Supporting Innovation through Regulation and Science: Ireland as an Innovation Hub for Health Products

Laurence O’Dwyer  Lorraine Nolan  Caitriona Fisher
Health Products Regulatory Authority, Dublin, Ireland

Keywords
Innovation · Medicines · Medical devices · Research · Translation · Ireland · Health Products Regulatory Authority · Regulatory advice · Collaboration

Abstract
New technologies and our ever-increasing knowledge provide an exciting potential to develop innovative health products that can address challenges such as chronic diseases and ultimately improve outcomes for patients. Ireland has a strategic focus on supporting innovation and offers an ideal environment for health product innovation. This is due to the expertise and experience that is available within the life sciences sector and an established national infrastructure which supports the translation of research into health products in a collaborative manner. The Health Products Regulatory Authority (HPRA) is committed to supporting innovation for health products. Anyone developing an innovative health product can obtain regulatory guidance via the HPRA’s Innovation Office. Scientific advice and a product classification service are also available. The HPRA is actively engaging with innovators through an outreach programme to discuss how regulation can support innovation and to raise awareness of available supports. In order to facilitate the appropriate regulation of innovative therapies, the HPRA is performing horizon scanning to identify innovations at an early stage of development, so that proactive action can be taken to put in place any additional regulatory tools or develop any expertise required to regulate such products and provide safe and timely access for patients.

Laurence O’Dwyer
Health Products Regulatory Authority
Kevin O’Malley House, Earlsfort Centre, Earlsfort Terrace
Dublin D02 XP77 (Ireland)
E-Mail innovationoffice@hpra.ie
Introduction

Patient-focused innovation within the life sciences sector is essential to improve and optimise patient outcomes and to meet the healthcare and economic challenges associated with changing population demographics. According to the United Nations, global life expectancy at birth has increased from 46.98 years during the period 1950–1955 to 70.79 years in the period 2010–2015 [1]. This increase has been made possible by a number of innovations related to the treatment of medical conditions including the development of novel medicines and medical devices, wider availability of vaccines to prevent disease, and organ transplantation. More recently, the sequencing of the entire human genome and the identification of disease-related biomarkers has increased our understanding of the causes of disease and facilitated the identification of potential treatment targets.

Increased life expectancy will result in increased prevalence and duration of long-term chronic diseases. Cancer, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes account for 60% of all deaths worldwide and 76% of deaths in Ireland [2]. The European Commission has highlighted that 70–80% of all healthcare costs in the EU (an estimated EUR 700 billion) are currently spent on chronic diseases [3]. Chronic diseases and related behavioural risk factors also have other economic effects such as reduced employment, lower productivity, reduction in hours worked and wages, and increased spending on social benefits [4].

The Council of the EU has highlighted the importance of patient-focused innovation and the need to facilitate the translation of scientific advances into innovative medicinal products that meet regulatory standards and to accelerate patients’ access to innovative therapies with added value for patients that are affordable to the EU Member States’ health systems [5]. The delivery of such innovations requires engagement and enhanced communication between multiple stakeholders within the life sciences sector including the biopharmaceutical industry, academia, researchers, small and medium enterprises (SMEs), public agencies charged with supporting innovation, and regulators.

The Irish government’s Innovation 2020 strategy reflects the importance which is attached to scientific research and innovation in Ireland [6]. It identifies a number of priority areas related to the health and medical sector and notes that innovation is critical to improving health and well-being. This policy drives a supportive business and research environment in Ireland and a growing culture of collaboration between stakeholders.

As the regulator of health products including medicinal products and medical devices in Ireland, the Health Products Regulatory Authority (HPRA) has identified supporting innovation as one of 5 key strategic goals [7]. This reflects both the high density of innovative industries across the life sciences sector in Ireland and also the presence of an extensive, research, development, and innovation sector within academia and in other areas. As part of this strategic goal, the HPRA has put in place a number of initiatives to strengthen its capabilities and to provide regulatory assistance to innovators developing new health products.

Health Product Innovation: Opportunities for Collaboration to Facilitate Successful Translation

Innovation involves the development of a novel concept, idea, or approach into a prototype, product, or technology that offers real and practical benefits for patients, health providers, or the life sciences sector. We live in an age where there are many exciting new technologies and approaches that offer the potential to significantly improve healthcare
outcomes. Examples of such advances include new chemical and particularly biological medicines, gene therapy and gene editing, personalised medicine, regenerative medicine, 3D printing, point-of-care diagnostics, and robotics. As our understanding of the causes of diseases increases so too does the complexity of products intended to treat and prevent these conditions. This has driven a move towards increased partnership and collaboration in the development of health products reflecting the diverse sources of innovation and the need for specialist expertise to develop more complex products. Products which involve convergence between different regulatory frameworks include drug-device combinations (such as drug-eluting stents) and companion diagnostics, where diagnostic tests based on critical biomarkers are used in conjunction with medicines to identify patients who are more likely to respond to the medicine and/or are less likely to experience significant adverse reactions.

The importance of collaboration is also evident when the sources of new medicines in both the EU and US are analysed. A review of new medicines authorised in the EU between 2010 and 2012 found that 44% of new medicines were originally developed by SMEs, academia, public bodies, or through public-private partnerships [8]. A similar trend is evident in new medicines approved in the USA, where 47% of the new medicines approved in 2016 were in-licensed or acquired through mergers and acquisitions [9]. These data show that although large and medium-sized pharmaceutical companies often act as the marketing authorisation holder for a medicine after it is authorised, the development of a new medicine often involves multiple stakeholders. Therefore, in order to facilitate innovation, it is important to establish an environment that facilitates such collaboration.

The development of new medicines also requires significant investment. The healthcare industry was responsible for 22% of global R&D spending in 2016 by industry, with only the computing and electronics sector making a greater contribution to global R&D spending [10]. The willingness of healthcare companies to invest in research and development is also reflected in the fact that the pharmaceutical and biotechnology industry consistently spent a greater proportion of total revenue on research and development compared to other sectors from 2013 to 2015 [11].

Despite the new technologies and additional knowledge now available and significant investment from many stakeholders, there is still a very high failure rate associated with the development of new medicines, and many commentators have referred to the "valley of death" in drug development. However, increased knowledge in relation to the causes of diseases and the identification of biomarkers to select target patient populations has had a positive impact on improving success rates. A review of clinical development success rates from 2006 to 2015 found that the probability of successfully transitioning from phase I trials to approval increased threefold when selection biomarkers were used to identify patients compared to when selection biomarkers were not used [12]. This is one example of how applying our increased knowledge and collaboration between different stakeholders (such as medicine and diagnostic manufacturers) can improve success rates and facilitate the translation of research into new treatments for patients.

Ireland – An Innovation Hub for Health Products

Ireland is widely recognised as one of the leading global locations for the pharmaceutical and medical devices industry. All of the world’s top 10 pharmaceutical companies have operations in Ireland and 6 of the world’s top 10 selling pharmaceutical products are produced in Ireland [13, 14]. In relation to medical devices, 13 of the largest 15 medical technology companies are based here [14]. Ireland is also seeing the arrival of many emerging interna-
tional companies focused on developing novel treatments and innovative products. There are also over 200 indigenous companies operating in the life sciences sector.

The life sciences industry currently employs over 50,000 people directly, and Ireland has the highest per capita employment of medical technology personnel in Europe. The expertise and experience that exists within Ireland is a key factor in our continued success in attracting international investment – for example EUR 10 billion has been invested in new biological production in Ireland in the last decade, which is one of the highest levels of investment in new biotech facilities anywhere in the world [13].

The Irish government's desire to ensure that Ireland firmly establishes itself as a global innovation leader is reflected in a highly supportive business environment which is facilitated by government agencies including the IDA and Enterprise Ireland. There has also been significant and sustained investment in research and development in recent years, and the Irish government's Innovation 2020 strategy aspires to significantly increase funding in research and development [6].

Public organisations such as Science Foundation Ireland and the Health Research Board are very actively promoting and supporting research and development in Ireland. The emphasis placed on scientific research is reflected in the fact that Ireland achieved a global ranking of 10th in 2016 for the overall quality of its scientific research, an increase of 26 places in only 13 years [15]. Ireland is also placed very highly in the global rankings for individual subjects related to health product innovation including a ranking of 2nd in the world for nanotechnology and immunology and 3rd for material sciences. A recent review found that Ireland has more innovative universities per capita than any other country in Europe [16]. The strong and vibrant academic research sector has also contributed significantly to Ireland's success in attracting funding from Horizon 2010, the EU's programme to support research and innovation. Higher education institutes accounted for EUR 233 million of the EUR 424 million secured by Ireland from this fund up to May 2017 [17].

A particular emphasis is placed on facilitating the translation of academic research into commercially viable products and technologies through collaboration. This is facilitated through a network of specialised, highly capable, and dynamic research centres, by organisations such as Knowledge Transfer Ireland which provide a framework for collaboration between researchers and industry and through a national network of Technology Transfer Offices. This has contributed to Ireland being ranked 1st in the world for knowledge diffusion and 3rd in the world for knowledge and technology output and knowledge impact [18].

The HPRA – Supporting Innovation through Regulation and Science

The HPRA's mission is to protect and enhance public and animal health. Supporting the development of innovative products through effective and appropriate regulation that facilitates safe and timely patient access is fundamental to this role. We have the broadest remit of any corresponding regulatory authority in Europe – it covers the regulation of human medicines (including clinical trials), veterinary medicines, medical devices (including clinical investigations), controlled drugs, blood and blood components, tissues and cells, organs intended for transplantation, and cosmetic products, and the protection of animals used for scientific purposes. As a result, we have significant expertise in many areas related to health products and are ideally placed to support and regulate innovative health products, including those that involve convergence between different product types such as drug-device combinations and companion diagnostics.

There is an ever-increasing awareness among regulators of the need to use our expertise and experience to actively support innovation from an early stage of development. Supporting
innovation in the life sciences sector in Ireland is a key strategic aim for the HPRA in the coming years.

The HPRA has for many years supported the health products sector in Ireland by providing regulatory and technical advice and ensuring compliance with regulatory standards. The strength and reputation of the regulatory system provided by the HPRA is recognised as a significant advantage to the Irish life sciences sector. In recent years, we have also expanded our support to include initiatives to address the needs of researchers and developers of novel health products and technologies. Figure 1 illustrates a number of ways by which the HPRA supports innovation.

Innovation Office

The HPRA Innovation Office was established in 2016 to act as an initial contact point for any organisation or individual developing an innovative health product or technology, who wishes to seek advice from the HPRA in relation to regulatory requirements. Queries can be submitted via a dedicated online query form on the HPRA website or via email, and responses are issued within 20 working days. Regulatory assistance has been provided in relation to human medicinal products (including advanced therapy medicinal products), veterinary medicinal products, medical devices, in vitro diagnostics, drug-device combinations, and cosmetics. The advice has related to novel products (including medicines and medical devices) and new manufacturing or testing technologies. Figure 2 illustrates the origin of queries to the HPRA’s innovation office.

The majority of queries have been received from SMEs, academia, or individuals who are considering the development of an innovative health product or technology. Our innovation office also actively participates in the EU Innovation network, which brings together the European Medicines Agency (EMA) and national competent authorities to discuss innovations related to medicinal products and how they can be best supported by the regulatory network.
**Education and Outreach**

The HPRA recognises the importance of contributing to both undergraduate and postgraduate courses aimed at those who wish to become involved in the development and production of health products. In recent years, we have supported an increasing number of such courses.

As the level of health product research and innovation in Ireland continues to grow, we have established an ongoing outreach programme to facilitate engagement with higher education institutes, research centres, SMEs, and other state agencies who support innovation. The HPRA held an innovation day in May 2017 to highlight available supports for innovation and over 250 people from various backgrounds registered to attend. We have also organised workshops to provide information and support to those engaged in medical device innovation.

In relation to medicines, a clinical trial protocol template has been published to assist sponsors (particularly non-commercial sponsors) when preparing clinical trial applications. We have also held seminars for academic sponsors and investigators in relation to the regulatory requirements for clinical trials.

**Horizon Scanning**

The pace of innovation within the health products sector means that it is a constant challenge for regulators to ensure that our skills and regulatory approaches keep pace with product innovation and new scientific developments. A multi-disciplinary horizon scanning and scientific affairs group has been established within the HPRA to identify innovations that may need new regulatory tools or frameworks, the development of additional expertise or the review of strategic priorities. This proactive approach is intended to identify areas of interest at an early stage of development (well in advance of regulatory submissions). This will help to ensure that the HPRA is in a position to effectively and appropriately regulate innovative products and technologies.

**Classification**

The HPRA has offered a classification service to stakeholders for many years to assist in clarifying whether a product should be classified as a medicinal product, medical device or other type of product. The classification of a product determines the legal and regulatory requirements that will apply to a given product. It is particularly critical to establish this at
an early stage in the development of new innovative products, particularly borderline products or products that involve convergence between different regulatory frameworks. This helps to ensure that the appropriate requirements are considered during product development and can help to avoid significant difficulties in regulatory submissions, which may arise if the appropriate set of requirements has not been followed.

**National Scientific Advice**

National scientific advice is offered by the HPRA to assist companies, academic institutions and/or investigators involved in the development of new or existing medicines. Advice can be sought on preclinical, quality, and specific clinical areas as well as a range of regulatory issues. Scientific advice has been provided for products intended for use in a range of disease areas including skin diseases, respiratory conditions, pain relief, treatment of narcotic overdose and ophthalmic conditions. This complements our ongoing active participation in scientific advice offered at EMA level. In relation to veterinary medicines, the HPRA is one of the main contributors to European scientific advice and Irish delegates chair the Committee for Veterinary Medicinal Products and the veterinary Scientific Advice Working Party in the EMA.

Our compliance department also advise companies establishing new manufacturing sites or making significant changes to existing manufacturing sites. Early discussions are encouraged from the concept stage to discuss the design of the facility, and voluntary engineering inspections are also offered to identify and address potential rate-limiting steps and to help to ensure that validation will meet regulatory requirements.

**Involvement in Groups and Projects Supporting Innovation**

The HPRA participates in a number of groups and projects which share the HPRA’s desire to support the development of innovative health products and technologies.

At a national level, the HPRA has actively contributed to Regulatory Science Ireland, which brings together industry, academia, regulators, and government agencies to facilitate an integrated Irish response to global regulatory science initiatives. Key achievements to date include research projects related to quality defects and biosimilars both of which were supported by the HPRA.

Pharmaceutical Education and Research with Regulatory Links (PEARRL) is a Horizon 2020-funded research and training programme which aims to train future medicinal product innovators. The HPRA is a partner organisation in this project and has facilitated work placements for 4 early stage researchers as well as provided speakers for a regulatory symposium held as part of the project.

The HPRA is an associate in the ADVANCE project, an Innovative Medicines Initiative project to develop a framework to rapidly provide robust data on post-marketing vaccine benefit-risk to support decision making in Europe. We are also a core partner in the Open Medicine project, which is seeking to identify standards and solutions to enable the unambiguous identification of medicinal products across the EU and allow patients to have their prescriptions dispensed in any EU country, thus facilitating the implementation of the cross-border directive.

**Conclusions**

New technologies and our ever-increasing understanding of diseases provide an excellent opportunity to develop new innovative products that offer patients a greater range of treatment options and can ultimately improve patient outcomes. This can be achieved by
stakeholders in the life sciences sector working together to develop new innovative health products and technologies and successfully overcome the challenges associated with clinical development. With its well-educated and highly skilled workforce, significant life sciences industry presence, and strategic focus on supporting research and development, Ireland has an exciting innovation-focused environment and is ideally suited as a location for health product-related innovation. The HPRA recognises the important role that it has to play in this regard and is committed to maintaining the robust and internationally respected regulatory system that facilitates the development of innovative health products and technologies and providing supporting mechanisms which most importantly ensure the best possible health outcomes for patients.

Disclosure Statement

All authors are employees of the HPRA.

Author Contributions

All authors contributed to drafting, reviewing, and editing this communication.

References

1 United Nations, Department of Economic and Social Affairs, Population Division: World Population Prospects: The 2017 Revision, DVD edition.
2 Health Service Executive: Preventing Chronic Disease: Defining the Problem, Report from the Prevention of Chronic Disease Programme. April 2014.
3 European Commission: Health EU Newsletter. Issue 169, February 2016.
4 OECD/EU: Health at a Glance: Europe 2016 – State of Health in the EU Cycle. Paris, OECD Publishing, 2016.
5 Council of the European Union: Council Conclusions on Innovation for the Benefit of Patients. Employment, Social Policy, Health and Consumer Affairs Council Meeting. Brussels, Council of the European Union, December 2014.
6 Department of Jobs, Enterprise and Innovation (Ireland): Innovation 2020. Ireland’s Strategy for Research and Development, Science and Technology. December 2015.
7 Health Products Regulatory Authority: Strategic Plan 2016–2020. March 2016.
8 Lincker H, Ziogas C, Carr M, Porta N, Eichler HG: Regulatory watch: where do new medicines originate from in the EU. Nat Rev Drug Discov 2014;13:92–93.
9 HBM Partners: Trends in US New Drug Approvals. January 2017. http://www.hbmpartners.com/media/docs/industry-reports/Trends-in-New-Drugs-Approvals-2007-2016.pdf (accessed July 25, 2017).
10 Statista. https://www.statista.com/statistics/270233/percentage-of-global-rundd-spending-by-industry/ (accessed July 13, 2017).
11 Statista. https://www.statista.com/statistics/270324/expenditure-on-research-and-development-by-industry-sectors/ (accessed July 13, 2017).
12 Biotechnology Innovation Organisation, Biomedtracker, Amplion: Clinical Development Success Rates 2006–2015. June 2016.
13 IDA: Biopharmaceutical Industry in Ireland. http://www.idaireland.com/how-we-help/resources/infographics/biopharmaceutical-industry-in-ireland/index.xml (accessed August 11, 2017).
14 Irish Exporter’s Association: Top 150 Born in Ireland 2016. http://www.irishexporters.ie/wp-content/uploads/2016/10/Top150_Born_in_Ireland_2016_Final.pdf (accessed July 25, 2017).
15 Science Foundation Ireland: Annual Report 2016.
16 Reuters: Europe’s Most Innovative Universities. 2017. http://www.reuters.com/article/us-reutersrankings-europeuniversities-idUSKBN17Z09T#list (accessed July 13, 2017).
17 Department of Jobs, Enterprise and Innovation: Research and Innovation Key to Sustainable Job Growth. https://www.dje.ie/en/News-And-Events/Department-News/2017/June/29062017.html (accessed July 13, 2017).
18 Cornell University, INSEAD, WIPO: The Global Innovation Index 2017: Innovation Feeding the World. Ithaca, Fontainebleau, Geneva, Cornell University, INSEAD, WIPO, 2017.