OECD Science, Technology and Innovation Outlook 2016

Policy Profile

Health Innovation for rare diseases

Rationale and objectives

Is our therapeutic innovation system in sync with public health needs? Many factors affect the health of individuals and communities. Global, socioeconomic determinants such as income and social status, education, families and communities, food and nutrition, environment, life style, and health care services have led to an epidemiological transition, leading to reduced fertility, lower mortality and ageing of populations OECD, 2016a). Despite significant advances in basic science and technology the vast majority of diseases can neither be prevented nor treated; rare diseases constitute a large part of these (Institute of Medicine, 2010). It has been argued that the current system of therapeutic innovation is not adequate to follow global health, societal and economic trends (Barker, 2016; OECD, 2015b). With a focus on rare diseases, this policy profile discusses policy measures in order to stimulate therapeutic innovation in areas of unmet medical needs.

Demographic changes come along with a massive urbanisation that impacts the spread of communicable diseases (i.e. bacterial and viral infections) and likely increases in psychological stress and mental disorders. Rapid and uncontrolled concentration of populations in cities is often seen in developing countries and can lead to new zoonotic diseases (disease that can be passed between animals and humans), epidemics, and mental illnesses. Peen et al. (2010) have shown that the prevalence of psychiatric disorders has increased by 38% in cities as compared to rural areas.

Population ageing, resulting from a declining fertility rate and rising life expectancy, will exert strong pressure on health systems around the globe (see also chapter 1 on Megatrends for STI and the Policy Profile on *Innovation for an ageing society*). In 2015, there were 608 million people aged 65 or over, accounting for 8.3% of the global population. According to UN estimates (2015) the share of populations 65 years and over is projected to grow between 2015 and 2050, for example in: Africa from 3.5% to 5.9%; in Asia from 7.5% to 18.2%; in Europe from 17.6% to 27.6%); in Latin America and the Caribbean from 7.6% to 19.5%); in North America from 14.9% to 22.7%; and in Oceania from 11.9% to 18.2%. Older people are especially vulnerable to both communicable and non-communicable diseases and are more likely to suffer degenerative diseases which dementia is one of the most frequently seen degenerative conditions, with Alzheimer's disease being its most common form (50-70% of dementia cases). In 2015 over 46 million people live with dementia worldwide; this number is estimated to increase to 131.5 million by 2050. The total worldwide societal cost of dementia in 2015 was USD 818 billion; projected to increase to USD 2 trillion in 2030 (Alzheimer's Disease International, 2015).

Socioeconomic shifts, therapeutic innovation and evolving health care models have contributed to a change in leading causes of mortality from communicable (infectious) diseases to non-communicable (mostly chronic) diseases. Non-communicable diseases, such as cardiovascular diseases, cancers, chronic respiratory diseases, diabetes, and mental disorders were responsible for 38 million (68%) of the deaths worldwide in 2012 and the economic losses are expected to amount to USD 7 trillion in 2025 (World Health Organization, 2014a).The distribution of disease burden is very different between regions and countries (Murray et al., 2012; Vos et al. 2015). In high income countries non-communicable and communicable diseases account for 92%/ 8% (respectively) of the disease mortality rates; in contrast non-communicable and communicable diseases account for 71%/ 29% (respectively) of the disease mortality rates in lower middle-income countries (World Health Organization, 2015). Communicable diseases in children dominate in developing countries and remain a key focus of the United Nations Sustainable Development Goals (SDGs)[1], in particular SDG3 "Ensure healthy lives and promote well-being for all at all ages".

Rare diseases affect 6-8% of the population in the world and can be characterised by a large variety of aetiologies. Their common denominator is a low prevalence in populations. For most of the approximately 6 000 rare diseases there is no treatment available and symptoms must be managed on a regular basis. Rare

diseases are also described as "orphan diseases" because of the limited response of stakeholders in terms of diagnosis, prevention and treatment (Gorry and Montalban, 2014; Online Mendelian Inheritance in Man®, 2016). The reasons for this lack of interest and inadequate progress in R&D are manifold: e.g. complex disease pathologies; knowledge gaps in the molecular and physiological underpinnings of the diseases; too small samples for clinical trials ; high R&D investment needs, and inadequate business models for small markets. Yet, rare diseases cause loss of life, and impose a huge physical, psychological on patients and their families. Despite their low prevalence, the socioeconomic burden of rare diseases is substantial, with indirect health costs (associated with patient or carer productivity losses) often exceeding the level of direct medical costs, such as physician visits, clinical tests and assessments, drugs, and medical devices and aids (Angelis, Tordrup, Kanavos, 2015). Therefore, the development of diagnostics and therapies for rare diseases is an important task that should be taken over by all stakeholders.

Major health challenges ahead relate to:

- **Epidemics**: Communicable diseases are not any more local public health issues. Viral infections become a global threat with a significant impact on health systems and economies. As a consequence of climate change and increasing global mobility regions so far not affected by certain diseases will become more vulnerable to the spread of bacterial and viral infections. Data from the International Air Transport Association (IATA) shows a 45% increase of flight numbers from 2004 (23.8 millions) to 2015 (33 millions)[2]. The emergence of the Middle East respiratory syndrome (MERS) in 2012, the Ebola outbreak in 2014, and the current Zika virus public health emergency are examples of global health threats and highlight the need for a R&D master plan in order to respond fast through vaccination in case of need (Stöhr, 2014).

- **Antibiotic-resistance**: We have entered the post-antibiotic age (World Health Organisation, 2014b). In the United States alone, antibiotic-resistant infections sicken more than two million Americans every year and kill at least 23.000 (2013), as reported by the Centers for Disease Control and Prevention. Failure in antibacterial drug discovery is an important factor in the rise in global resistance (Brown and Wright, 2016). During the last two decades only 22 new antibiotics have been approved by the United States Food and Drug Administration (FDA) – with four in 2015 only (Informa plc, 2016). With these numbers the management of bacterial infection through the use of safe, cheap and plentiful antibiotics can no longer be taken for ensured and collaborative action would be needed in order to deliver global solutions on antimicrobial resistance (O'Neill, 2016).

- **Mental disorders**: According to the World Health Organization around 450 million people currently suffer from mental disorders, placing these conditions among the leading causes of disability worldwide. There is, as yet, no effective treatment for Alzheimer's disease or any other form of dementia. For more than a decade progress on dementia therapy has been limited with a near 100% failure rate of clinical trials for Alzheimer's disease (Cummings, Morstorf, and Zhong, 2014).

- **Paediatric medicines**: Often the effects of drugs have not been studied or licensed for the use in children; age-appropriate formulations for drugs are generally not available (Council of the Canadian Academies, 2014; World Health Organization, 2007; World Health Organization, 2013). The off-label use and 'manufacturing' of medicines (unregulated use of a marketed medicine in certain indications and populations) for treating children is widespread. In January 2007 the "Paediatric Regulation"[3] entered into force in the European Union; aiming to improve the health of children in the European Union through facilitating and incentivising R&D in paediatric medicines. With nine products approved by the European Medicines Agency EMA under the "Paediatric-use Marketing Authorisation" (PUMA) in 2015 alone this policy initiative could prove effective.

Recent advances in precision medicine are encouraging investors to discover the interplay of genes, the environment and life-style in individuals rather than in large populations and in the 'average' patient. New and emerging technologies (e.g. DNA sequencing, genome editing, multimodality imaging, and the use of "big data") have spurred interest in the elucidation of the molecular underpinnings of rare diseases and opened new therapeutic avenues. Pharmaceutical companies no longer disregard rare disease treatments – orphan drug research represents one of the most dynamic business segments (Gorry and Useche, 2016). The question may even be raised whether the vigorous dynamics of orphan drug R&D is just the tip of the proverbial iceberg: a paradigm shifts towards personalized medicine with a new "nichebuster" model (Kakkar and Dahiya, 2014).

Yet, there is still a significant imbalance between medical needs and traditional business strategies in therapeutic innovation (World Health Organization, 2013). Portfolio decisions and R&D investment in the pharmaceutical industry are influenced by scientific, regulatory, strategic, and pharmacoeconomic factors, such as near-term patent expirations for many top-selling drugs, increasing regulatory requirements, and risks of failure during drug development. Pharmaceutical innovators are forced to continuously re-evaluate portfolio strategies and to adopt new, more efficient systems in collaboration with other stakeholders. The leading therapeutic indications of patent approval are: infectious diseases, 15%; oncology, 14%; cardiovascular diseases, 10%; and immune disorders, 8% (Schumacher, Hinder, Gassmann, 2016).

In the pharmaceutical sector the management of intellectual property (IP) constitutes a legal and strategic issue – an important source of competitive advantage. IP rights are important for innovators to protect their inventions and to allow for an adequate return of investment. Successful applications to the major patent offices and regulatory authorities in Europe, Japan, and the United States – key markets for innovative diagnostics and therapies – are widely used as an indication for innovation activity. Besides, substantial growth of patent applications and business is expected in emerging economies such as Brazil, China and India with a strengthening of discovery research and local technological innovation through science-based industries (Deuten, 2015).

Major aspects and instruments

The pharmaceutical market is highly regulated with regulations as important factors that impact therapeutic research and innovation on several levels. Innovators must proof safety, clinical efficacy and cost-effectiveness of their products before and after obtaining marketing authorisation; ethical, legal, and social aspects play an important role during research processes. Major regulatory agencies, for example, the European Medicines Agency (EMA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), and the United States Food and Drug Administration (FDA), are undertaking market-pull initiatives in collaboration with patent offices to incentivise R&D activities in areas of unmet medical needs and significant public health threats, for example, rare diseases, paediatric medicines, and antibiotics.

Beyond public financial support to business R&D, mechanisms for patent term extension and market exclusivity are government policy tools to foster R&D and to strengthen therapeutic innovation in areas of greatest health needs and where investment has been limited. Patent-based indicators are an important measure of R&D trends and technological outputs (OECD, 2014a; OECD, 2016a).

How long are drugs protected by IP rights against imitation and replication? In general, pharmaceutical companies obtain patent rights (20 year patent protection) during upstream research, long before their product candidates are reaching the market. Due to the complex and long R&D processes (8-12 years on average for a truly innovative drug) the effective patent protection period of a marketed drug can be short. Companies need to use the window of patent protected market access to reap the commercial benefits of their innovation in order to compensate for significant R&D investments (Schumacher, Hinder, Gassmann, 2016).

How do medicines regulation, intellectual property rights (IPRs) and market exclusivity work together in health innovation? Recent OECD (2014; 2015b) reports state that IP policy has become a mainstream framework condition that has a broad effect on innovation, among other areas such as trade, competition, taxes and consumer protection. Patents are a form of intellectual property rights that can be granted anywhere along the trajectory of therapeutic R&D. Though many other factors can affect the duration of drug patents, they usually expire 20 years after the filing date. Regulatory authorities evaluate the safety and efficacy of medicines for market approval. The benefit-risk assessment of therapies, disease severity, and the possible impact on health systems are key factors that influence regulatory decision making (Schumacher, Hinder, Gassmann 2016).

Medicines regulation and IPRs play a key role to support research and innovation while balancing societal needs with the requirements of innovators and investors. Overreliance by the pharmaceutical industry on patent protection for already established drugs and risk aversion in genuine innovation can be seen as a short-term strategy to respond to changing markets, limited breakthrough research, and increasing complexity of regulations. In order to encourage private R&D engagement and to compensate pharmaceutical innovators for long development and regulatory review timelines and in order to strengthen their position against generic competitors, governments have stablished policy frameworks that allow for an extension of IP rights and offer market/ data exclusivity, for example:

- **In the United States**: In order to stimulate R&D and to compensate for the long development and regulatory review period innovators in United States can apply for an extension of patent life of a

new human drug product that has never before been approved by the FDA (New Chemical Entity Exclusivity). Under the "Patent Term Restoration Programme"[1] a maximum of 5 years can be restored to the patent after FDA marketing approval, however, the total patent life for the product with the patent extension cannot exceed 14 years. Also, innovators that conduct additional clinical trials on an already established (approved) drug may profit from three years of Clinical Investigation Exclusivity.

- **In the European Union**: Innovators can obtain "Supplementary Protection Certificates" (SPCs) that only become active upon expiration of the original patent and normally have a maximum lifetime of 5 years (total combined duration of patent and SPC normally cannot exceed 15 years). Given the competitive importance of SPCs and their impact on R&D portfolios, markets and health systems the effectiveness and sustainability of SPCs has been subject to considerable scrutiny; related jurisprudence is still evolving (Hayes, 2015). Complementary to the provision of SPCs for innovative medicinal products the EU "Data Exclusivity Directive" came into force in 2005 and offers up to 11 years of non-patent exclusivity (ten years plus one year extension, the so-called 8+2+1 regimen). Medicinal products that fall under the directive profit from ten years of market exclusivity, during which competitor generic products cannot be placed on the market; this includes eight years of data exclusivity, during which generic applicants cannot rely on the dossier (data) of the innovative, original product for the purposes of submitting an application (European Commission, 2013; Hathaway, Manthei, Scherer, 2009).

Policy makers, innovators, and civil society organisations recognise the urgent need for joint action to address persistent gaps in diagnosis and therapy of rare diseases. Despite the small markets rare diseases seem to have become commercially attractive for innovators. There is a recent trend amongst small and medium-sized companies and the pharmaceutical industry towards product development in rare diseases. The confluence of biomedical research, use of new technologies, implementation of policy initiatives, and the stronger engagement of firms provide opportunities to make orphan diseases a public health imperative. An important contribution to the progress made has been to incentivise the development of orphan drugs through the extension of patent lifetime and market exclusivity as policy measures by governments (Table 1). The first legislation to help innovation in orphan drug development was introduced in the United States in 1983 (Orphan Drug Act, ODA), followed by other jurisdictions, such as in Japan (1993), Singapore (1997), Australia (1998) and the EU (2000) (Hall and Carlson, 2014). In addition to the incentives offered through market exclusivity rights and R&D cost reduction, there are accelerated regulatory pathways that aim to expedite the development and approval of drugs for conditions of unmet medical needs..

The most impactful incentive of the EU Orphan Regulation for innovators is 10 year market exclusivity for designated orphan drugs. This includes the protection of products on EU markets from subsequent authorisation of a similar product for the same indication. This market exclusivity can be extended to 12 years if a paediatric investigation plan (PIP) is completed. Market exclusivity is awarded by the Europe Medicines Agency and is linked to a granted orphan designation. Of note: A medicine that has several separate orphan designations for different indications can have several separate market exclusivities if these refer to separate designated conditions. However, there are situations under which the innovator may lose its exclusivity, for example, if the innovator is unable to supply enough of the drug or if a competitor demonstrates that its drug is safer, more effective or otherwise clinically superior. Since the adoption of the EU Orphan Regulation in 1999 and its subsequent implementation in member states there was more than a 50% increase in both the number of orphan drug applications submitted and the number of designations granted during 2009-2015, in comparison with 2000-2008 (European Commission, 2016).

Market exclusivity for orphan drugs in the United States is provided to promote a balance between new drug innovation and generic drug competition. At the FDA the Office of Orphan Products Development (OOPD) aims to advance the evaluation and development of medicinal products that demonstrate promise for the diagnosis and/or therapy of rare diseases. Under the Orphan Drug Act (ODA), signed in 1983, a medicinal product intended to treat a rare disease can receive an orphan designation (or orphan status). In the United States market exclusivity is exclusive marketing rights granted by the FDA upon approval of a drug and can run concurrently with a patent or not (see Table 1).

Table 1. Examples of regulatory initiatives to foster therapeutic R&D in rare diseases

Regulatory authority; name of regulation/ initiative; description and goal	Key measures and incentives for innovation
European Medicines Agency (EMA): Regulation (EC) N° 141/2000 on orphan medicinal products (OMPs) In 1999, the Council and the European Parliament adopted Regulation (EC) No 141/20001 on orphan medicinal products ("the Orphan Regulation") to incentivise research, development and marketing of medicinal products for rare diseases. An orphan designation can also be obtained for drugs with an expected insufficient return on investment.	• Establishment of an "Orphan Medicinal Product Designation"; • 10 years of market exclusivity in which other industry operators are prevented from entering the market with a similar product for the same therapeutic indication. This may be reduced to 6 years if the product is sufficiently profitable; • Access to a centralised procedure allowing immediate marketing authorisation in all Member States and facilitating the availability of medicines to all patients in the EU; • Reduced fees for regulatory procedures; • Assistance by the expert Committee for Orphan Medicinal Products (COMP); • Clinical trial protocol and regulatory assistance; • A repository of all designated and authorised OMP.
United States Food and Drug Administration (FDA): Orphan Drug Act, Public Law 97-414 In the United States, Congress passed the Orphan Drug Act in 1983 to provide incentives for industry investment in treatments for such rare conditions.	• Establishment of an "Orphan drug designation"; • 7 years market exclusivity, but may be reduced if the product is sufficiently profitable; • Federal funding of grants and contracts to perform clinical trials of orphan products; • Tax credits (up to 50% of clinical development costs); • Exemption/ waiver of application (filing) fees; • Assistance by the Office of Orphan Products Development (OOPD) during the development process.
Japan Pharmaceuticals and Medical Devices Agency (PMDA): The Article 77-2 of the Pharmaceutical Affairs Law In Japan the Orphan System was established in Japan by amending the Pharmaceutical Affairs Law (PAL) in April 1993 and entered into force in 1st October.	• Applicants can receive subsidies through the National Institute of Biomedical Innovation (NIBIO) to compensate for development costs; • Applicants can receive guidance and consultation from the Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA), and NIBIO on research and development activities. PMDA provides a priority consultation system; • Preferential tax treatment: 12% of study expenses incurred can be reported as a tax credit; • Priority review for marketing authorization. Lower user fees are applicable to review for marketing authorization; • Extension of re-examination period: After approval, the re-examination period will be extended up to 10 years for drugs and up to 7 years for medical devices.

Note: At the FDA, the Orphan Drug Act (ODA) provides for granting special status to a drug to treat a rare disease or condition upon a sponsor's request. This status is referred to as an orphan designation, or sometimes "orphan status" (see 21 CFR Part 316 - Orphan Drugs). At the EMA, an orphan designation is based on the criteria laid down in Regulation (EC) No 141/2000. Orphan designation is free of charge, and may be obtained at any stage of development before an application for marketing authorisation is made, provided proper scientific justification of the intended use is submitted. In Japan, drugs can be designated as orphan drugs under Article 77-2 of the Pharmaceutical Affairs Law.

Marketing approval does not equal availability: Despite joint efforts EU member states do not homogenously grant access to orphan drugs (Gammie, Lu, Babar, 2015; Schuller, Hollak, Biegstraaten, 2015). The variability of access and pricing schemes between European countries remains a major policy issue for patients, payers and health systems. In the United States patient access to high-priced orphan drugs is dependent on the patient's health insurance status and their ability to pay the portion of the cost of their treatment not covered by the insurance plan (Hall and Carlson, 2014).

Recent policy trends

Pharmaceutical research is entering a new era of open science and use of converging technologies to uncover the genetic and biochemical underpinnings of diseases. Technological advances in DNA sequencing, omics technologies, synthetic biology, and gene editing have given researchers new tools to decipher and treat chronic, non-communicable diseases, that often come with multifactorial pathologies (OECD, 2015b). Several factors have contributed to increasing R&D costs, for example: Decades of 'time lag' between discovery and the translation of potential new drugs into interventions; long development timelines from first in-human testing to market approval (13 years on average today), the increasing use of resource-intensive technologies, and capitalized costs of failure (only 1 out of 100 compounds entering clinical development achieves market approval) have led to an increase in investment costs.

There is a growing understanding amongst stakeholders that the pharmaceutical industry cannot be solely responsible for most of the drug discovery and development in disease areas characterised by complex pathologies, high resource-needs, and limited investment. During the last decade the traditional R&D model of closed innovation has shifted to a new concept of open science and innovation in order to, for example: improve the efficiency in research; increase knowledge spill overs, innovation and efficiencies across the economy and society; foster data-driven science; strengthen the translation of disruptive research from academia into business; address grant challenges; provide evidence for policy making (OECD, 2015b). Multi-stakeholder partnerships have been evolving to share resources, benefits and risks throughout the value chain of therapeutic development to counterbalance decreasing productivity and to fulfil the demand for therapies addressing unmet medical needs (OECD, 2015a).

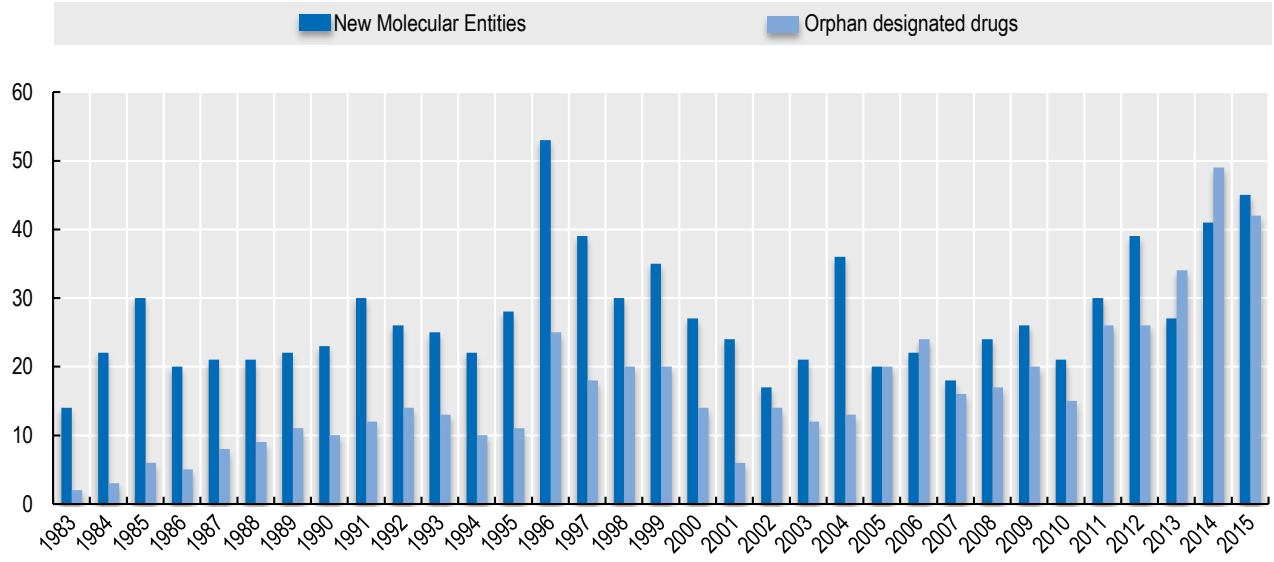
To a large extent, public and private stakeholders have complementary roles and investment strategies, as each has distinct strengths in basic science and pharmaceutical development. The 2016 fiscal year budget of the United States National Institutes of Health (NIH), the largest public funder of biomedical research globally, is USD 32.3 billion[5]. The total private biopharmaceutical R&D investment in the United States was USD 51.2 billion[6] in 2014. Industry investment in pharmaceutical R&D remains high (15% of total revenue), but concentrated in a handful of therapeutic areas that offer sufficiently large and economically viable markets. For example, therapeutics in oncology, diabetes, pain, autoimmune diseases, and hypertension were among the top indications of global pharmaceutical sales in 2015 (Statista, 2016). A similar picture emerges when looking at the recent new novel FDA drug approvals: key indications are oncology, cardiology, infectious diseases, and metabolism and endocrinology (Food and Drug Administration, 2016; Mullard, 2016).

Initially, small markets of rare diseases were unattractive for the pharmaceutical industry. Orphan drug legislations in the United States and the European Union have been successful in terms of research output and delivery of medicines for rare diseases that would otherwise never have been developed: 448 orphan products in the United States and 78 in Europe. Notably, 21 of 45 novel new drugs (mostly new molecular entities, NMEs) approved by the FDA in 2015 were approved to treat rare diseases (17 of 41 in 2014; 9 of 27 in 2013; 13 out of 39 in 2012) (Mullard, 2016).

Innovators see great potential in rare diseases market: from 2012 to 2013 the global orphan drug sales increased by 6.8% to USD 90 billion. EvaluatePharma® (2015) finds that the global market for orphan drugs will grow by 12% per year (compound annual growth rate) between 2015 and 2020 to USD 178 billion. Whilst there is no doubt that the incentives have been of great benefit, the cause of the recent increased interest of pharmaceutical innovators in orphan drug development is likely to be multifactorial; reasons are, for example: patent expiration of mass-market drugs; the need to diversify and increase the value of drug development pipelines; advances in molecular biology and research tools to understand disease pathologies; potential faster market uptake and often high price tags. Also, advances in precision medicine help the identification of small patient populations and the development of highly specific, patient-centred therapeutics.

Figure 1. United States FDA market approvals, 1983-2015

Number of approved new molecular entities and approved orphan designation drugs.



Note: As stated by the FDA[7], many novel new drugs contain active entities that have not been approved by FDA previously, either as a single ingredient drug or as part of a combination product; these products frequently provide important new therapies for patients. Certain drugs are classified as new molecular entities ("NMEs") for purposes of FDA review. An innovator may request orphan drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug.

Source: US FDA (2016), "Novel drug approvals for 2015", http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm; Informa plc (2016), Citeline real-time R&D intelligence, https://citeline.com.

StatLink http://dx.doi.org/10.1787/888933445090

Policy makers and payers, on the other hand, see the expected rise of the orphan drug market in the coming years with concerns about the sustainability of health care budgets. Policy makers aim to ensure that advances in biomedical research and technology that improve quality of life and healthy ageing are made available to populations. At the same time, limited resources and increasing health care demands require an efficient allocation of resources injected in health systems. Governments and other health care payers are increasingly relying on health technology assessment, including economic evaluation, to inform coverage and pricing decisions and understand how to best implement diagnostic and therapeutic innovations into public health systems. Applying standard evaluation methods and cost-effectiveness thresholds to orphan drugs has proved difficult and orphan drugs are often accepted at very high prices. Studies show that the average orphan drug costs per patient was USD 111.820 versus USD 23.331 for a non-orphan drug in 2014 (EvaluatePharma®, 2015). Key policy issues in the current orphan drug market are: lack of harmonisation of orphan designations and R&D incentives across jurisdictions; high drug prices of some orphan drugs; exemption of orphan drugs from standard criteria for reimbursement and pricing; pressure on governments and payers to support R&D in rare diseases and to reimburse treatment costs.

Recently, the Commission's Directorates-General for Health and Food Safety and for Research and Innovation, and the EMA proposed to establish a voluntary cooperation between EU Member States and other relevant stakeholders (industry, patients, health professionals, insurers, etc.) in a project group on a mechanism for coordinated access to orphan drugs. Amongst other priorities, this initiative aims to share experiences and best practices in orphan drug pricing and reimbursement policies to: facilitate decision making (the 'transparent value framework'); support R&D through reduced fees for registration and academic clinical trials, tax reductions or waivers; support early access through 'compassionate-use' programmes to bring unauthorised medicinal products to market (European Commission, 2016).

Notes

1 https://sustainabledevelopment.un.org/?menu=1300.

2 https://www.iata.org/pressroom/facts_figures/fact_sheets/Documents/fact-sheet-industry-facts.pdf.

3 Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006.

4 http://www.uspto.gov/web/offices/pac/mpep/s2750.html.

5 http://www.nih.gov/about-nih/what-we-do/budget.

6 http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf.

7 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm.

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