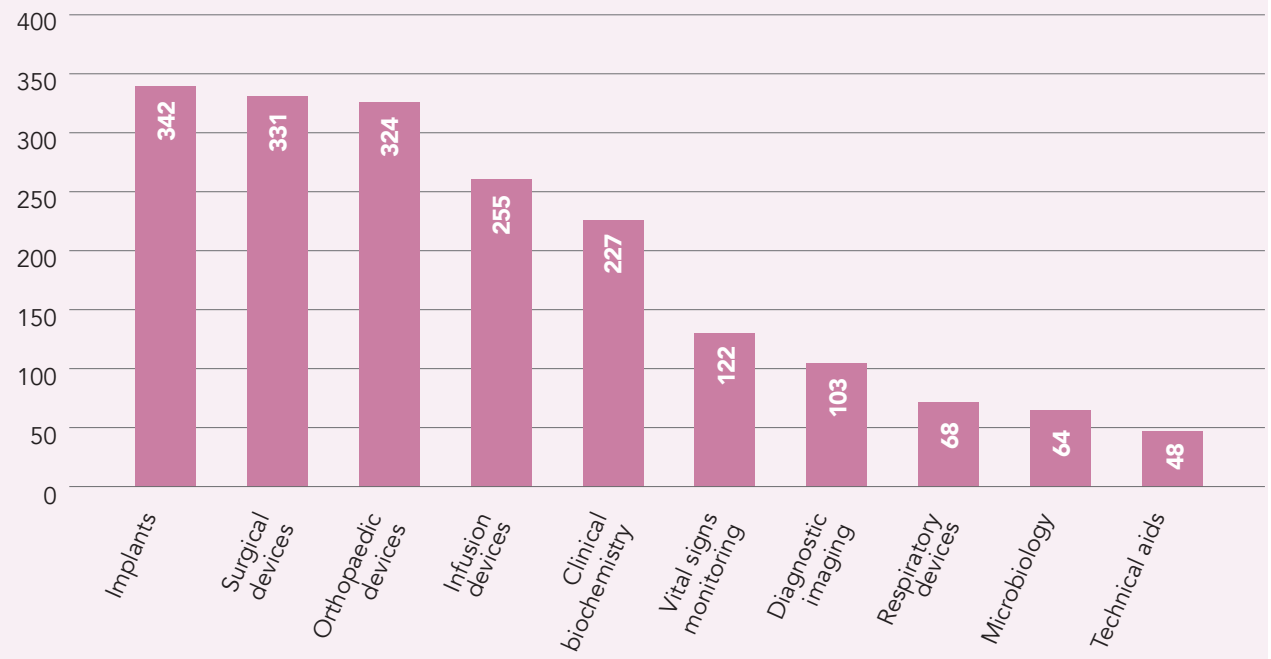
- We continue to develop and reinforce our market surveillance activities, with particular emphasis on proactive rather than reactive actions. Of note in 2018:
  - We utilised a lifecycle market surveillance strategy and planning mechanism to ensure continued safety and performance of devices throughout their lifetime;
  - We led or participated in various elements of both technical work packages of the EU Joint Action on Market Surveillance (JAMS) of medical devices initiative which is funded by the European Health Programme and aims to develop market surveillance activities;
  - A total of 38 COEN notices were sent to the European network relating to medical device compliance concerns;
  - Two information notices were published in relation to medical device issues, relating to the use of HIV self-tests and food intolerance tests;
  - There were 1,604 market surveillance cases* undertaken in 2018. The increase in cases, when compared to 2017, is in part the result of a 37% increase in the number of EU notifications received by the HPRA relating to notified body certificates.

Market Surveillance Cases

* Please note that from the start of 2014, the HPRA changed the way we define market surveillance cases and so the figures in the graph have been adjusted* by applying the pre-2014 definition to allow for comparison with 2012 and 2013 figures.

- We continued to focus our vigilance activities during 2018 on the areas of user reporting and dissemination of HPRA medical device safety communications. This included:
  - The receipt and assessment of 2,358 medical device vigilance cases, similar to numbers received in 2017. Of the 1,067 incident reports notified to the HPRA, 23% came from users of medical devices. Manufacturers accounted for 55% of all reports received in 2018 while 33% came from other competent authorities;
  - There were 415 field safety corrective actions (FSCA) affecting the Irish market relating to medical devices including 133 product removals conducted in Ireland during 2018;
  - The HPRA also issued 74 national competent authority reports, 13 notified body forms and 11 vigilance enquiry forms;
  - The HPRA issued 39 safety notices in relation to medical device issues and 26 direct to healthcare professional communications;

Vigilance Reports Received - Top 10 Product Types



– Implants, surgical devices, orthopaedic devices and infusion devices accounted for 53% of the total vigilance reports. Reports continue to be received relating to diagnostic imaging and radiotherapy devices. During the year, we also continued development work on signal detection of medical device issues;

– In the second half of 2018, we received a significant number of reports from members of the public in relation to urogynaecological mesh implant devices.

- As part of its market surveillance activities, the HPRA undertakes proactive and 'for-cause' audits of manufacturers, notified bodies and authorised representatives with the objective of monitoring compliance of devices emanating from Irish based organisations. During 2018, 15 audits were performed at notified bodies, medical device manufacturers and authorised representative facilities, of which:

  – six were for cause audits, one of which was in the US;

  – nine were based on proactive market surveillance projects and notified body surveillance/ assessment.

Legislation and Regulation

- The two new European Regulations on medical devices will become fully applicable in 2020. We continued our work during 2018 to help ensure an effective and timely implementation of these EU Device Regulations (EUDR) at national and European level. This included:
  - Formalising a HPRA programme plan for development of appropriate resources, process and systems to meet our obligations under the new EUDR;
  - Preparing detailed information relating to the new requirements with respect to the need for national legislation, the timelines and impact on existing national legislation;
  - Contributing to the European Commission's development of the secondary legislation involving implementing and delegating acts;
  - Participating in the new EU Medical Device Coordination Group (MDCG). Chaired by the EU Commission, this group is responsible for the overall coordination and governance of the regulatory system;
  - Participating in the EU steering group for development of the new European database (MDR EUDAMED) envisaged under the new Regulations. The HPRA also participated in a number of the associated technical working groups on certificate and registration, unique device identification (UDI) and clinical aspects with a view to developing the system requirements and functional specifications.

We continued to engage with the Department of Health throughout 2018 on policy and legislative issues arising from implementation of the new EU Regulations. At national level, we further developed our national fee-based funding model for medical devices to recover costs associated with our medical device activities. The model was revised in 2018 to streamline and address some of the comments and feedback received in response to the model's original introduction in 2017.

- The HPRA continues to play a significant role in the development of EU regulatory systems and mechanisms to promote coordination, cooperation and consistency. In 2018, this included:
  - Re-election to the Executive Group of the Competent Authorities for Medical Devices (CAMD) network. This group has successfully worked in partnership with the EU Commission over the last number of years to develop the regulatory system in Europe;
  - Participation in the CAMD's Implementation Task Force (ITF) and Transition Subgroup (TSG) which aim to improve coordination and consistency of implementation of the new EU Regulations;
  - Continuing to lead the work of the clinical investigation and evaluation working group (CIEWG), acting as the co-chair along with the EU Commission.

- We continued to participate actively in initiatives to promote regulatory convergence and harmonisation of medical devices globally through the International Medical Device Regulators Forum (IMDRF). This involved:
  - Participation in the IMDRF Management Committee as part of the European delegation (along with the EU Commission, France and Germany);
  - Continuing to act as the IMDRF secretariat for the National Competent Authority Report (NCAR) Exchange programme. We also participated in a number of different IMDRF working groups including the group on regulated product submissions (RPS) and the Medical Device Single Audit Programme (MDSAP);
  - Contributing to discussions and development of the Good Regulatory Review Practice (GRRP) working group which is now developing a scheme similar to MDSAP but that relates to product reviews. We will place further priority on this work in 2019;
  - Contributing to briefings for the EU Commission for the purposes of the MDSAP Regulatory Authority Committee discussions and encouraging discussions at EU level to further Europe's future engagement in the programme.

Stakeholders and Partners

- We continued to work on developing our stakeholder engagement and communication with medical devices stakeholders throughout 2018. This included the promotion of direct reporting of incidents and medical devices issues by device users and members of the public. We also continued our engagement with health services and healthcare professionals to encourage reporting and raise awareness of the roles and activities of the HPRA. We again promoted the adoption and communication of the HPRA step-by-step guide to user reporting which is targeted at healthcare providers.

- The HPRA undertook a number of communication initiatives to raise awareness of the impact and requirements being introduced as a result of the new EUDR. During 2018, we:
  - Held an information day on the new Regulations in Galway. The event was attended by around 250 participants;
  - Continued to update the HPRA website to provide information and guidance regarding EUDR;
  - Provided briefings, advice and workshops on the new Regulations to a range of different stakeholders including notified bodies and distributors.

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

- The HPRA continues to deliver a programme of presentations and talks to a range of external stakeholders. A full list of all presentations related to the regulation of medical devices that were delivered during 2018 is provided in Appendix 2.

Medical Devices: Key Figures

Year	2016	2017	2018
Lead Competent Authority role on specific vigilance issues	98	89	74
NCARs and vigilance related communications	116	96	111
Vigilance cases received/ opened	2,242	2,339	2,358
Field safety notices uploaded	476	519	475
Medical device safety notices	46	44	39
Medical device targeted healthcare professional communications	33	23	37
NCARs managed as IMDRF NCAR secretariat	18	8	8
COEN reports (market surveillance and vigilance) to EU network	45	44	38
Medical device information notices	0	5	2
Market surveillance cases (unadjusted)	335	411	353
Notifications relating to notified body certificates	959	844	1,174
Classification requests	35	51	37
Compassionate use applications	5	5	8
Medical device free sale certificates	2,122	2,371	2,581
Medical device queries received	477	496	547

Blood, Tissues and Organs

The HPRA is responsible for monitoring the safety and quality of blood and blood components, and of tissues and cells. Along with the HSE, we are joint Competent Authority for organs intended for transplantation.

Authorisation and Registration

The authorisation of blood establishments, tissue establishments and organ procurement organisations / transplantation centres permits those facilities to carry out specified activities. The total number of authorisations in place at year end for the past five years is presented by category in the accompanying table.

Number of Authorisations	2014	2015	2016	2017	2018
Blood establishments	4	3	3	3	3
Tissue establishments	24	24	25	25	26
Organ procurement/ transplantation	0	4	4	4	4

Safety and Quality

- Following collaboration with the National Haemovigilance Office (NHO), we submitted an annual report of serious adverse reactions and events to the EU Commission during 2018. The report reflected information received by the NHO in 2017 and included information on 59 serious adverse reactions and 139 serious adverse events which met the mandatory legislative reporting requirements.
- We also submitted an annual report on serious adverse reactions and events associated with tissues and cells to the EU Commission during 2018. The report reflected information received in 2017 and consisted of some 59 reports, 49 of which met the legislative reporting requirements, including seven serious adverse reactions and 42 serious adverse events.
- The Joint Action on Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation (VISTART) programme concluded in 2018. As part of the HPRA's contribution to VISTART activities, we led Work Package 9 which involved a voluntary programme of inter-member state auditing of inspection systems. Consequently, we carried out pilot audits using tools developed under this work package.

Further updates to the common approach for defining reportable serious adverse reactions and events and other vigilance activities in Europe are being continued under the Expert Sub-Group on Vigilance for Blood Tissues and Cells (VES), in which the HPRA is actively participating.

- We continued to liaise with the HSE lead and colleagues from Organ Donation and Transplant Ireland (ODTI) in relation to our respective roles under EU and national legislation on the Quality and Safety of Human Organs intended for Transplantation. During the past year, this included:
  - The exchange of relevant information on serious adverse reactions and events. In 2018, the HPRA received 20 reports of serious adverse reactions and events associated with organ donation / transplantation;
  - Updates to the serious adverse reaction / event report form;
  - Contribution to the review of the framework for quality and safety.

- We inspect relevant establishments, organisations and centres to monitor compliance with applicable national and EU legislation and guidelines on the quality and safety of blood, blood products, tissues and cells, and human organs intended for transplantation. Our inspection programme in 2018 included:
  - 9 tissue establishment inspections of which two were non-routine;
  - 7 routine inspections of blood establishments; and
  - 3 routine inspections of organ establishments.

Legislation and Regulation

- As part of our ongoing contribution to the review of relevant legislation, we provided feedback to the Department of Health on draft statutory instruments (SIs) for transposition of EU Directives on coding and import of human tissues and cells.

- In relation to assisted human reproduction, we engaged with the Department of Health on development of related legislation. We also engaged in respect of the commencement of parts 2 and 4 of the Children and Family Relationships Act 2015.

Veterinary Medicines

Our role is to grant licences for veterinary medicines subject to a review of their safety, quality and effectiveness. We continuously monitor the use of the products concerned in animals once they become available on the market in addition to authorising clinical field trials and inspecting / licensing manufacturing sites.

Authorisation and Registration

- There are a number of procedures through which a veterinary medicine can be authorised by the HPRA. These include the national procedure, the mutual recognition procedure (MRP) and the decentralised procedure (DCP). The following applications were issued by the HPRA during 2018:
  - 11 new national applications;
  - 53 new applications made under the DCP;
  - 6 new applications made under the MRP.

  We acted as reference (lead) Member State for the assessment of three of the MRPs and ten of the DCPs. We also led a further ten applications as RMS under the repeat use procedure.

  The centralised route administered by the EMA is another mechanism whereby veterinary medicines can be authorised for supply in Ireland. In 2018, HPRA experts acted as rapporteur or co-rapporteur in respect of three new veterinary medicines. An additional 13 new medicine applications were issued through the centralised route where HPRA experts played a supporting role in the overall assessments.

  By end of year, there was a record total of some 1,800 veterinary medicines authorised by the HPRA.

- During 2018, HPRA experts acted as co-ordinator for three requests under the EMA scientific advice procedure.

- With regards to Brexit planning and preparation (see also pages 11 to 13), we focused on the HPRA's key strategic aim of protecting the availability of veterinary medicines on the Irish market while also optimising our role within the European regulatory network. During the past year, this included:
  - Changes to transfer procedure made to mitigate against Brexit related shortages. There was a total of 180 transfers of the RMS role to the HPRA;
  - Engagement with industry to identify potentially vulnerable products;
  - Recruitment and training of additional staff in response to anticipated increase in workload;
  - Agreement with the UK's Veterinary Medicines Directorate for a work-sharing arrangement post Brexit.

- Medicine shortages continue to be a challenge for many veterinary practitioners tasked with treating many different species and conditions. Problems of non-availability can arise from a number of issues

and different solutions are needed depending on the issues involved. In 2018:

- We conducted planned quarterly reviews of AR18 and AR16 lists which provide details of veterinary medicines that have been granted special import licences by the Department of Agriculture, Food and the Marine. The HPRA strategy is to review the lists to identify required medicines and to encourage an applicant to seek a standard marketing authorisation where practicable.
- Carried out gap analysis and prioritised applications linked to shortages.
- Meetings were held with the Department of Agriculture, Food and the Marine to discuss shortages related issues including the need to develop an inter-departmental process in respect of potential shortages arising from Brexit.
- Communicated and met with applicants regarding transfer of RMS to Ireland. We also revised the relevant procedure and established a register of products for transfer.
- We worked closely with EU competent authorities to enable the use of common packs.

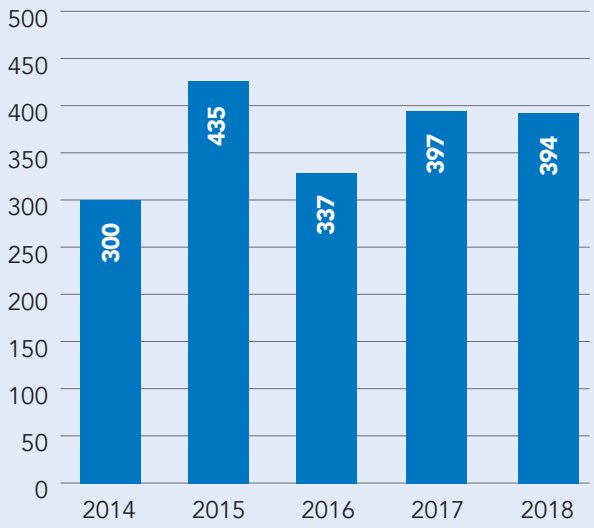
Authorisation and registration: Key figures

Year	2016	2017	2018
Classification enquiries	16	11	26
Clinical trials	1	2	10
New centralised as (co-) rapporteur	11	16	3
New MR/DCP as RMS	14	30	34
New MR/DCP as CMS	78	44	57
New homeopathic applications	0	3	0
New national applications	8	8	11
Renewals, national and MR	100	108	148
Variations, national and MR	1,341	1,366	1,820
Manufacturers of veterinary medicines	24	20	23
Export certificates	155	111	109

Safety and Quality

- The operation of a national pharmacovigilance system for veterinary medicines is dependent on the submission of reports by veterinarians, pharmacists, licensed merchants and others involved in dispensing or using the medicines concerned. These reports may be submitted either directly to the HPRA or to the companies marketing the medicines. The companies, in turn, must relay the data to the HPRA.

Adverse Event Reports



- Over the course of 2018, we received 394 national reports of suspected adverse events to veterinary medicines with the vast majority of reports, as in previous years, received from pharmaceutical companies.

- We processed 1,233 periodic safety update reports (PSURs) which incorporated the assessment of individual medicines on the market in Ireland as well as a work-sharing initiative where we led, or contributed to, the assessment of a class of veterinary medicines for the European Union.

- Containment of the development of antimicrobial resistance (AMR) is essential for public and animal health. Our work in this area includes the collection of annual information on the sale of veterinary antibiotics from each marketing authorisation holder. This information, which is included in the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), is important as it allows us

to benchmark our usage rate against those of our European neighbours and to follow any developing trends. The data show that due to a variety of factors there are significant fluctuations in sales annually and, consequently, that a clear trend is not identifiable.

Veterinary antibiotic use	2013	2014	2015	2016	2017
Tonnes sold	99.1	89.4	96.9	103.4	99.7

Additionally in 2018, we collaborated with the Department of Agriculture, Food and the Marine to support the development of a database for antimicrobial consumption as per 'Ireland's National Action Plan on Antimicrobial Resistance 2017-2020'.

- The analytical testing of products is a key component of the HPRA's risk based sampling and analysis programme. Five samples of veterinary medicines were taken under the programme and all were subjected to laboratory testing. While the majority of the samples tested were compliant with their specifications, a number of issues, such as crumbling of tablets, were noted. Appropriate follow-up actions were taken as necessary.

- We investigate, on a risk basis, reports of suspected quality defects in medicines and active substances, and co-ordinate subsequent recalls from the Irish market where necessary. There were 125 quality defects pertaining to medicines for veterinary use reported or identified. The risk classifications that were assigned, along with the corresponding figures for the previous two years, are outlined in the accompanying table.

Year	2016	2017	2018
Critical quality defects	7	5	26
Major quality defects	12	13	43
Minor quality defects	22	30	56
Number of reports not justified	0	0	0
Total Number Quality Defects	41	48	125

Companies (50%), including manufacturers, distributors and/or authorisation holders, and other competent authorities (47%) were the primary sources of reports received.

In certain cases, in order to protect animal and / or public health, it is deemed necessary to withdraw, or recall, a veterinary medicine from the Irish market. Six recalls of medicines occurred which was one less than in 2017. Of these, three were recalled due to a lack of sterility assurance.

- Our inspections and audits programme focuses on ensuring industry compliance with relevant standards and legislation. In 2018, there were:
  - 12 good manufacturing practice (GMP) inspections of sites that manufacture / test veterinary medicines;
  - 2 pharmacovigilance inspections.

Legislation and Regulation

- We continued to engage with the Department of Agriculture, Food and the Marine in respect of the proposed new EU veterinary medicines legislation. Meetings were held to review the proposals and we presented feedback to the Department. We continued to consider and plan for the potential impact of the legislation on HPRA procedures and published a broader impact analysis in the Veterinary Journal publication.

  We note that discussions in the European Council and Parliament on the new legislation reached a successful conclusion by year end and work can now begin on the planning for its implementation.

- We completed a report on the potential impact of the ongoing judicial review proceedings contending that the labelling and packaging of veterinary medicines should be in both the Irish and English languages.

Stakeholders and Partners

- As part of our ongoing stakeholder engagement, in 2018:
  - We held a Veterinary Medicines Information Day to inform stakeholders of ongoing issues and recent developments. In addition to HPRA updates, presentations were also delivered by the Department of Agriculture, Food and the Marine and the UK's Veterinary Medicines Directorate. Among the topics discussed were:
    - The new EU legislative framework for veterinary medicinal products;
    - Brexit developments and the preparations undertaken by the HPRA;
    - Information on GMP and pharmacovigilance;
    - HPRA performance data.
  - In respect of support for innovation, we were appointed as rapporteur for three veterinary vaccines in addition to taking over the RMS role for a number of vaccine products from the UK. We also undertook a peer review of a stem cell product. Additionally, we held a number of meetings with stakeholders during the year as part of our review and audit of the current level of national regulatory and scientific advice provision at each stage of product development.
  - As part of our commitment to enhance our stakeholder communication on safety issues, we developed and published a number of safety notices on our website in relation to product recalls and changes to withdrawal periods, and specific topics including diethanolamine and enrofloxacin.

- Throughout 2018, we continued our involvement across the EU regulatory network which includes active participation at the EMA and the HMA.

- As in recent years, we delivered a programme of presentations to veterinarian students and veterinary nursing students on the role of the HPRA and the promotion of veterinary pharmacovigilance. We also presented at a number of industry stakeholder events. A full list of all presentations delivered during 2018 is provided in Appendix 2.

- Our Medicinal Products Newsletter provides updates for those working in the veterinary medicines sector on Irish and European legislation, new / revised HPRA regulatory publications and stakeholder events such as information days. Three editions were published on our website in 2018 and are available to download from the 'Publications' section.

  We also contributed a number of articles to the Veterinary Ireland Journal and the It's Your Field publication. Details are included in Appendix 3.

Scientific Animal Protection

The HPRA is the competent authority in Ireland responsible for the implementation of EU legislation (Directive 2010/63/EU) for the protection of animals used for scientific purposes.

Authorisation and Registration

- The HPRA carries out evaluations of applications for the authorisation of research establishments and projects in addition to evaluating applications from individuals to allow them to manage projects or to conduct procedures or euthanasia of animals.

  As shown in the accompanying table, there was an increase in the total number of projects authorised in 2018. In addition to the new individual authorisations issued during the year, there were also 152 renewals of individual authorisations. Please note that the higher level of individual authorisations during 2014 was due to the legal requirement for existing establishment personnel to apply for individual authorisations, which are valid for five years, before the end of 2014.

Authorisations

- In November, we published the fifth annual statistical report on the use of animals for scientific purposes in Ireland. The HPRA is required to collect and make publicly available, on an annual basis, statistical information on the use of animals in procedures, including information on the actual severity of the procedures.

Authorisation and registration – Key 2018 figures:

Individual authorisations	308
Individual renewals	152
Project authorisation	143
Individual amendments	45
Project amendments	253
Establishment renewals	3

Safety and Quality

- During 2018, there were 23 inspections completed to monitor animal welfare standards and compliance with legislation, of which 39% were unannounced. This total incorporated one establishment authorisation inspection and 22 compliance inspections.

  Of the 54 non-compliances recorded under the annual inspection programme, 37% were self-reported to the HPRA by personnel at the authorised establishment with the remainder detected on inspection. Non-compliances are categorised as Type 1, Type 2 and Type 3 with Type 1 being the most serious and Type 3 being more minor in nature. In 2018, 20% of non-compliances were Type 1, 61% were Type 2 and 19% were Type 3. The most common non-compliances recorded related to (i) breaches of project authorisations, (ii) failure to carry out routine health checks and (iii) issues with supply of food or water to animals.

Stakeholders and Partners

- In 2018, we published and disseminated four 'Regulatory Updates' to provide stakeholders with the latest news and guidance from the HPRA including information on best practices in respect of the 3Rs and compliance with the legislation.

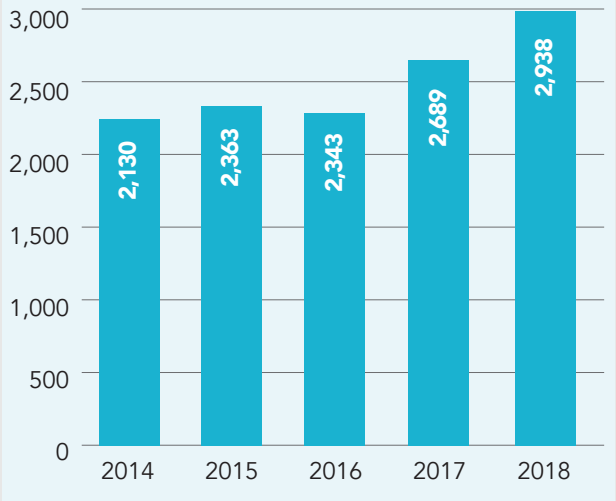
- We delivered a number of Laboratory Animal Science and Training (LAST) lectures in relation to the legislative and regulatory aspects of scientific animal protection. In April, we delivered a lecture at the British Society of Animal Science Annual Conference 2018, in relation to the application of the legislative requirements in agricultural research. In October, we delivered a lecture at a workshop held by the National Committee for the Protection of Animals used in Science regarding the HPRA's evaluation of the 3Rs in project applications.

Controlled Drugs and Precursor Chemicals

Authorisation and Registration

- Import, export and holding of controlled drugs (for legitimate purposes) are subject to licensing. The Department of Health is the licensing authority while the HPRA handles the administrative aspects of the application and licensing process. Licensing activity consists primarily of export and import licences, and letters of no objection. Data for the past five years are outlined in the accompanying graph.

Controlled Drugs Licensing Activity



- The HPRA is the licensing authority for precursor chemicals. These are subject to different licensing requirements, dependant on specific categories. The following table shows the licensing activity since 2014.

Precursor Chemicals Licensing Activity	2014	2015	2016	2017	2018
Total	46	32	16	23	23

Legislation and Regulation

- Throughout 2018, the HPRA provided support to the Department of Health in their preparations to establish the Medical Cannabis Access Programme. Clinical guidance, developed by an Expert Reference Group established by the Minister, is available from the Department's website and it is anticipated that the legislation required to underpin the programme for Irish patients will be published during 2019. This will permit consultants on the specialist medical register to initiate treatment with specified cannabis based products for patients with any of three specified conditions:
  - Spasticity associated with multiple sclerosis resistant to all standard therapies and interventions;
  - Intractable nausea and vomiting associated with chemotherapy, despite the use of standard anti-emetic regimes;
  - Severe, refractory epilepsy that has failed to respond to standard anticonvulsant medications.

The products for use via the Medical Cannabis Access Programme are not considered to be medicines. Consequently, a separate framework for their importation, supply, prescribing, dispensing and possession is required under the Misuse of Drugs legislation. Only cannabis based products for medical use that meet criteria set out in the associated legislation will be permitted under the Medical Cannabis Access Programme. Further information will be available on the Department of Health website during 2019.

Cosmetic Products

The role of the HPRA is to regulate the manufacture, sale and supply of cosmetic products in Ireland. We identify and address cosmetic product quality and safety issues, in conjunction with the HSE, so that a cosmetic product will not compromise the health and safety of the consumer or the person applying the product.

Authorisation and Registration

- We issued 193 cosmetics free sale certificates which were requested by companies intending to export products to non-European Economic Area countries.

Safety and Quality

- As part of proactive market surveillance activities, we conducted five inspections of cosmetic distributors and two inspections of cosmetics manufacturers to assess compliance with the Cosmetics Regulation. Distributors and manufacturers were informed of any non-compliances identified and requested to implement corrective actions.

- Our reactive market surveillance includes investigation of quality-related complaints (compliance cases), reports of adverse events relating to the use of cosmetics (vigilance cases) and serious risk alerts received from other countries (RAPEX). There were 379 reactive surveillance cases initiated which is a 21.5% increase on 2017.

Stakeholders and Partners

- In May, we were invited to present at the Irish Cosmetics, Detergent and Allied Products Association (ICDA) workshop: Potential Regulatory Impact of Brexit for Cosmetic and Detergent Companies. The workshop was attended by Irish cosmetics and detergent manufacturers and also by UK companies intending to set up their designated Responsible Person in Ireland.

- We hosted an information stand at the Professional Beauty Show held in the RDS, Dublin, in October. Manufacturers and distributors of cosmetic products participated in this trade show. We provided relevant information on their responsibilities under the Cosmetics Regulation and distributed the HPRA cosmetic products information pack and leaflet on selling cosmetic products in Ireland to stakeholders as additional information.

  This show was also attended by a number of consumers and students who we informed of the risks associated with buying cosmetic products online and counterfeit products. We included a display at our stand comparing a counterfeit cosmetic product with the genuine product to highlight the features for which to be vigilant when purchasing cosmetic products.

- In December, we launched a media information campaign to raise awareness amongst consumers of the dangers presented by counterfeit cosmetics in the run up to the Christmas period. The information was published by both print and online media and we participated in a number of national and regional radio interviews. Consumers were informed of how to spot a counterfeit cosmetic and of the risks these products can pose.

Other Regulatory Programmes

Inspections, Audits and Market Compliance

- The Joint Audit Programme (JAP) is a key element of the quality system adopted by good manufacturing practice (GMP) inspectorates in Europe and aims to ensure consistency of GMP inspection standards and a harmonised approach throughout Europe. In 2018, the HPRA participated in the JAP evaluation of the GMP compliance programme of another member state.

- In relation to the US/EU mutual recognition agreement (MRA) on GMP inspections for human medicines, the US FDA had, in 2017, been an observer of the JAP audit of the HPRA's GMP inspectorate as part of its review of the equivalency of HPRA systems. Following the successful close out of that audit, a detailed data package was prepared and presented to the FDA for its consideration as part of competency assessment. The FDA subsequently confirmed that the HPRA has the capability, capacity and procedures to carry out GMP inspections at an equivalent level. As a result, Ireland was included on the list of recognised member states under the MRA on 1 June 2018 and from that point forward the FDA can rely on HPRA inspections of manufacturers in place of conducting its own inspections.

- Other EU contributions included participation in / leading on
  - the drafting group tasked with revision of EU GMP Guide Annex 1 on the manufacture of sterile medicinal products;
  - the drafting group for the new EU GMP Guide Annex 21 on importation;
  - the development of a new risk assessment tool for the selection of medicinal products and active substances for surveillance testing;
  - a new risk-based tool to support inspection and surveillance relating to heparin manufacturers and their related products; and
  - the development of a communication tool-kit for the Official Medicines Control Laboratory (OMCL) Network.

Innovation Support

- The HPRA continues to focus on supporting innovation as one of our five strategic goals. This reflects our role not just to protect but also to enhance public and animal health. Our supports for innovation aim to facilitate safe and timely access to innovative health products and to increase and improve treatment options for patients. They also benefit the HPRA by helping to inform our future

development and allowing us to identify novel product types and technologies that require new or adapted regulatory science approaches. Our actions to support innovation in 2018 included the following:

– The HPRA's Innovation Office continues to offer regulatory support and advice to anyone developing an innovative health product or technology. Over 60% of the queries to Innovation Office originate from academia or small and medium enterprises who may have limited access to specialist regulatory advice. Medical devices was the most frequent area addressed through Innovation Office queries followed closely by medicines.

– Having previously established a national horizon scanning process, in 2018 the HPRA focussed on supporting the development of similar processes on a European and international level. Horizon scanning is intended to identify novel health products at an early stage and inform the development of appropriate regulatory tools and approaches to ensure the effective regulation of such products and thereby facilitate patient access. We have taken a lead role in the development of a coordinated approach to horizon scanning within the European Innovation Network culminating in the presentation of an agreed proposal to the HMA in November 2018. The HPRA has also acted as overall project lead for the innovation project among members of the International Coalition of Medicines Regulatory Authorities (ICMRA). One of the three work-streams, which relates to leveraging the outcomes of horizon scanning, is jointly led by the HPRA and the EMA.

– Our classification process continues to offer advice to stakeholders on the borderline between different regulatory frameworks including medicines, medical devices, cosmetics and other products. 2018 saw the implementation of an integrated medicines and medical devices classification system designed to optimise the decision-making process. The implementation of this approach also reflects the ever increasing level of convergence between these two areas and it is also timely given the classification-related changes introduced by the new medical devices regulation.

– The HPRA was part of a consortium of European medicines regulatory agencies who successfully applied to the European Commission for a Horizon 2020 funded coordination and support action. This project entitled 'Strengthening regulatory sciences and supporting regulatory scientific advice' (STARS) will begin in January 2019 and will seek to support academic-led health product innovation by increasing regulatory knowledge and awareness.

Improving the Management of Shortages

Establishment of a medicine shortages framework

Medicine shortages are increasingly prevalent globally, and Ireland, like all countries, has the potential to be affected. In order to address this at a national level, the HPRA created a new internal function to co-ordinate the management of shortages of human medicines. The HPRA's medicines shortages team works closely with various stakeholders who have fully committed to working together to address this important area in the interests of patients.

Multi-stakeholder collaboration

2018 saw the establishment of a national framework outlining a multi-stakeholder approach to the management of medicine shortages and the reduction of the impact they can have. Shortages can effect patients in particular and the multi-stakeholder approach places the patient right at the centre so that their needs underpin all planning and mitigating actions. The development of the framework involved the collaborative participation of groups representing key stakeholders in the supply and use of medicines:

- Government / State agencies: Department of Health, Health Products Regulatory Authority, Health Service Executive
- Patients: Irish Platform for Patient Organisations, Science and Industry (IPPOSI)
- Healthcare professionals: Irish Pharmacy Union, Hospital Pharmacists Association of Ireland, Irish Medication Safety Network, Irish College of General Practitioners
- Manufacturers / Distributors: Irish Pharmaceutical Healthcare Association, Medicines for Ireland, Pharmaceutical Distributors Federation, Association of Irish Pharmaceutical Parallel Distributors

The consultation process culminated in a stakeholder workshop hosted by the HPRA in July. The framework went live in September and has resulted in a co-ordinated national response to the management of medicine shortages. The HPRA has created a dedicated section on its website to provide information on medicines which are in short supply, and their anticipated return to the market. This is regularly updated as new information becomes available and a weekly update is sent to subscribers to the HPRA website.

The number of shortage notifications received by the HPRA from various sources, including industry, patients and healthcare professionals, has increased since September, indicating stakeholders' willingness to engage in the framework. The same collaborative engagement has also ensured that no patient has gone without treatment as a result of a shortage.

Adrenaline auto-injectors (AAIs) – A shortages case study

What are AAIs?

Life-saving medicines that people carry with them in case there is an emergency, such as a potentially life-threatening allergic reaction to stings or certain foods (e.g. nuts).

What was the issue?

A shortage of one particular brand led to increased demand for other AAIs, which coincided with the seasonal increase in demand for all AAIs linked to the seasonal vaccination and back-to-school periods. This led to supply constraints for AAIs in the second half of 2018.

What was the benefit of the multi-stakeholder framework?

1. The HPRA, in collaboration with the other AAI suppliers and healthcare professionals, were able to respond quickly and establish the potential gap in supply as soon as the potential shortage was identified. This allowed a number of actions to be taken prior to the seasonal increase in demand.
2. Alternative AAI suppliers were advised of the anticipated increased demand for their products in advance so that they could increase production and supply to Ireland to fill the gap left by the shortage. This communication continued during the period of supply constraints to ensure mitigation of the shortage.
3. The HPRA liaised with the pharmacy regulator, hospital pharmacy medication safety networks and the community pharmacy representative body to provide information on the supply issues so that appropriate guidance and information could be disseminated to pharmacists to ensure a pragmatic response to the shortage.
4. The HPRA maintained regular communication with specialist prescribers who provided clarification to colleagues on appropriate prescribing of AAI strengths.
5. As some patients may have received an alternative AAI that they may have been previously unfamiliar with, communications highlighted that patients and their carers should become familiar with the new device and that pharmacists could provide advice in this regard at the point of dispensing.
6. The shortages section of the HPRA website was updated regularly with information on the supply and became a 'go-to' site for information to patients and healthcare professionals.

Was Ireland the only country impacted?

The supply constraints were a global issue that impacted many countries, including the USA and the UK. Whilst the supply situation in Ireland was challenging, the actions taken ensured that a suitable AAI was available to dispense to patients at all times which is in contrast to the situation observed in other countries.

International influence

Whilst the primary focus for the HPRA's shortages function in 2018 was on the establishment of the national approach to co-ordinate the management of shortages, the HPRA has also been involved internationally in shaping the development of a European-wide response to medicine shortages. The HPRA is an active participant in the HMA/EMA Task Force on Availability of Authorised Medicines and presented at a two-day European stakeholder workshop organised by this group. The Irish approach to the management of medicines shortages has also been referenced in publications such as the British Medical Journal.

Focus for next year

The focus in 2019 will be on further developing the shortages framework and to develop and implement preventative strategies to reduce the likelihood of shortages occurring in the first instance. In many cases, these will be aimed at the underlying causes of shortages to ensure that shortage prevention is actively considered as part of the life cycle management of the medicine.

Outreach and Engagement

The HPRA is committed to a strategic focus on outreach and engagement with key partners and stakeholders so as to enhance and maximise the effectiveness of the regulatory system.

- In our outreach activities to support innovation developments in Ireland:
  - The HPRA continued to meet and interact with a number of other state agencies and organisations who seek to support innovation in Ireland including the IDA, Enterprise Ireland, Health Innovation Hub Ireland, Knowledge Transfer Ireland and a number of third level institutions. We also met with individuals and organisations who are seeking to develop innovative health products and technologies to provide guidance on the regulatory requirements that will apply to their products.
  - The HPRA participated in a number of events around Ireland to promote our supports for innovation. We presented at an Innovation in Medtech event organised by the Tyndall National Institute in Cork and a symposium organised by the Research Quality Association on innovation for health products. The HPRA attended the Spark Summit organised by the National Doctors Training and Planning section of the HSE, which was held in RCSI in October. We also presented and exhibited at the Taking Care of Business event organised by the Department of Business, Enterprise and Innovation in Limerick.
  - The HPRA continues to contribute to education programmes at both undergraduate and postgraduate levels. As part of our review of our contribution to such programmes which seeks to explore the use of online learning tools, we worked with the Affiliation for Pharmacy Practice Experiential Learning (APPEL) to develop on online training module for 4th year pharmacy students which provided an overview of medicines regulation and discussed the use exempt medicinal products. We also provided training placements to two 4th year pharmacy students as part of the new five-year integrated pharmacist training programme.

- Stakeholder communications and engagement:
  - In October, we launched our new public information campaign: Zero Gains. The campaign is focused on building awareness of the many and often serious side effects associated with the non-medical use of anabolic steroids. See page 48 for more details.
  - The HPRA's first ever national information campaign was launched in September 2016. The campaign, which incorporated radio, digital and print advertising, was repeated in 2017 and again between September and October 2018. The focus of the HPRA adverts was to highlight

the importance of the safe use of medicines as well as medication adherence in general. Our key message to members of the public is to take care when taking medication and specifically to be aware of and read the information and directions for use that come with every medicine. Our 2018 media plan focussed particularly on national and regional radio stations in addition to digital online advertising.

– Throughout the year, we continued our media communications programme to proactively communicate important safety messages and to build awareness of the role of the HPRA. We issued 20 press releases and website statements concerning safety and regulatory matters to ensure consumers, healthcare professionals and other stakeholders received timely and accurate information and advice. In a number of instances, these communications resulted in national and regional media interviews with a HPRA spokesperson. In addition, we responded to approximately 500 initial and follow-up queries from national, local and specialist media during the year.

– The HPRA was pleased to participate as one of a number of education partners working with the Irish Platform for Patient Organisations, Science & Industry (IPPOSI) to deliver a Patient Education Programme in the area of health innovation. The programme, which was specifically tailored for Irish patient communities, was piloted from September 2017 to March 2018 based on a 'blended learning' approach consisting of e-learning and face-to-face sessions. The HPRA module, which ran for five weeks, was focused on regulatory affairs, medicines safety and pharmacovigilance. Our Chief Executive participated in the informal programme graduation which took place in March.

– The HPRA website – www.hpra.ie – is a key communications channel and we continuously monitor and analyse key visitor and usage statistics. Among the key findings from 2018 were:

  - Almost 526,000 unique visitors accessed our website during the past twelve months representing a significant 67% increase compared to 2017.
  - There were in excess of one million visits in total throughout the year which is the highest annual number recorded for our website.
  - Of those who accessed the site, more than 50% were new or first time users.

– The @TheHPRA Twitter account was launched in late 2016 as a tool to support our communications activities and direct additional traffic to the HPRA website. We continued to develop our Twitter activity during 2018 and by year end we had more than doubled our number of followers to 1,804. We tweeted 222 times resulting in more than 789,000 impressions. Among the highlights was our participation in an international social media campaign to promote the reporting of suspected side effects from medicines. This campaign was supported by a range of patient organisations and other national health agencies.

– Also during 2018, we launched a corporate Instagram account to highlight and promote certain activities and events. This included the use of an Instagram wall during ICDRA 2018 in Dublin and the use of Instagram stories as a key component of our Zero Gains anabolic steroids information campaign.

- European and international contribution:

  – Details of the extensive Brexit preparatory work carried out by the HPRA during 2018 are outlined on pages 11 to 13.

  – The HPRA hosted the 18th International Conference of Drug Regulatory Authorities (ICDRA) in collaboration with the World Health Organization (WHO) in Dublin from 3 to 7 September 2018. This biennial event, which was opened by the Minister for Health, is the largest global gathering of medicines regulators and provides delegates with a unique forum to meet and discuss ways to strengthen global collaboration in the area of medicines' regulation. The theme for ICDRA 2018 was 'Smart Safety

Surveillance – A life-cycle approach to promoting safety of medical products'. The initial two-days, known as Pre-ICDRA, were open to both regulators and industry representatives and attracted 350 delegates. Topics discussed included regulatory collaboration, certification of pharmaceutical products, biosimilars and medical devices. The remaining three days of ICDRA were open to regulatory authorities and attracted 300 delegates from 83 WHO member states. There was a focus on a wide range of topics including haemovigilance, regulation of clinical trials and supply chain integrity. In advance of the conference, the HPRA team was also engaged in significant preparatory work in collaboration with the WHO. This included venue management, operation of the online booking process and the launch and updating of the official event website, icdra2018.ie

– The HPRA leads the coordination of the overall International Coalition of Medicines Regulatory Authorities (ICMRA) innovation project as well as co-leading on a work stream with the EMA. The work from this project was presented at DIA Europe in Basel and interim work stream reports were prepared and presented at the ICMRA Summit which took place in Washington in September. This was followed by further discussions at DIA in Japan in November. The final report will be presented at DIA Europe taking place in Vienna in February 2019.

– During the year, the HPRA was appointed as a member of the European Heads of Medicine Agencies (HMA) Management Board. Alongside the HMA meetings which took place in Lisbon, Sofia and Vienna, we also participated as part of the secretariat for the monthly meetings of the HMA Brexit Task Force.

– We attended the quarterly EMA management board meetings in London. The coordination of Brexit related issues and the planned EMA relocation to Amsterdam were two items dominating the agenda throughout the year. Other ongoing issues included the new veterinary legislation and clinical trials regulation implementation.

– We continued providing technical assistance to the Zambia Medicines Regulatory Authority with our consortium partners. This included hosting a study visit from a ZAMRA human medicines assessor. A report on cost containment and income generating strategies was also issued to the Zambian agency following a short term expert visit by a member of the HPRA finance team.

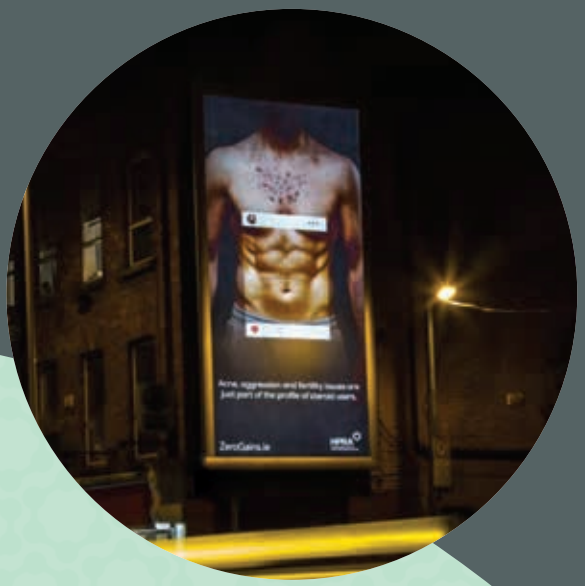
– HPRA information seminars and training events provide regulatory guidance and updates to a range of stakeholders. The HPRA also partners with other regulatory organisations to co-host relevant sessions. During 2018, we hosted the following events:

  - Joint Action for Market Surveillance meetings - 26th March, 31st May, 20th June
  - Medical Devices Information Day – 23rd May
  - Veterinary Information Day – 13th June
  - Medical Devices Work Package Conference – 4th and 5th September
  - VISTART (Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation) Joint Action project - 11th September, 12th and 13th September
  - Scientific Animal Protection 3Rs Training Day – 4th October
  - Good Clinical Practice (Compliance Information Day) – 23rd October

Key outreach and engagement figures 2018

Year	2018
Public consultations launched: - Proposed regulatory fees for human and veterinary medicines - Proposed regulatory fees for medical devices - Framework for multi-stakeholder approach to handling medicines shortages	3
Public consultations we responded to: - Included HMA, PSI, Health Information and Quality Authority, and Health Research Board	7
Events managed by HPRA events teams	10
Freedom of information requests	32
Requests received in accordance with the Data Protection Acts	12
Parliamentary questions	46
Queries from government departments or members of the Oireachtas	71
Protected disclosures received by external persons under section 7(2) of the protected Disclosures Act, of which investigation is: - Concluded - Ongoing	 5 1
Protected disclosures from HPRA staff members	0
Complaints	2
Customer service queries	3,454

Dangers of anabolic steroids highlighted by new HPRA 'Zero Gains' campaign



In October, the HPRA launched a new month long public information campaign to raise awareness of the potentially serious side effects and health risks of using unprescribed anabolic steroids.

The 'Zero Gains' campaign, which was launched by the Minister for Health, Simon Harris T.D., targets young Irish men and was developed in light of growing evidence of an increased use of anabolic steroids for body enhancement as well as new research showing a significant lack of awareness of the serious health complications posed by these products. The potential physical effects include heart failure, liver issues, kidney damage, and infertility as well as acne and hair loss. The psychological and emotional impacts include mood swings and aggression or 'roid rage' leading to possible depression. In addition, there are the very real risks associated with injecting anabolic steroids into the body while for younger males in particular, where their bodies are still growing and developing, there may be specific consequences such as stunted growth and premature ageing of the bones.

This national campaign, incorporating social and digital media in addition to outdoor and in-gym adverts, will be repeated during 2019 and 2020. A new website **www.zerogains.ie** was launched as part of the campaign to provide reliable and trustworthy information on the real risks of anabolic steroid use. It also provides practical advice to help anyone who is suffering from issues with use and provides details on how members of the public can report concerns about the illegal sales and supply of steroids to the authorities.

The sale and supply of anabolic steroids to the public outside of a registered pharmacy is illegal. As authorised prescription-only medicines, they are only available on foot of a prescription from a doctor to treat specific medical conditions. Growing evidence ranging from the increasing levels of illegal products detained by the HPRA each year, as well as needle exchange figures and a number of tragic deaths highlighted in the media in recent times, point to a growth in non-medical use in Ireland. The HPRA, working in conjunction with An Garda Síochána and Revenue's Customs Service, detained more than 650,000 dosage units of illegal anabolic steroids during the three years 2016 to 2018.

New HPRA research carried out in 2018 found that a significant proportion of Irish people are unaware of the many serious side effects caused by anabolic steroid use. Almost half of Irish adults (48%) are unaware/not sure about the side effects of steroid use meaning that lack of awareness of specific health risks

Pictured at the launch of the "Zero Gains" campaign in October were Minster Simon Harris T.D. and HPRA Chief Executive, Dr Lorraine Nolan

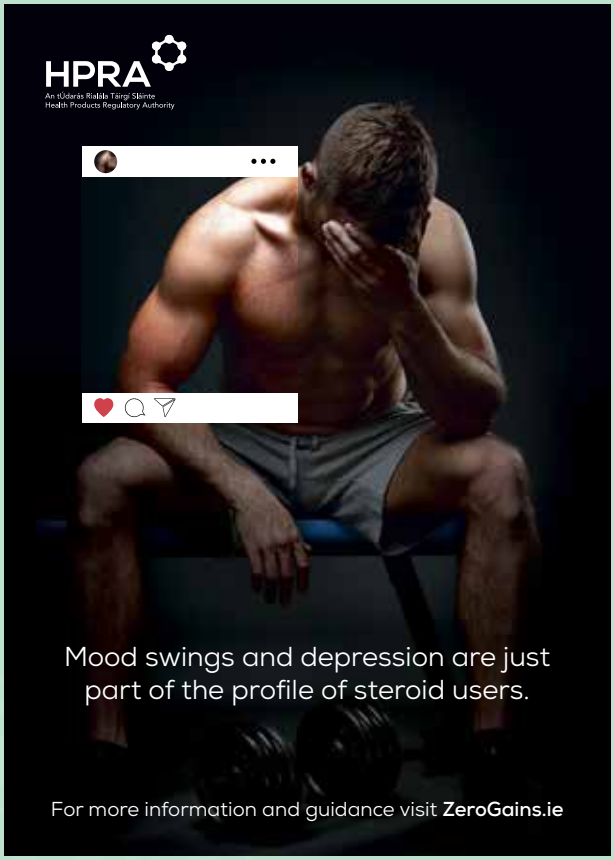
is significant. While almost 1 out of every 5 (19%) is aware (unprompted) that using anabolic steroids can cause heart problems, awareness levels of other known health risks are quite significantly lower. Only 8% of respondents referred to mood swings, 7% to aggression and just 4% to liver damage. Also of concern were the findings that:

- more than 1 in 4 people claim to know someone who has previously used unprescribed anabolic steroids;
- 1 in 10 adults would consider taking anabolic steroids to enhance physical performance or gain a more muscular physique, rising to more than 1 in 5 of those aged 18-34 (22%).

The 'Zero Gains' campaign makes clear and trustworthy information on real risks of use available to young men through media platforms, imagery and language they will relate to. It is focused on changing attitudes and dispelling the myth that non-medical use of these products is safe and that users have nothing to lose by taking them. On the contrary, young men have a lot to lose starting with their health and wellbeing. Taking everything into account, including the range of physical, psychological and emotional damage they can cause, the HPRA campaign is intended to challenge the preconception among healthy young Irish men that they only stand to gain from anabolic steroid use.

Campaign Creatives

The HPRA's visual campaign highlights the negative health impacts of anabolic steroids including mood swings and aggression (often referred to as roid-rage), depression, acne and hair loss, heart and liver issues, infertility and fluid retention. Further information on the many dangers associated with steroid use can be found on **zerogains.ie**.



Campaign Performance

- One month after the campaign launched, research showed that that more than 1 in 5 of all 18 to 24 year olds in Ireland recalled seeing the adverts.
- There were more than 10,000 visitors to the zerogains.ie website by end of December. Of these, 57% were male with the age group 25-34 accounting for the most visitors. 70% of the users of the site visited using a mobile device.
- A key component of the campaign media plan, given the highly visual nature of the campaign creatives, was the use of Instagram stories on the hugely popular photo-sharing social media network. This element of the campaign alone delivered a reach of 803,173.
- Geofencing, which enables targeted mobile users to be presented with digital adverts within online apps, was also part of the HPRA campaign. This component of the media plan delivered 827,919 impressions and additionally delivered 3,466 click throughs to the zerogains.ie website.

Next Steps

The campaign will be repeated on a number of occasions during 2019. The HPRA is very much open to engaging with relevant stakeholders to ensure this critically important public health message reaches the intended audience. We will also endeavour to enhance our media mix and creative approach to ensure the campaign evolves and remains both fresh and relevant.

Organisational Development

The HPRA is committed to having the necessary corporate functions, systems and supports in place to deliver on our public health mission. We must ensure that our organisational capabilities continue to expand and evolve in line with regulatory and scientific developments and that we adapt to other changes in our operating environment.

Human Resources and Change

Our HR and Change Strategy 2016 – 2020 continued to provide the framework for the development of our internal capabilities in the HPRA. The six core themes identified within the strategy drive our progress with various initiatives delivered throughout the year.

During the year:

- Delivery of our Management Development Programme (MDP) continued with the completion of phase one and the design and commencement of delivery of phase two. Our Management Committee members also began our Institute of Leadership and Management (ILM) accredited Leadership Development Programme (LDP) in 2018, sponsored by our Chief Executive.
- Our cross organisational working group continued the development of skills matrices for our various scientific roles in the HPRA.
- Our graduate recruitment programme commenced officially in September 2018 with our first graduates joining the organisation. Recruitment for the second programme, due to commence in 2019, was conducted at the end of the year.
- 2018 was a hugely successful year for the HPRA in terms of our health and wellbeing agenda. During the year we became the first public sector body to receive the KeepWell Mark accreditation while we were also recipients of a national HR award for Best Health and Wellbeing Initiative. The receipt of a gold Active@Work award from the Irish Heart Foundation was further recognition of our efforts in this area.

- We strengthened our presence on social media and increased the focus on our employer brand via LinkedIn and Instagram. This included the development, working closely with our communications colleagues, of an 'About Us' recruitment video which we will use on social media to support other efforts to grow our brand as an employer of choice.
- Resourcing plans were developed to manage the impact to business operations posed by Brexit.
- Following the appointment of a Deputy Director for Medical Devices, a significant piece of work was undertaken in leading a restructure project for the new medical devices department. Project managed by the HR and Change team, a new proposed structure was identified for approval by year end.

IT Developments

- EOLAS, the HPRA's new workflow technology solution, will provide the organisation with a single workflow and data management system to support its regulatory activities. It will also incorporate new EU standards for regulatory data management. During 2018, the second phase (wave 2) covering the implementation for human medicines and clinical trials was completed. This incorporated extensive rounds of testing, detailed end user training and a stabilisation period once deployed. Since go-live, end users have worked closely with the project team to identify and manage any issues or adjustments required.
- There were 423,473 regulatory submissions made through the Common Electronic Submission Portal (CESP), which is managed by the HPRA on behalf of the wider EU regulatory community. By year-end, there were 5,442 organisations availing of CESP with over 18,846 individual users.

Quality Management

- The HPRA's quality management team was responsible for overseeing the introduction of the General Data Protection Regulation (GDPR) which came into effect across Europe on 25 May 2018. This included the development and deployment of necessary policies and procedures in addition to the publication of a number of public and staff notices. There were 12 data subject requests received in 2018. Eight of these were received prior to 25 May so were dealt with under the legislation in place at that time. The remaining four were processed under GDPR requirements. All requests were managed within the required timelines.
  - New guidance documents for stakeholders, each of which was published on our website, included a guide for distributors of medical devices, a guide to the sale of paracetamol-containing medicines by non-pharmacy retailers and a guide to new applications and variations to wholesale distribution authorisations. In addition, the ICT and Business Services department began a project to implement ISO 20000-1 for service desk management.

Finance

- The HPRA is committed to the highest standards of corporate governance. During 2018, the financial statements for the previous year were prepared and submitted for audit to the Comptroller and Auditor General and subsequently published in the HPRA's 2017 Annual Report. All financial transactions during the period were reflected and reported upon in these statements.
- The annual review of regulatory fees for 2019, incorporating a public consultation, was completed followed by the publication of required fee changes.
- Internal audit reviews took place and reports were issued on ICT operations and GDPR readiness.
- New salary scales were received and systems were updated both in January and October.

Energy Usage

- The HPRA, as a public sector body, is required to report annually on its energy usage and actions taken to reduce consumption in accordance with the European Union (Energy Efficiency) Regulations 2014 (S.I. No. 426 of 2014). As an organisation, we use electricity for lighting, air conditioning or heating as required and the provision of hot water; natural gas is used for central heating. In 2018, the HPRA consumed 773.5 MWh* of energy consisting of:
  - 565.3 MWh of electricity
  - 208.2 MWh of fossil fuels
  - 0 MWh of renewable fuels.

  Total energy reduction at year end was 33.7%, exceeding the goal of 33% by 2020 (as calculated and published by the Sustainable Energy Authority of Ireland (SEAI).

  * published by the SEAI

Authority and Committees

- The Authority of the HPRA met six times in 2018 and considered a number of strategic matters including corporate policy, planning and financial matters. The latter included monthly management accounts, annual budgets and the financial statements for 2017. The Authority also reviewed update reports from the Statutory Advisory Committees and the Audit and Risk Committee. In addition, it reviewed the licences for all medicinal healthcare products as approved by the Management Committee.

  The number of meetings attended by each Authority member during 2018 was as follows:

Authority Member	Number of meetings held during the period the member was on the Authority	Number of meetings attended during the period the member was on the Authority
Ms. Ann Horan (Chairperson)	6	6
Mr. Pat Brangan	6	6
Mr. Wilf Higgins	6	6
Mr. David Holohan	6	6
Prof. Mary Horgan	4	1
Mr. Brian Jones	6	5
Prof. Elizabeth Keane	6	5
Prof. Caitriona O'Driscoll	6	6
Dr. Diarmuid Quinlan	6	5

  - The Audit and Risk Committee, a subcommittee to the Authority, met four times in 2018. Further details are provided in the HPRA's Financial Statements.
  - The Advisory Committee for Human Medicines met on two occasions in 2018. The Clinical Trials Sub-Committee is a sub-committee to the Advisory Committee for Human Medicines and it met twelve times in the past year.
  - The Advisory Committee for Veterinary Medicines met twice as did the Advisory Committee for Medical Devices.
  - The National Committee for the Protection of Animals Used for Scientific Purposes, a statutory committee to provide guidance to the regulator and those working in this area, met twice in 2018.

- Decisions of the Authority:

  The terms of reference of the Authority, which are published on the HPRA website, include an overview of how the Authority operates, an overview of all decisions taken by the Authority and those devolved to the Management Committee.

  The following decisions are reserved functions of the Authority:

  - The Authority takes decisions relating to very significant and serious public and/or animal health matters except in circumstances where a meeting of the Authority cannot be convened, in which case the Management Committee takes the decision and informs the Chairperson at the earliest opportunity and the Authority as soon as is practical.

– The Authority refuses applications, or suspends, revokes or terminates authorisations as set out in legislation except in circumstances where:

  (a) the urgency is such that a meeting of the Authority cannot be convened, or

  (b) the application or authorisation is subject to a binding European decision, or

  (c) the application or authorisation is for a clinical trial or clinical investigation; in which case the Management Committee takes the decision and informs the Authority.

– Through its Audit Committee, the Authority approves the internal financial controls and the financial audit function and satisfies itself that the financial controls and systems of risk management are robust and defensible. The Authority appoints the internal financial auditor.

- The Authority approves the investment policy, major investments, capital projects and the terms of major contracts.

- Significant acquisitions and the disposal or retirement of assets above a threshold set by the Authority are subject to Authority approval.

- The Authority approves treasury policy and risk management policies.

- The Authority approves corporate plans as required.

- The Authority approves the annual budget, monitors expenditure and supervises the preparation and submission of the annual statutory accounts.

- The Authority makes an annual report on the activities of the HPRA, including a financial statement, to the Minister for Health. This report is then published.

- The Authority selects and appoints the Chief Executive, with the consent of the Minister for Health. The terms of office and the remuneration of the Chief Executive are determined by the Minister for Health, after consultation with the Authority and with the consent of the Minister for Finance. The Authority, through its Performance Review Committee, conducts a process of annual performance appraisal of the Chief Executive. Succession planning for the role of Chief Executive is also undertaken by the Authority.

Financial Statements

for the Year Ended 31 December 2018

Authority Members and Other Information

Authority:	*Most recent appointment date*	*Expiry date*
Ms. Ann Horan (Chairperson)	01/01/2016	31/12/2020
Mr. Pat Brangan	22/05/2017	31/12/2019
Mr. Wilfrid Higgins	22/05/2017	31/12/2019
Mr. David Holohan	27/01/2016	26/01/2021
Prof. Mary Horgan	01/01/2016	Resigned 20/07/2018
Mr. Brian Jones	27/01/2016	26/01/2021
Dr. Elizabeth Keane	22/05/2014	21/05/2019
Prof. David Kerins	22/03/2019	31/12/2020
Prof. Caitriona O'Driscoll	01/01/2016	31/12/2020
Dr. Diarmuid Quinlan	22/05/2014	21/05/2019

All Authority members are appointed by the Minister for Health.

Bankers:

Allied Irish Bank
1-3 Lower Baggot Street
Dublin 2

Bank of Ireland Corporate
2 Burlington Plaza
Burlington Road
Dublin 4

KBC Bank Ireland
Sandwith House
Dublin 2

Solicitors:

Eugene F. Collins
Temple Chambers
3 Burlington Road
Dublin 4

Eversheds
1 Earlsfort Centre
Earlsfort Terrace
Dublin 2

Byrne Wallace
88 Harcourt Street
Dublin 2

Head Office:

Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2

Auditors:

Comptroller and Auditor General
3A Mayor Street Upper
Dublin 1

Governance Statement and Authority Member's Report

Governance

The Health Products Regulatory Authority (the HPRA) was established under the terms of the Irish Medicines Board Act, 1995 (as amended), and is governed by an Authority which was appointed by the Minister for Health. The Authority of the HPRA (the Authority) consists of a chairperson and eight non-executive members. The Authority is accountable to the Minister for Health and is responsible for ensuring good governance, and performs this task by setting strategic objectives and targets and taking strategic decisions on all key business issues. The regular day-to-day management, control and direction of the HPRA are the responsibility of the Chief Executive and the Management Committee. The Chief Executive and the Management Committee must follow the broad strategic direction set by the Authority, and must ensure that all Authority members have a clear understanding of the key activities and decisions related to the HPRA, and of any significant risks likely to arise. The Chief Executive acts as a direct liaison between the Authority and management of the HPRA.

On 1 July 2014 the organisation changed its name from the Irish Medicines Board, as provided for in Section 36 of the Health (Pricing and Supply of Medical Goods) Act 2013 and SI (205/2014) Health (Pricing and Supply of Medical Goods) Act 2013 (Commencement) order 2014.

Authority Responsibilities

The work and responsibilities of the Authority are set out in the Irish Medicines Board Act, 1995 (as amended), as well as in the 'Terms of Reference and Rules of Procedure' of the HPRA, which also contains the matters specifically reserved for Authority decision. Standing items considered by the Authority include:

- declaration of interests,
- reports from committees,
- financial reports / management accounts,
- performance reports, and
- reserved matters.

The Authority is required by the Irish Medicines Board Act, 1995 to prepare financial statements for each financial year which give a true and fair view of the state of affairs of the HPRA and of its surplus or deficit for that period.

In preparing those statements the Authority is required to:

- select suitable accounting policies and apply them consistently,
- make judgements and estimates that are reasonable and prudent,
- prepare the financial statements on a going concern basis unless it is inappropriate to presume that the HPRA will continue in existence, and
- state whether applicable accounting standards have been followed, subject to any material departures disclosed and explained in the financial statements.

The Authority is responsible for keeping adequate accounting records which disclose, with reasonable accuracy at any time, the financial position of the HPRA and which enable it to ensure that the financial statements comply with the Irish Medicines Board Act, with accounting standards generally accepted in Ireland and with accounting directions issued by the Minister for Health. The maintenance and integrity of the corporate and financial information on the HPRA's website is the responsibility of the Authority.

The Authority is responsible for approving the annual plan and budget. It is also responsible for safeguarding the assets of the HPRA and hence for taking reasonable steps for the prevention and detection of fraud and other irregularities.

The Authority considers that, except for the non-compliance with the requirements of FRS102 in relation to retirement benefits, the financial statements of the HPRA give a true and fair view of the financial performance and the financial position of the HPRA at 31 December 2018.

Audit and Risk Committee

The HPRA has an audit and risk committee comprising three Authority members, which met on 4 occasions during 2018. This committee is responsible for reviewing internal control matters, together with any other issues raised by the external auditors, the Authority or management. The external auditor is invited annually to meet with the audit and risk committee to brief them on the outcome of the external audit, and the audit and risk committee also meets annually with the internal auditor. During 2018 the internal auditor carried out internal audits on the areas of IT operations and data protection review, as well as a review of the system of internal financial controls. The audit and risk committee has also been involved with the review of the quality systems as described below.

Quality Systems

During 2018, the finance section of the HPRA continued the process of implementing and reviewing standard operating procedures (SOPs) under the quality management system. This process involved a critical review and analysis of internal controls and processes throughout the section with particular emphasis on risk management. This system now underpins the internal control environment and feeds into the internal audit process and ultimately into the audit and risk committee.

Remuneration Policy - Authority Members and Executive Directors

Remuneration and travel expenses paid to Authority members are disclosed in note 17 to the Financial Statements. The Chairperson receives remuneration as directed by the Minister for Health in accordance with the Irish Medicines Board Act, 1995. Other Authority members receive remuneration under the terms of the Health (Miscellaneous Provisions) Act 2017. All Authority members are entitled to receive travel expenses in accordance with circulars issued by the Department of Health. The Chief Executive is remunerated in accordance with guidelines issued from Government and other Executive Directors are paid in accordance with Department of Health pay scales. The remuneration of the Chief Executive and Executive Directors are disclosed in note 18 to the Financial Statements.

Internal Control

The Authority is responsible for the HPRA's systems of internal control. Such systems can only provide reasonable and not absolute assurance against material misstatement or loss. The systems of internal controls in use in the HPRA are described more fully in the Chairperson's report on pages 58 to 59.

Disclosures Required by Code of Practice for the Governance of State Bodies (2016)

The Authority is responsible for ensuring that the HPRA has complied with the requirements of the Code of Practice for the Governance of State Bodies, as published by the Department of Public Expenditure and Reform in August 2016. The following disclosures are required by the Code, and are contained in the notes to the financial statements:

- employee short term benefits breakdown,
- consultancy costs,
- legal costs and settlements,
- travel and subsistence expenditure, and
- hospitality expenditure.

Statement of Compliance

The Authority has adopted the Code of Practice for the Governance of State Bodies (2016) and has put procedures in place to ensure compliance with the Code. The HPRA was in full compliance with the Code of Practice for the Governance of State Bodies for 2018.

On behalf of the Authority

Ms. Ann Horan
Chairperson

Mr. David Holohan
Authority Member

Date: 25 June 2019

Statement on Internal Control

Scope of Responsibility

I, as Chairperson, acknowledge the Authority's responsibility for ensuring that an effective system of internal control is maintained and operated. This responsibility takes account of the requirements of the Code of Practice for the Governance of State Bodies (2016).

Purpose of the System of Internal Control

The system of internal control is designed to manage risk to a tolerable level rather than to eliminate it. The system can therefore only provide reasonable and not absolute assurance that assets are safeguarded, transactions authorised and properly recorded and that material errors or irregularities are either prevented or detected in a timely way.

The system of internal control, which accords with guidance issued by the Department of Public Expenditure and Reform, has been in place in the HPRA for the year ended 31 December 2018 and up to the date of approval of the financial statements.

Capacity to Handle Risk

The HPRA has an audit and risk committee comprising three Authority members, which met on 4 occasions during 2018.

The HPRA has outsourced the internal audit function to an independent professional firm, who conduct a programme of work as agreed with the audit and risk committee. During 2018 two internal audit reviews were conducted. Following a tendering process in 2018, a new firm of internal auditors were appointed. During 2018 the new internal auditors carried out a review of the system of internal financial controls.

The HPRA have developed a risk management framework, which sets out its risk appetite, the risk management processes in place and details the roles and responsibilities of staff in relation to risk. This framework has been made available to all staff, who are expected to work within the HPRA's risk management policies, to alert management on emerging risks and control weaknesses, and assume responsibility for risks and controls within their own area of work.

Risk and Control Framework

The HPRA has implemented a risk management system which identifies and reports key risks and the management actions being taken to address, and to the extent possible, to mitigate those risks.

A risk register is in place which identifies the key risks facing the HPRA, and these have been identified, evaluated and graded according to their significance. The register is reviewed and updated by management, considered by the audit and risk committee and presented to the Authority. The outcome of these assessments is used to plan and allocate resources to ensure risks are managed to an acceptable level.

The risk register details the controls and actions needed to mitigate risks and responsibility for operation of controls assigned to specific staff. I confirm that a control environment containing the following elements is in place:

- procedures for all key business processes have been documented,
- financial responsibilities have been assigned at management level with corresponding accountability,
- there is an appropriate budgeting system with an annual budget, which is kept under review by senior management,
- there are systems aimed at ensuring the security of the information and communication technology systems, and
- there are systems in place to safeguard the assets.

Ongoing Monitoring and Review

Formal procedures have been established for monitoring control processes, and any control deficiencies are communicated to those responsible for taking corrective action, and to management and the Authority, where relevant, in a timely manner.
I confirm that the following ongoing monitoring systems are in place:

- key risks and related controls have been identified, and processes have been put in place to monitor the operation of those key controls and report any identified deficiencies,
- reporting arrangements have been established at all levels where responsibility for financial management has been assigned, and
- there are regular reviews by senior management of periodic and annual performance and financial reports, which indicate performance against budgets.

Procurement

I confirm that the HPRA has procedures in place to ensure compliance with current procurement rules and guidelines, and that during 2018 the HPRA complied with those procedures.

Review of Effectiveness

I confirm that the HPRA has procedures to monitor the effectiveness of its risk management and control procedures. The HPRA's monitoring and review of the effectiveness of the system of internal control is informed by the work of the internal and external auditors, the audit and risk committee which oversees their work, and the senior management within the HPRA, responsible for the development and maintenance of the internal control framework.

I confirm that the Authority conducted an annual review of the effectiveness of the internal controls for 2018. This review was carried out at its meeting on 14 March 2019.

Internal Control Issues

No weaknesses in internal control were identified in relation to 2018 that require disclosure in the financial statements.

Ms. Ann Horan
Chairperson to the Authority

Date: 25 June 2019

Comptroller and Auditor General

Report for presentation to the Houses of the Oireachtas

Qualified opinion on financial statements

I have audited the financial statements of the Health Products Regulatory Authority (the Authority) for the year ended 31 December 2018 as required under the provisions of section 18 of the Irish Medicines Board Act, 1995. The financial statements have been prepared in accordance with Financial Reporting Standard (FRS) 102 – *The Financial Reporting Standard applicable in the UK and the Republic of Ireland* and comprise

- The statement of income and expenditure and retained revenue reserves
- The statement of financial position
- The statement of cash flows and
- The related notes, including a summary of significant accounting policies.

In my opinion, except for the non-compliance with the requirements of FRS 102 in relation to retirement benefit entitlements referred to below, the financial statements give a true and fair view of the assets, liabilities and financial position of the Authority at 31 December 2018 and of its income and expenditure for 2018 in accordance with FRS 102.

Basis for qualified opinion on financial statements

In compliance with the directions of the Minister for Health, the Authority accounts for the costs of retirement benefit entitlements only as they become payable. This does not comply with FRS 102 which requires that the financial statements recognise the full cost of retirement benefit entitlements earned in the period and the accrued liability at the reporting date. The effect of the non-compliance on the Authority's financial statements for 2018 has not been quantified.

I conducted my audit of the financial statements in accordance with the International Standards on Auditing (ISAs) as promulgated by the International Organisation of Supreme Audit Institutions. My responsibilities under those standards are described in the appendix to this report. I am independent of the Authority and have fulfilled my other ethical responsibilities in accordance with the standards.

I believe that the audit evidence I have obtained is sufficient and appropriate to provide a basis for my opinion.

Report on information other than the financial statements, and on other matters

The Authority has presented certain other information together with the financial statements. This comprises the annual report, the governance statement and Authority members' report and the statement on internal control. My responsibilities to report in relation to such information, and on certain other matters upon which I report by exception, are described in the appendix to this report.

I have nothing to report in that regard.

Andrew Harkness

For and on behalf of the Comptroller and Auditor General

26 June 2019

Appendix to the report

Responsibilities of Authority Members

As detailed in the governance statement and Authority members' report, the Authority members are responsible for

- The preparation of financial statements in the form prescribed under section 18 of the Irish Medicines Board Act 1995
- Ensuring that the financial statements give a true and fair view in accordance with FRS 102
- Ensuring the regularity of transactions
- Assessing whether the use of the going concern basis of accounting is appropriate, and
- Such internal control as they determine is necessary to enable the preparation of financial statements that are free from material misstatement, whether due to fraud or error.

Responsibilities of the Comptroller and Auditor General

I am required under section 18 of the Irish Medicines Board Act 1995 to audit the financial statements of the Authority and to report thereon to the Houses of the Oireachtas.

My objective in carrying out the audit is to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement due to fraud or error. Reasonable assurance is a high level of assurance, but it is not a guarantee that an audit conducted in accordance with the ISAs will always detect a material misstatement when it exists. Misstatements can arise from fraud or error and are considered material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of these financial statements.

As part of an audit in accordance with the ISAs, I exercise professional judgement and maintain professional scepticism throughout the audit. In doing so,

- I identify and assess the risks of material misstatement of the financial statements whether due to fraud or error; design and perform audit procedures responsive to those risks; and obtain audit evidence that is sufficient and appropriate to provide a basis for my opinion. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the override of internal control.
- I obtain an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the internal controls.
- I evaluate the appropriateness of accounting policies used and the reasonableness of accounting estimates and related disclosures.
- I conclude on the appropriateness of the use of the going concern basis of accounting and, based on the audit evidence obtained, on whether a material uncertainty exists related to events or conditions that may cast significant doubt on the Authority's ability to continue as a going concern. If I conclude that a material uncertainty exists, I am required to draw attention in my report to the related disclosures in the financial statements or, if such disclosures are inadequate, to modify my opinion. My conclusions are based on the audit evidence obtained up to the date of my report. However, future events or conditions may cause the Authority to cease to continue as a going concern.
- I evaluate the overall presentation, structure and content of the financial statements, including the disclosures, and whether the financial statements represent the underlying transactions and events in a manner that achieves fair presentation.

I communicate with those charged with governance regarding, among other matters, the planned scope and timing of the audit and significant audit findings, including any significant deficiencies in internal control that I identify during my audit.

Information other than the financial statements

My opinion on the financial statements does not cover the other information presented with those statements, and I do not express any form of assurance conclusion thereon.

In connection with my audit of the financial statements, I am required under the ISAs to read the other information presented and, in doing so, consider whether the other information is materially inconsistent with the financial statements or with knowledge obtained during the audit, or if it otherwise appears to be materially misstated. If, based on the work I have performed, I conclude that there is a material misstatement of this other information, I am required to report that fact.

Reporting on other matters

My audit is conducted by reference to the special considerations which attach to State bodies in relation to their management and operation. I report if I identify material matters relating to the manner in which public business has been conducted.

I seek to obtain evidence about the regularity of financial transactions in the course of audit. I report if I identify any material instance where public money has not been applied for the purposes intended or where transactions did not conform to the authorities governing them.

I also report by exception if, in my opinion,

- I have not received all the information and explanations I required for my audit, or
- The accounting records were not sufficient to permit the financial statements to be readily and properly audited, or
- The financial statements are not in agreement with the accounting records.

Statement of Income and Expenditure and Retained Revenue Reserves
For the year ended 31 December 2018

	Note	2018 €	2017 €
Fee Income	3	**23,901,603**	24,033,010
Department of Health Funding	3	**4,316,000**	2,941,000
Other Income	4	**888,884**	655,238
		29,106,487	27,629,248
Salaries and Wages	5	**21,160,214**	20,284,686
Other Operating Costs	6	**5,885,565**	6,650,642
Depreciation	2	**1,593,390**	1,983,059
		28,639,169	28,918,387
Surplus/(Deficit) for the year before write back of Superannuation contributions		**467,318**	(1,289,139)
Staff Superannuation Contributions		**696,116**	924,064
Surplus/(Deficit) for the year		**1,163,434**	(365,075)
Balance brought forward		**28,324,679**	28,689,754
Balance carried forward	12	**29,488,113**	28,324,679

The Statement of Income and Expenditure and Retained Revenue Reserves includes all gains and losses recognised in the year. The Statement of Cash Flows and the notes on pages 66 to 75 form part of the financial statements.

On behalf of the Authority

Ms. Ann Horan
Chairperson

Mr. David Holohan
Authority Member

Date: 25 June 2019

Statement of Financial Position
As at 31 December 2018

	Note	2018 €	2017 €
Fixed Assets			
Property, Plant and Equipment	2	24,427,830	25,339,839
Current Assets			
Debtors and Prepayments	7	2,198,340	1,404,687
Inventory of Stationery		3,498	5,133
Cash and Cash Equivalents	9	10,162,555	3,884,050
Short Term Deposits	10	8,216,814	12,302,427
		20,581,207	17,596,297
Current Liabilities - Amounts falling due within one year			
Creditors and Accruals	8	10,760,912	9,058,113
Mortgage	13	793,332	793,332
		11,554,244	9,851,445
Net Current Assets		9,026,963	7,744,852
Long Term Liabilities - Amounts falling due after more than one year			
Mortgage	13	3,966,680	4,760,012
NET ASSETS		29,488,113	28,324,679
Reserves			
Retained Revenue Reserves	12	29,488,113	28,324,679
		29,488,113	28,324,679

The Statement of Cash Flows and the notes on pages 66 to 75 form part of the financial statements.

On behalf of the Authority

Ms. Ann Horan
Chairperson

Mr. David Holohan
Authority Member

Date: 25 June 2019

Statement of Cash Flows
For the year ended 31 December 2018

	Note	2018	2017
		€	€
Cash flows from Operating Activities			
Surplus/(Deficit) for financial year		1,163,434	(365,075)
Depreciation of property, plant and equipment		1,593,390	1,983,059
(Profit)/Loss on Disposal of property, plant and equipment		26	0
(Increase)/Decrease in Debtors		(793,653)	(275,497)
(Increase)/Decrease in Stock		1,635	(104)
Increase/(Decrease) in Creditors - amounts falling due within one year		1,702,799	622,819
Deposit Interest		(16,064)	(21,965)
Bank Interest		181,171	200,601
Cash from Operations		3,832,738	2,143,838
Bank Interest Paid		(181,171)	(200,601)
Net Cash generated from Operating Activities		3,651,567	1,943,237
Cash flows from Investing Activities			
Deposit Interest Received		16,064	21,965
(Increase)/Decrease in Bank Deposits		4,085,613	3,289
Payments to acquire property, plant and equipment		(681,407)	(1,283,637)
Receipts fom sales of property, plant and equipment		0	0
Net cash from Investing Activities		3,420,270	(1,258,383)
Cash flows from Financing Activities			
Repayment of Borrowings		(793,332)	(793,332)
Net cash used in Financing Activities		(793,332)	(793,332)
Net increase/(decrease) in Cash and Cash Equivalents		6,278,505	(108,478)
Cash and Cash Equivalents at beginning of year		3,884,050	3,992,528
Cash and Cash Equivalents at end of year	9	10,162,555	3,884,050

Notes to the Financial Statements
For the year ended 31 December 2018

1. Accounting Policies

A. General information
The Health Products Regulatory Authority (HPRA) is a public statutory body established under the Irish Medicines Board Act 1995 (as amended). The principal place of business is at Earlsfort Centre, Earlsfort Terrace, Dublin 2. The Health Products Regulatory Authority is the competent Authority for the regulation of medicines, medical devices and other health products in Ireland.

B. Compliance with FRS 102

The financial statements of the HPRA for the year ended 31 December 2018 have been prepared in accordance with FRS 102 (the financial reporting framework applicable in the UK and Ireland), as modified by the directions of the Minister for Health in relation to superannuation.

In compliance with the directions of the Minister for Health, HPRA accounts for the costs of superannuation entitlements only as they become payable (see K). This basis of accounting does not comply with FRS102, which requires such costs to be recognised in the year in which the entitlement is earned.

The HPRA is availing of the reduced disclosures allowed by FRS 102 in relation to legal provisions, in instances where full disclosure might prejudice seriously its position in relation to disputes with other parties on the subject matter of the provision.

In all other respects, the financial statements comply with FRS 102.

C. Basis of preparation

The financial statements have been prepared under the historical cost convention. The following accounting policies have been applied consistently in dealing with items which are considered material in relation to the Health Products Regulatory Authority's financial statements.

D. Critical accounting estimates and judgements

The preparation of the financial statements requires management to make judgements, estimates and assumptions that affect the amounts reported for assets and liabilities as at the reporting date and the amounts reported for revenues and expenses during the year. However, the nature of estimation means that actual outcomes could differ from those estimates. The following may involve a higher degree of judgement and complexity:

(a) Provisions
Provisions for legal obligations which it knows to be outstanding at the period-end date. These provisions are generally made based on historical or other pertinent information, adjusted for recent trends where relevant. However, they are estimates of the financial costs of events that may not occur for some years. As a result of this and the level of uncertainty attaching to the final outcomes, the actual outturn may differ significantly from that estimated.

(b) Bad and Doubtful Debts
The HPRA makes an estimate of the recoverable value of trade and other receivables. The HPRA uses estimates based on historical experience in determining the level of bad debts, which the Authority believes will not be collected. These estimates include such factors as the current credit rating, the ageing profile, historical experience of the particular trade receivable and objective evidence of impairment of the asset. Any significant reduction in the level of bad debt provision would have a positive impact on the annual surplus/deficit. The level of provisioning required is reviewed on an on-going basis and has been disclosed in the notes to the financial statements.

Notes to the Financial Statements
For the year ended 31 December 2018

E. Revenue recognition

Revenue is measured at the fair value of the consideration received.

- In the case of applications for marketing authorisations (new applications, variations to existing authorisations, or transfers) and clinical trial applications, income is recognised on a straight line basis over the specified timeline for the processing of the application by the Authority.

- In the case of wholesale and manufacturing licences and maintenance of marketing authorisations, fees are payable annually and a full year's income is accrued in each financial year.

F. Expenditure recognition

Expenditure is recognised in the financial statements on an accruals basis.

G. Reporting currency and currency translation

The financial statements are prepared in euros. Transactions in currencies other than euro are recorded at the rates ruling at the date of the transactions or at a contracted date. Monetary assets and liabilities are translated into euro at the reporting date or at a contracted date. Exchange differences are dealt with in the statement of income and expenditure and retained revenue reserves.

H. Property, plant and equipment

Plant and equipment excluding Premises

Plant and equipment excluding premises are stated at cost less accumulated depreciation.

Depreciation is calculated in order to write off the cost of property, plant and equipment to their estimated residual values over their estimated useful lives by equal annual instalments.

The estimated useful lives of property, plant and equipment by reference to which depreciation has been calculated are as follows:

Fixtures and Fittings:	5 years
Computer Equipment :	3 years
Improvements to Premises :	10 years

Premises

The HPRA purchased its premises at Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2 on 22 December 2004. The value capitalised was equal to the purchase price plus those costs directly attributable to bringing the asset into use.

No depreciation has been calculated on the value of premises, as the remaining useful economic life is estimated to be greater than 50 years.

I. Taxation

The HPRA is exempt from liability to Corporation Tax under Section 227 of the Taxes Consolidation Act, 1997.

Notes to the Financial Statements
For the year ended 31 December 2018

J. Debtors

Known bad debts are written off and specific provision is made for any amount the collection of which is considered doubtful.

K. Superannuation

The superannuation scheme operated by the HPRA is in accordance with the Local Government (Superannuation Revision) (Consolidation) Scheme, 1986. It is an unfunded statutory scheme and benefits are met from current income as they arise.

The scheme is a defined benefit scheme for employees. No provision has been made in respect of benefits payable. Pension payments under the scheme are charged to the income and expenditure account when paid. Contributions from employees who are members of the scheme are credited to the income and expenditure account when received. The surplus/(deficit) for the year is shown both before and after superannuation deductions.

HPRA also operate the Single Public Service Pension Scheme. All new entrants into the public sector with effect from 1 January 2013 are members of this scheme, where all employee pension deductions are paid to the Department of Public Expenditure and Reform.

By direction of the Minister for Health, no provision has been made in respect of benefits payable in future years in relation to the Local Government (Superannuation Revision) (Consolidation) Scheme 1986 or the Single Public Service Pension Scheme.

In order to help meet the cost of benefits payable in future years, reserves have been split between retained reserves and superannuation reserves, which consist of employee superannuation contributions.

This split is shown in note 12 - Movement on Income and Expenditure Reserves.

L. Provisions

A provision is recognised when the HPRA has a present obligation as a result of a past event, it is probable that this will be settled at a cost to the HPRA and a reliable estimate can be made of the amount of the obligation.

M. Library

No value has been placed on the books, audio-visual resources and electronic databases in the library. Expenditure on these items is written off in the year in which it is incurred.

N. Leases

All leases are treated as operating leases and the rentals thereunder are charged to the Statement of Income and Expenditure and Retained Revenue Reserves on a straight line basis over the lease period.

O. Loans

Loans are recognised initially at the transaction price (present value of cash payable, including transaction costs). Loans are subsequently stated at amortised costs. Interest expense is recognised on the basis of the effective interest method and is included in finance costs.

Loans are classified as current liabilities unless there is a right to defer settlement of the loan for at least 12 months from the reporting date.

Notes to the Financial Statements
For the year ended 31 December 2018

2. Property, plant and equipment	Fixtures and Fittings	Computer Equipment	Leasehold Improvements	Improvements To Premises	Premises	Total
	€	€	€	€	€	€
Cost						
Balance as at 1 January 2018	1,227,396	15,783,805	502,445	4,374,608	23,156,037	45,044,291
Additions for the year	12,145	669,262	-	-	-	681,407
Disposals for the year	(960)	(11,451)	-	-	-	(12,411)
As at 31 December 2018	1,238,581	16,441,616	502,445	4,374,608	23,156,037	45,713,287
Depreciation						
Balance as at 1 January 2018	1,171,859	14,132,920	502,445	3,897,228	-	19,704,452
Charge for the year	25,358	1,457,728	-	110,304	-	1,593,390
Disposals for the year	(934)	(11,451)	-	-	-	(12,385)
As at 31 December 2018	1,196,283	15,579,197	502,445	4,007,532	-	21,285,457
Net Book value at 31 December 2018	42,298	862,419	-	367,076	23,156,037	24,427,830
Net Book value at 1 January 2018	55,537	1,650,885	-	477,380	23,156,037	25,339,839

3. Income	2018	2017
	€	€
Fee Income		
Clinical Trials	210,844	192,843
Human Medicine - National Fees	6,927,684	6,196,699
Human Medicine - European Fees	7,311,717	7,050,808
Veterinary Medicine - National Fees	1,856,343	1,553,918
Veterinary Medicine - European Fees	1,662,060	1,499,930
Compliance Department	4,925,873	4,765,340
Medical Devices	1,565,944	2,920,161
	24,460,465	24,179,699
Movement in deferred revenue	(558,862)	(146,689)
	23,901,603	24,033,010
Dept Of Health Funding (Vote 38 Subhead E1)	4,316,000	2,941,000
Other Income (Note 4)	888,884	655,238
Total Income	29,106,487	27,629,248

Certain fees received by the Authority under the Irish Medicines Board Act 1995 (as amended), totalling €19,258,941 in 2018, shall be paid into or disposed of for the benefit of the Exchequer in such manner as the Minister for Public Expenditure and Reform directs.

The HPRA is in discussions with its parent department, as it is some years since the Minister has issued a directive in relation to the fees under Section 13 of the IMB Act.

Notes to the Financial Statements
For the year ended 31 December 2018

4. Other Income

	2018	2017
	€	€
Conference Fee Income	181,842	58,900
Deposit Interest	16,064	21,965
(Loss)/Gain on Disposal of Fixed Assets	(26)	-
IT Income	614,250	519,250
Zambia Project Income	76,754	55,123
	888,884	655,238

5. Salaries and Wages

Basic Pay	18,265,668	17,333,455
Overtime	12,465	6,250
Allowances	169,636	167,802
Staff Short Term Benefits	18,447,769	17,507,507
Retirement Benefit Costs	885,825	1,061,363
Employer's Contribution to Social Welfare	1,826,620	1,715,816
	21,160,214	20,284,686

The average number of staff employed during the year was 332 (2017 - 327).
Payroll numbers at 31 December 2018 can be analysed across the following departments:

Chief Executive	3	3
Compliance	63	69
Finance, Corporate & International	24	23
Human Products Authorisation & Registration	101	110
Human Products Monitoring	33	49
Human Resources & Change	9	9
IT & Business Services	21	19
Medical Devices	36	-
Quality, Scientific Affairs & Communications	13	12
Veterinary Sciences	32	28
Staff	335	322
Authority Members	7	7
Pensioners	39	38
	381	367

One termination or severance payment was made during the year.
Pension related deductions for Public Servants of €874,626 were deducted from staff during the year and paid over to the Department of Health.
Pension deductions for Public Servants who are members of the Single Public Service Pension Scheme of €254,928 were deducted from staff during the year and paid over to the Department of Public Expenditure and Reform.

Notes to the Financial Statements
For the year ended 31 December 2018

Employee's short term benefits are categorised into the following bands:

Salary Band	2018	2017
€0 to €60,000	213	202
€60,001 to €70,000	47	63
€70,001 to €80,000	27	13
€80,001 to €90,000	11	15
€90,001 to €100,000	20	22
€100,001 to €110,000	10	3
€110,001 to €120,000	4	1
€120,001 to €130,000	1	2
€130,001 to €140,000	1	-
€140,001 to €150,000	-	1
€150,001 to €160,000	1	-
	335	322
Average Salary	€54.6K	€52.4K

Higher salaries relate primarily to scientific and other professional staff e.g. clinicians, pharmacists, veterinarians, lawyers etc and are in accordance with Department of Health salary scales.

For the purposes of this disclosure, short-term employee benefits in relation to services rendered during the reporting period include salary, overtime, allowances and other payments made on behalf of the employee, but exclude employer's PRSI.

6. Operating Costs

	2018 €	2017 €
Accommodation Costs	1,210,891	1,177,395
Travel, Representation and Training	1,304,837	909,186
Bank Charges and Interest	187,696	207,643
Legal Fees	657,437	614,829
Audit Fees	32,791	28,578
Stationery, Publications, Postage and Communications	578,144	637,177
Consultancy	331,390	325,354
Sampling and Analysis	252,748	244,789
Other Operating Costs	1,329,631	2,505,691
	5,885,565	6,650,642

Travel costs include an amount of €14,973 related to staff hospitality, and an amount of €537,121 related to travel and subsistence, of which €213,826 is national and €323,295 is foreign.

No costs were incurred in relation to client hospitality. Legal fees are in relation to ongoing legal proceedings, and do not include any amounts in relation to conciliation, arbitration or settlement payments.

Consultancy costs comprise €151,086 related to public relations/marketing, €163,343 related to human resources/ pensions and €16,961 related to other.

Notes to the Financial Statements
For the year ended 31 December 2018

7. Debtors (all due within one year)

	2018	2017
	€	€
Trade Debtors	1,852,256	991,758
Prepayments	211,940	256,440
Other Debtors	134,144	156,489
	2,198,340	1,404,687

Trade debtors are shown net of the bad debt provision.

8. Creditors (amounts falling due within one year)

Trade Creditors	189,511	226,101
Accruals	8,129,067	7,018,843
Deferred Revenue	1,808,497	1,249,634
Revenue Commissioners	633,837	563,535
	10,760,912	9,058,113

9. Cash and Cash Equivalents

Cash at Bank and in Hand	4,027,728	730,979
Demand Deposits (Convertible to Cash on Demand)	6,134,827	3,153,071
	10,162,555	3,884,050

10. Short Term Deposits

Short Term Deposits (not immediately convertible to cash)	8,216,814	12,302,427
	8,216,814	12,302,427

11. Administration Expenses

Surplus for the year was calculated having charged:		
Auditor's Remuneration	18,000	18,000

Notes to the Financial Statements
For the year ended 31 December 2018

12. Movement on Income and Expenditure Reserves

	As At 01/01/2018 €	Income & Expenditure €	Transfer To Pension Reserve €	As At 31/12/2018 €
Retained Reserves	18,544,652	467,318	(400,000)	18,611,970
Staff Superannuation Contributions	9,780,027	696,116	400,000	10,876,143
	28,324,679	1,163,434	0	29,488,113

Our Audit and Risk Committee recommended the transfer of a further €400,000 in 2018 from retained reserves to the superannuation reserve as a result of a number of recent and upcoming retirements, where the costs are quite significant.

13. Long Term Liabilities

Mortgage

On 22 December 2004 the HPRA purchased its premises at Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. The purchase was financed by way of a mortgage, secured on the premises of €20,400,000 over 20 years from Bank of Ireland Corporate Lending.

The HPRA is committed to making the following capital repayments on its mortgage :

	2018 €	2017 €
- within one year	793,332	793,332
- between one and five years	3,173,328	3,173,328
- after five years	793,352	1,586,684
	4,760,012	5,553,344

14. Interest Rate Exposure

The HPRA have taken all necessary steps to minimise its interest rate exposure by fixing 2/3s of the borrowings for the mortgage duration. The balance of the borrowings are fully offset by cash reserves. As the mortgage is at a fixed rate, the Authority has no interest rate exposure.

Notes to the Financial Statements
For the year ended 31 December 2018

15. Financial Commitments

Accommodation Costs (Note 6) includes expenditure of €285,984 in relation to operating leases.

On 28 January 2005 the HPRA signed a leasehold interest in respect of the 5th floor, Alexandra House, Earlsfort Centre, Dublin 2. At 31 December 2018 this lease had 3 years and four months remaining.

	2018	2017
	€	€
The amounts due under this lease are as follows:		
- within one year	285,984	285,984
- between one and five years	667,296	953,280
- after five years	-	-
	953,280	1,239,264

16. Capital Commitments

Contracted For (Contract Signed)	1,404,356	1,775,842
	1,404,356	1,775,842

17. Authority Remuneration

	Fees	Expenses
	€	€
Ms. Ann Horan (Chairperson)	11,970	659
Mr. Pat Brangan	7,695	1,159
Mr. Wilfrid Higgins	7,695	379
Mr. David Holohan	7,695	762
Prof. Mary Horgan	0	711
Mr. Brian Jones	7,695	3,041
Dr. Elizabeth Keane	7,695	572
Prof. Caitriona O'Driscoll	0	924
Dr. Diarmuid Quinlan	7,695	179
	58,140	8,386

Up to the 15 February 2017, other than the Chairperson, no other Authority Member received a salary. On 16 February 2017, the Health (Miscellaneous Provisions) Act was enacted, which made provision for payment of fees to other Authority members, provided that they were in compliance with the 'one person one salary' principle. Two Authority members do not receive a fee under this principle.

Authority expenses comprise €6,410 domestic and €1,976 foreign.

Notes to the Financial Statements
For the year ended 31 December 2018

18. Key Management Personnel Remuneration

	2018	2017
	€	€
Chief Executive	151,500	146,123
Senior Management	832,051	862,273
	983,551	1,008,396

All payments to key management personnel were in respect of salaries and short term employee benefits. No post-employment benefits or termination benefits were paid.

The Chief Executive's and senior management's pension entitlements do not extend beyond the standard entitlements in the model public sector defined benefit superannuation scheme.

19. Related Party Transactions

There have been no transactions with related parties which require disclosure under Financial Reporting Standard 102.

20. Prompt Payment of Accounts

The Health Products Regulatory Authority (HPRA) confirms that it is complying with EU law in relation to prompt payment of accounts.

21. Exchange Rates

The exchange rates used in preparing these financial statements were as follows:

2018 €1 = STG £0.85680
2017 €1 = STG £0.86470

22. Provisions

The HPRA has been notified of a number of legal proceedings or potential proceedings. The Authority has provided in full for its 'best estimate' of the expenditure it is likely to incur in relation to those cases. The Authority is availing of the reduced disclosures allowed by FRS 102 in instances where full disclosure might prejudice seriously its position in a dispute with other parties on the subject matter of the provision.

23. Going Concern

The HPRA has a reasonable expectation, at the time of approving the financial statements, that the HPRA has adequate resources to continue its operations. For this reason, the HPRA continues to adopt the going concern basis in preparing the financial statements.

24. Approval of Financial Statements

The financial statements were approved by the Authority of the HPRA on 02 May 2019.

Appendix 1

2018 Committee Members

Management Committee

Dr. Lorraine Nolan
Chief Executive

Ms. Rita Purcell
Deputy Chief Executive

Dr. Gabriel Beechinor
Director of Veterinary Sciences

Dr. Caitríona Fisher
Director of Quality, Scientific Affairs and Communications

Dr. Joan Gilvarry
Director of Human Products Monitoring

Mr. Kevin Horan
Director of Information Technology and Business Services

Mr. John Lynch
Director of Compliance

Dr. Niall MacAleenan
(Appointed February 2018)
Deputy Director of Medical Devices

M. Lynsey Perdisatt
Director Human Resources and Change

Ms. Grainne Power
(Appointed July 2018)
Director of Human Products Authorisation and Registration

Authority (Board)

Ms. Ann Horan – Chairperson

Dr. Patrick Brangan

Mr. Wilfrid Higgins

Prof. Mary Horgan
(Resigned July 2018)

Mr. David Holohan

Mr. Brian Jones

Prof. Elizabeth Keane

Prof. Caitriona O'Driscoll

Dr. Diarmuid Quinlan

Audit Committee

Dr. Patrick Brangan – Chair

Mr. David Holohan

Prof. Elizabeth Keane

Advisory Committee for Human Medicines

Prof. Mary Horgan – Chair
(Resigned July 2018)

Dr. Kevin Connolly

Prof. Desmond Corrigan

Ms. Maria Egan

Prof. Tom Fahey

Prof. David Kerins

Ms. Fionnuala King

Prof. Patrick Murray

Dr. Fionnuala Ní Ainle

Dr. Brian O'Connell

Mr. Ronan Quirke

Dr. Patrick Sullivan

Advisory Committee for Veterinary Medicines

Mr. Patrick Brangan – Chair

Dr. Ruadhrí Breathnach

Ms. Eugenie Canavan

Dr. Martin Danaher
(Resigned September 2018)

Dr. Helena Kelly

Dr. Nola Leonard

Dr. Bryan Markey

Dr. Ciaran Mellett

Dr. Warren Schofield

Dr. Robert Shiel

Dr. Christina Tlustos

Advisory Committee for Medical Devices

Mr Wilfrid Higgins – Chair

Prof. David Barton
(Resigned December 2018)

Dr. Vivion Crowley

Mr. Ger Flynn

Dr. Fergal McCaffrey

Ms. Margaret O'Donnell

Prof. Martin O'Donnell

Prof. Richard Reilly

Prof. Mary Sharp

Mr. Sean-Paul Teeling

Prof. Sean Tierney

Clinical Trial Sub-Committee of Advisory Committee for Human Medicines

Dr. Patrick Sullivan – Chair
Dr. Liam Bannan
Dr. Geraldine Boylan
Dr. Paul Browne
Dr. Peter Crean
Prof. Lee Helman (CT Expert)
Dr. Filip Janku (CT Expert)
Dr. Catherine Kelly
Dr. Patrick Morris
Dr. Thomas Peirce
Dr. Bryan Whelan
Dr. Jennifer Westrup

Experts Sub-Committee of the Advisory Committee for Human Medicines

Prof. Mary Horgan – Chair (resigned July 2018)
Dr. Linda Coate
Dr. Kevin Connolly
Mr. James Colville
Dr. Noreen Dowd
Dr. Stephen Eustace
Prof. Stephen Flint
Dr. Tim Fulcher
Dr. Joseph Galvin
Dr. Patrick Gavin
Dr. Paul Gallagher
Dr. Kevin Kelleher
Dr. Catherine Kelly
Dr. Mary Keogan
Prof. David Kerins
Dr. Mark Ledwidge
Dr. Frank Murray
Dr. Yvonne O'Meara
Dr. Cormac Owens
Dr. Jogin Thakore
Dr. Gerry Wilson

Advisory Sub-Committee for Herbal Medicines

Prof. Des Corrigan – Chair
Dr. James Barlow
Dr. Kevin Connolly
Mrs. Ingrid Hook
Ms. Claudine Hughes
Ms. Anna-Maria Keaveney
Dr. Celine Leonard
Dr. Donal O'Mathuna
Dr. Camillus Power
Dr. Helen Sheridan
Dr. Emma Wallace

Appendix 2

Presentations 2018

Third Level / Professional Development Presentations and Training

Institution	Course	Presentation Title
An Garda Síochána	Garda Seminar	Approaches to Combating the Unauthorised Sale of Medicines
DG SANTE	Better Training for Safer Food (BTSF)	Approaches to Combating the Online Sale of Prescription Medicines
DIT	Clinical Laboratory Science	Medical Devices and HPRA
DIT	Clinical Laboratory Science	Near Patient Testing And Vigilance
GMIT / IT Sligo	Medical Technology Regulatory Affairs and Quality	New European Regulations on Medical Devices
INFARMED	Joint Action on Market Surveillance (JAMS)	JAMS Work Package 5 Status Update
IT Sligo	Medical Biotechnology and Pharmaceutical Science	GMP, Quality Defects, Biological Medicines and Pharmacovigilance (Case Study based Workshop)
Letterkenny IT	Veterinary Nursing	Regulation of Veterinary Medicinal Products
NIBRT/AbbVie	Bioprocessing and Biologic Medicines	Regulation of Biological and Biosimilars
RCSI	Careers Seminar	Career Overview including Information on Pharmacovigilance
RCSI	Nurse / Midwife Prescribing	The Role of the HPRA and Pharmacovigilance
RCSI	Pharmacy	Quality Defect Investigations and Product Recalls
RCSI	Pharmacy	Regulation Biotech Therapeutics
RCSI	Pharmacy	Regulation of Biosimilars
RCSI	Pharmacy	Regulation of Biotechnological Therapeutics
RCSI	Pharmacy	Regulation of Generic Medicines
RCSI	Pharmacy	Regulation of Generic Medicines and Interchangeable Medicines
RCSI	Pharmacy	Regulation of Medicines
St Johns, Cork	Veterinary Nursing	Regulation of Veterinary Medicinal Products

St Patrick's University Hospital	Staff Seminar	Approaches to Combating the Unauthorised Sale of Medicines
TCD	Immunology	Regulation of Biological Medicinal Products
TCD	Immunology	Regulation of Medicines
TCD	Pharmaceutical Medicine	Biological Medicinal Products: A Regulatory Perspective
TCD	Pharmaceutical Medicine	Biological Medicine Products: A Regulatory Perspective
TCD	Pharmaceutical Medicine	Communication of Safety Data and Overview of WHO Programme for International Drug Monitoring
TCD	Pharmaceutical Medicine	Legal Provisions Governing Product Information
TCD	Pharmaceutical Medicine	Supporting Innovation through Regulation and Science
TCD	Pharmaceutical Medicine	The Role of the CMDh
TCD	Pharmacy	Authorisation of Medicines
TOPRA	Writing Effective Product Information	The SmPC: Regulators Perspective
UCC	Pharmacy	Quality Defect Investigations and Product Recalls
UCC	Safe Prescribing Workshop	Notification of adverse reactions
UCD	Nurse / Midwife Prescribing	The Role of the HPRA and Pharmacovigilance
UCD	Regulatory Affairs	Regulation of Biological Medicinal Products
UCD	Regulatory Affairs	Regulation of Biological Medicinal Products
University of Limerick	Regulatory Affairs	Compiling a Successful Clinical Trial Application

Regulatory Presentations

Event / Organiser	Presentation Title
AdvaMed	MDR/IVDR Implementation
AESGP	Impact of the new European Medical Devices Regulation
Animal Health Awards	HPRA Introduction
BEAI Information Session	Introduction to UDI in the MDR / IVDR
BEAI Information Session	New EU Medical Devices Regulations
Biopharma Ambition Conference	European Regulation for the 21st Century - The Path Forward
British Pharmacology Society	Comparability of Biomedicines: Acceptable Differences in Quality Attributes
CAMD	Brexit - HPRA Perspective on Medical Devices
CAMD	Joint Action on Market Surveillance of Medical Devices
CAMD	Medical Device Fees in Ireland
CAMD	Outcome of Questionnaire on Fees for Medical Devices
CAMD	Outputs of the UDI Taskforce
Clinical Research Development Ireland (CRDI)	Regulation of Clinical Research of Medical Devices
CRDI	The Perspective of the Regulator
Danish Medicines Agency	The EU Regulatory Framework for the Application of 3Rs in Developing and Testing Veterinary Medicines
DCU Brexit Institute	Brexit – Medicine and Public Health
Department of Health, Department of Agriculture, Food and the Marine, HSE	European Antibiotics Awareness Day (HPRA information stand)
DIA CMC Workshop	Drug-Device Combinations: Some Regulatory Considerations
DIA CMC Workshop	How to Maximise the Effectiveness of Prior Knowledge in CMC Submissions
DIA EuroMeeting	A Regulatory Authority Perspective on the New EU Devices Regulations
DIA Europe ICMRA Plenary	Governance Project Update
DIA Japan	Recent Trends in Pharmaceuticals Regulations Globally
DIA Japan ICMRA Plenary	Introduction to ICMRA and the Innovation Project
EMA Stakeholder Workshop	Process Validation and Accelerated Access – Challenges and Solutions
ENVI Committees (European Parliament)	Implementation of the Medical Devices Regulations
European Compliance Academy (ECA)	Continuous Manufacturing
GIRP	Safety Features – Implications for Wholesalers
GIRP Annual Conference	Smart Regulation for Healthcare Innovation in Europe

HMA Working Group of Enforcement Officers	The Road Ahead: WGEO and the HMA Strategy
ICDA	Irish Cosmetic Regulatory Landscape
IDA (India)	Research, Collaboration, Funding and Regulatory Landscape for Global Biopharma Companies in Ireland
IDA Ireland	Medical Devices Regulation in Ireland
IMSTA Information Session	HPRA Brexit Preparedness for Medical Devices
IMSTA Information Session	Regulation (EU) 2017/746 on IVDs
IPU Seminar	Brexit and the Supply of Medicines
Ireland Active Conference	Zero Gains Campaign - The Dangers of Using Anabolic Steroids
Irish Medical Organisation	Responding to Brexit Challenges and Opportunities
Irish Medtech Association	Changing Medical Devices Regulation
ISPE ATMP Seminar	ATMPs - A Regulatory Perspective
Medicines for Europe Conference	Responding to Brexit Challenges and Opportunities
MHRA / JAMS	Status Update on JAMS Work Package 5
Nordic Regulatory Affairs Meeting	HPRA's Initiative to Maintain Medicine Supplies Post Brexit
PDA/FDA Regulatory Conference	The Evolving Regulatory Landscape: An EU and PIC/S Perspective
PFIPC (Enforcement Forum)	Approaches to Combating the Unauthorised Sale of Medicines
Pharma Technical Seminar (EU Commission)	HPRA Brexit Preparedness
PHECC	Inspection of Controlled Drug Sites with Advanced Paramedic and Paramedic Access
Pompidou Group (Council of Europe)	Investigating of the Online Supply of Medical Products
RAPS	CAMD and Roadmap Update
Reducing Medication Errors in Healthcare Services Conference	Medication Errors – The Role of the Regulator
TOPRA Annual Symposium	Cooperation on Combinations and Borderlines
TOPRA Annual Symposium	Outcomes of ICDRA Dublin 2018
TOPRA Annual Symposium	Progress on MDR / IVDR

Appendix 3

Publications and Articles 2018

Drug Safety Newsletters

Edition	Topics
March 86th Edition	– Esmya (ulipristal acetate) – Important new warnings of serious liver injury and recommendations for liver monitoring – Xofigo (radium-223 dichloride) – Contraindication in combination with Zytiga (abiraterone acetate) and prednisolone/prednisone – Mycophenolate – Updated contraceptive advice for male patients – Oral retinoids – Outcome of EU review and updated warnings – Zinbryta (daclizumab beta) – EMA recommendation for immediate suspension and recall – Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter
April 87th Edition	– Epilim (valproate) – New contraindications, strengthened warnings and measures to prevent exposure during pregnancy – Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter
June 88th Edition	– Granulocyte Colony Stimulating Factors (G-CSFs) – Risk of aortitis – Ocaliva (obeticholic acid) – Risk of serious liver injury in patients with pre-existing moderate or severe hepatic impairment – Reminder of differential dosing recommendations – Clarithromycin – Reminder regarding cardiovascular safety and risk minimisation advice – Adverse Reaction Reporting – Reminder – Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter
August 89th Edition	– Xofigo (radium-223 dichloride) – New restrictions for use – Champix (varenicline) – Product information Update – Reports of Transient Loss of Consciousness – Oral Methotrexate – Updates to product Information – Adverse Reaction Reporting – Update – Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

November 90th Edition	– Xarelto (rivaroxaban) – Increase in all-cause mortality, thromboembolic and bleeding events in patients after transcatheter aortic valve replacement in a prematurely stopped clinical trial. – Insulin-containing products – Risk of medication errors associated with extraction of insulin from pre-filled pens and cartridges for reusable pens. – Hydrochlorothiazide (HCTZ) – Risk of non-melanoma skin cancer (NMSC) – Dolutegravir – Neural tube defects reported in infants – Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter
December 91st Edition	– Fluoroquinolone antibiotics – EU review advises restrictions for certain infections and warns of rare but serious long lasting adverse reactions – Adverse Reaction Reporting – Reminder

Human Medicines Articles – External Publications

Month	Publication	Topics
January	MIMS	– Quinine – Reminder of safety profile and potential for Drug-Drug interactions particularly where used for nocturnal leg cramps
February	IMF	– New CPD e-learning module on reporting suspected adverse reactions
	MIMS	– Educational materials and tools for medicines published on HPRA website
	MIMS Respiratory Supplement	– Amoxicillin-very rare reports of DRESS
March	MIMS	– New contraindication for injectable methylprednisolone products containing lactose in patients with cows milk allergy
	MIMS Cardiovascular Supplement	– Domperidone containing medicines - reminder of the risk of cardiac adverse reactions, restricted indication, contraindications, reduced dose and duration of use
April	MIMS	– Gabapentin – Respiratory depression without concomitant opioid use
	MIMS Oncology Supplement	– Xofigo (radium-223 dichloride) – Contraindication in combination with Zytiga (abiraterone acetate) and prednisone/prednisolone
May	MIMS	– Epilim (valproate) – New contraindications, strengthened warnings and measures to prevent exposure during pregnancy
June	MIMS	– Mycophenolate – Updated contraceptive advice for male patients
	MIMS Diabetes Supplement	– Educational materials and tools for medicines published on HPRA website

July	MIMS (July/August issue)	– Clarithromycin – Reminder of cardiovascular safety and risk minimisation advice
	MIMS Respiratory Supplement (July/ August issue)	– Adverse Reaction Reporting - Reminder
August	IMF	– Epilim (valproate) – New contraindications, strengthened warnings and measures to prevent exposure during pregnancy
September	MIMS	– Xofigo (radium-223 dichloride) – New restrictions for use
	MIMS Rheumatology Supplement	– Oral Methotrexate – Updates to Product Information
October	MIMS	– Ocaliva (obeticholic acid) – Risk of serious liver injury with pre-existing moderate or severe hepatic impairment
	MIMS Women's Health Supplement	– Epilim (valproate) – New contraindications, strengthened warnings and measures to prevent exposure during pregnancy
November	MIMS	– Champix (varenicline) – Product Information update – Reports of Transient loss of consciousness
	MIMS Diabetes Supplement	– Insulin-containing products – Risk of medication errors associated with extraction of insulin from pre-filled pens and cartridges for reusable pens
December	MIMS	– Hydrochlorothiazide (HCTZ) – Risk of non-melanoma skin cancer (NMSC)
	MIMS Compendium	– Epilim (valproate) – New contraindications, strengthened warnings and measures to prevent exposure during pregnancy

Veterinary Medicines Articles – External Publications

Publication	Topic
Veterinary Ireland Journal	Brexit impact on availability
It's Your Field	Availability of veterinary medicines in Ireland
It's Your Field	The future availability of veterinary medicines: Latest developments
It's Your Field	Factors affecting the availability of veterinary medicines in Ireland
It's Your Field	Use of antibiotics in dairy cows

New Industry Guidance Documents

Document Title	Month
Guide for distributors of medical devices	February
Guide to new applications and variations to wholesale distribution authorisations	December

Appendix 4

European and National Committee / Working Group Participation

Committee/Working Group	Organisation	Meetings in 2018
Counterfeiting of Medical Products (CMED)	Council of Europe	1
Market Surveillance Forum	Department of Business, Enterprise and Innovation	3
Working Group on Cybercrime	Council of Europe	1
Good Distribution Practice for Veterinary Medicines	Department of Agriculture, Food and the Marine	1
Medicinal Cannabis Expert Reference Group	Department of Health	8
National Clinical Effectiveness Committee (NCEC)	Department of Health	4
Safety features – National coordination group	Department of Health	8
National Interdepartmental AMR Consultative Committee	Departments of Health / Agriculture, Food and the Marine	1
EDQM Committee Meetings	EDQM	1
European Network of Official Cosmetics Control Laboratories (OCCL)	EDQM	1
National Pharmacopoeia Authorities – Annual Meeting	EDQM	1
OMCL (Official Medicines Control Laboratories) Network	EDQM	2
OMCL Network Active Pharmaceutical Ingredient (API) Working Group	EDQM	2
OMCL Network Centrally Authorised Products (CAP) Working Group	EDQM	1
OMCL Network Communications Working Group	EDQM	2
OMCL Network Counterfeit Products Working Group	EDQM	1
OMCL Network Mutual Recognition and Decentralised procedures (MRP/DCP) Working Group	EDQM	1
OMCL Network Uncertainty of Measurement Working Group	EDQM	2
Tissues & Cells Good Practice Guidelines – drafting group	EDQM	2
Biological Working Party	EMA	11
Biosimilar Medicines Working Party (BMWP) – including telecons	EMA	7

Committee for Advanced Therapies (CAT)	EMA	11
Committee for Herbal Medicinal Products (HMPC)	EMA	6
Committee for Medicinal Products for Human Use (CHMP)	EMA	11
Committee for Medicinal Products for Veterinary Use (CVMP)	EMA	11
Committee for Orphan Medicinal Products (COMP)	EMA	11
Efficacy Working Party – Veterinary	EMA	4
Good Clinical Practice (GCP) Inspectors' Working Group (including training seminar)	EMA	3
Good Manufacturing and Distribution Practice (GMDP) Inspectors' Working Group (including meeting of Brexit sub-group)	EMA	3
Heparin Working Group	EMA	1
Immunological Working Party - Veterinary	EMA	3
MAH Good Manufacturing Practice (GMP) responsibilities Working Group	EMA	4
Paediatric Committee (PDCO)	EMA	12
Pharmacovigilance (PV) Inspectors' Working Group (human)	EMA	4
Pharmacovigilance (PV) Inspectors' Working Group (veterinary)	EMA	4
Pharmacovigilance Business Team	EMA	8
Pharmacovigilance Risk Assessment Committee (PRAC)	EMA	11
Pharmacovigilance Working Party - Veterinary	EMA	6
Plasma Master File Meetings - telecon	EMA	5
Process Analytical Technology – including telecon	EMA	4
Quality Defects - Best Practices Working Group	EMA	1
Quality Defects - Risk Working Group	EMA	2
Quality Defects and Rapid Alert Working Group	EMA	2
Quality Review of Documents Working Groups	EMA	3
Quality Working Party	EMA	4
Safety Working Party – Human	EMA	12
Safety Working Party – Veterinary	EMA	4
Scientific Advice Working Party – Human	EMA	11
Scientific Advice Working Party – Veterinary	EMA	11
Signal Management Review Technical Working Group (Methods) – PRAC	EMA	2
Signal Management Review Technical Working Group (SMART) Processes – PRAC	EMA	8
Competent Authorities on Blood and Blood Components	European Commission	2
Competent Authorities on Organ Donation and Transplantation	European Commission	1
Competent Authorities on Tissues and Cells	European Commission	1
Expert Group on Clinical Trials	European Commission	3
Expert Group on Precursor Chemicals	European Commission	1

Expert Sub-Group on Vigilance for Blood, Tissues and Cells, and Organs (VES)	European Commission	2
Expert Working Group on Safety Features (including meetings, telecons & workshop with EMVO)	European Commission	10
IVD Classification working group	European Commission	5
IVD Technical Group	European Commission	3
IVD-CIE Working group	European Commission	3
Joint Action Market Surveillance of Medical Devices (MDs) (including telecon)	European Commission	7
Medical Device – Vigilance MIR Form Development	European Commission	2
Medical Device Compliance and Enforcement working group (COEN)	European Commission	2
Medical Device Coordination Group	European Commission	4
Medical Device Expert Group Vigilance Working group	European Commission	2
Medical Device Periodic Safety Update Reports Working Group	European Commission	3
Medical Device Periodic Summary Report Working Group	European Commission	14
Medical Device Regulatory Committee	European Commission	1
Medical Device Vigilance Eudamed Working Group	European Commission	4
Medical Device Vigilance Guideline Revision 9	European Commission	4
Notified Body Operations Group	European Commission	2
Platform of European Market Surveillance Activities in Cosmetics (PEMSAC) – Market Surveillance	European Commission	2
Rapex System	European Commission	1
Standing Committee on Cosmetic Products	European Commission	3
Working Group on Cosmetic Products	European Commission	3
Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation (VISTART)	European Commission / Health and Food Executive Agency	1
Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation (VISTART)	European Commission / National Competent Authorities	2
Operation MisMed	Europol	1
Operation Viribus	Europol	1
Food Fraud Task Force	Food Safety Authority of Ireland (FSAI)	2
Clinical Trials Facilitation Group (CTFG)	HMA	6
CMDh / GCP Inspectors Sub-Group	HMA	1
Co-ordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh)	HMA	11
Co-ordination Group for Mutual Recognition and Decentralised procedures – Veterinary (CMDv)	HMA	11
Homeopathic Medicinal Products Working Group	HMA	3

Pharmacovigilance Worksharing Procedures Working Party	HMA	11
Risk-based Surveillance Testing – Drafting Group (including telecons)	HMA	6
Working Group of Communications Professionals	HMA	2
Working Group of Enforcement Officers (WGEO) (including management committee)	HMA	4
Working Group of Quality Managers	HMA	2
Device Specific Vigilance Guidance for Insulin Pumps and integrated pump and meter systems	HPRA	2
National Cosmetics Surveillance Forum	HPRA / HSE	4
International Medical Device Regulators Forum (IMDRF) Management Committee	IMDRF	1
Operation Pangea (including liaison meetings)	Interpol	6
Safety features – Irish Medicines Verification Organisation (IMVO)	IMVO	3
Competent Authorities for Medical Devices (CAMD)	National Competent Authorities	2
Quarterly Haemovigilance Meetings	NHO / HPRA	4
National Standards Authority of Ireland (NSAI) – Cosmetic Standards	NSAI	2
Organ Vigilance Working Group	ODTI / HPRA	2
Permanent forum on International Pharmaceutical Crime (PFIPC) annual meeting	PFIPC	2
Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Committee of Officials	PIC/S	1
PIC/S Executive Bureau	PIC/S	2
PIC/S Expert Circle on Quality Risk Management (QRM) (including telecon)	PIC/S	9
PIC/S Sub-Committee on Compliance (including telecon)	PIC/S	2
PIC/S Sub-Committee on Harmonisation	PIC/S	2
UN office of Drugs and Crime (UNODC) – Expert Groupon Falsified Medicinal Products	UNODC	1
Member State Mechanism on Substandard and Falsified Medical Products	WHO	1
WHO Annual National Centres Meeting of Countries participating in the Programme for International Drug Monitoring (PIDM)	WHO	1

HPRA

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