





A CRITICAL INCENTIVE – NOT A BARRIER!

How IP incentives spur biopharmaceutical innovation and the creation of new health technologies

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LIST OF ABBREVIATIONS

BCI	Biopharmaceutical Competitiveness & Investment Survey
СТ	Clinical Trial
EMA	European Medicines Agency
EU	European Union
FDA	United States' Food and Drug Administration
FDI	Foreign Direct Investment
GDP	Gross Domestic Product
GMP	Good Manufacturing Practices
IP/IPR	Intellectual Property / Intellectual Property Rights
IRB	Institutional Review Board
MoH	Ministry of Health
MoU	Memorandum of Understanding
OECD	Organisation for Economic Cooperation and Development
PCT	Patent Cooperation Treaty
PhRMA	Pharmaceutical Research and Manufacturers of America
PTE	Patent Term Extension
R&D	Research & Development
RDP	Regulatory Data Protection
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UNCTAD	United Nations Conference on Trade and Development
USPTO	United States Patent and Trademark Office
USTR	United States Trade Representative
WTO	World Trade Organization



EXECUTIVE SUMMARY

The debate over the role of IP incentives in innovation is not new. Discussions over the impact – positive or negative; rarely neutral – that IP rights have had and continue to have on the creation and dissemination of new ideas and commercial products is as emotional as it is part of economic and social history.

This is particularly the case for medical and biopharmaceutical innovation where IP incentives are frequently lambasted. At heart of much of this criticism is a deep skepticism of the value that IP rights bring to innovation and biopharmaceutical innovation in particular. It is argued that IP rights per definition limit access to medical products and technologies; lead to high prices; and instead of rewarding 'real' break-through innovation encourage 'ever-greening' and, in effect, rentseeking. Yet while superficially credible, these arguments ignore some of the most basic and elemental facts of the biopharmaceutical R&D process, the nature of IP rights and patient access to medical technologies.

To begin with is the actual process, time required and cost of developing new biopharmaceutical products and technologies. Developing new medicines is not an easy process. The fixed costs in terms of laboratory, research facilities and researchers is high. Compared to many other high tech industries - for example, computer software - developing the next ground-breaking treatment for cancer requires more than just a laptop and a great idea. In 1979, the total cost of developing and approving a new drug stood at USD138 million. Three decades later the total cost of drug development is estimated at approximately USD1.5 billion. On average, only one to two of every 10,000 synthesized, examined and screened compounds in basic research will successfully pass through all stages of R&D and go on to become a marketable drug. This high cost, high failure rate and complexity in creating new medical products and technologies necessitates that innovators have IP based incentives to recoup their R&D investments.

Similarly, looking at the issue of access to medicines (to both new and older products) this is a complex subject that does not lend itself to generalizing. Access involves many different factors such as health system infrastructure, health financing, logistics, transportation networks, proper storage and distribution as well as regulatory capacity. Within this equation the protection of IP plays a relatively small role. For example, the vast majority – over 90% – of medicines viewed as essential (as compiled on essential drugs lists by the WHO and numerous individual countries) are off-patent. Yet patients in many countries – not just least developed countries, but richer middle income countries too – struggle to access these products. Given these are generic medicines IP rights are, per definition, not an influencing or limiting factor.

Report overview

This report provides a drill-down analysis and a sample of case studies showing how IP based incentives have been absolutely key in spurring biopharmaceutical innovation and R&D. The case studies examined include examples of how targeted IP incentives have had a pronounced and positive impact on incentivizing R&D, commercialization of new products and helped many countries build and expand their life sciences sector. The studies range from looking at the availability and impact of special R&D incentives for rare diseases; to IP incentives for new uses of existing biopharmaceutical products; to the impact of IP policies in Singapore, Israel and the US on their domestic life science sectors. Each of these cases show - in concrete, measurable outputs - how IP incentives stimulate new clinical research and the creation and development of new products and technologies.

Key findings

Key finding 1: Orphan drug laws and their provision of market exclusivity incentives have led to significant new research, clinical trials and the development of new drugs for rare diseases

First developed in the US in the mid-1980s, IP based market exclusivity provisions have been at the core of the most successful schemes used to stimulate research into rare diseases globally. The most successful orphan drug schemes are the ones that include a clear and strong IP/market exclusivity incentive. The EU and the US are the leaders in developing new products and technologies for rare diseases and critically both have in place a strong and pronounced IP incentive. Other countries with strong IP incentives (e.g. Japan) have other regulatory barriers in place. Looking at concrete outputs orphan drug schemes in the US and EU have led to sustained and increased number of designations, clinical trials and the approval of new products:

- The number of orphan drug designations in the US, EU and Japan has grown from 150 in 2001 to 557 in 2016.
- A significant and sustained increase in new clinical trials for drugs treating rare diseases has been registered since the introduction of orphan drugs schemes; particularly in Europe. In the EU, orphan drug clinical trials grew by 84% from 2005 to 2015.

- The annual numbers of orphan drug product approvals has also steadily increased. The US continues to have the highest total number of approvals. Only 10 products were approved between 1973 and 1983 compared to more than 575 since then.
- As of end 2016, EU designations have resulted in authorized medicinal products for 101 conditions.

Key finding 2: IP incentives are a key driver in incremental improvements in some of the most heavily prescribed medicines (including insulin, statins, oral contraceptives and beta-blockers) that over time have resulted in radically improved and effective products that are safer and easier to use for patients

Second and new uses for existing drugs and treatments are an essential part of biopharmaceutical innovation. Incentives, such as the ability to patent second and new uses of existing products, are fundamental to continue encouraging investment into continuous improvement and R&D. First generation products are barely comparable to later generation technologies with improvements in delivery, efficacy and a reduction in unwanted side effects some of the most common innovations. Examples of incrementally improved products include:

• Beta-blockers: The first generation of betablockers were non-selective, meaning that they



blocked both types of adrenoceptors (β 1 and β 2). In contrast, second generation beta-blockers are more selective for which types of adernoceptors they block (cardioselective). Third generation beta-blockers also have blood vessel relaxing properties ("vasodilator actions") through their blocking of vascular alpha-adrenoceptors.

• Oral contraceptives: The first generation of oral contraceptives contained very high levels of both estrogen and progestogen which were found to raise the risk of blood clots. Gradually, the concentration of estrogen has been reduced to the minimum amounts needed for safe and effective contraception; from a high of 150 µg with some pills today containing under 20 µg of estrogen. Moreover, modern contraceptives have also introduced phased hormonal dosages through the contraceptive cycle.

• Anti-retrovirals: The first generation of antiretroviral drugs had both serious side effects and were combination therapies requiring the consumption of large volumes of medication several times per day. New therapies have been introduced based on incremental innovations that allow for combination pills. Instead of an array of pills taken every few hours, the most recent products only require a single pill be taken once daily.

Key finding 3: Targeted IP incentives on biotech patentability standards and technology transfer laws introduced in the 1980s are key drivers of the American biotechnology innovation revolution

The US Supreme Court's 1980 decision *Diamond v. Chakrabarty* holding that living matter is patentable when created by human ingenuity put the conditions in place for the development of new biotech based products and technologies. Since 1985 the US has accounted for the largest share of triadic biotechnology patenting activity in the world at just over 43%. Equally the Bayh Dole technology transfer framework and accompanying IP regulations for publicly funded research has had a dramatic impact on the American economy and the life sciences sector. Since the mid-1990s the contribution of academic licensing to gross industry output was estimated at USD282-1,180 billion (measured in 2009 USD), contributions to

GDP at USD130-518 billion creation of 1.1million-3.8million person years of employment. Looking at licensing income for the top US universities and research institutes over USD977million (over 97%) of the USD1billion in total gross licensing income in 2013 came from the life sciences sector.

Key finding 4: IP incentives have been a critical part of national high-tech economic development and the building of cutting-edge biopharmaceutical sectors

Singapore and Israel have relied on IP reforms to build and improve their national life sciences sectors:

- The 2003 implementation of the US-Singapore FTA (negotiations began in 2000) and biopharmaceutical IP reform coincided with a strong rise in biomedical investment levels which grew 10-fold between 2000-2008.
- During this time Singapore grew from a limited manufacturing base to a regional and global biopharmaceutical manufacturing hub – manufacturing in 2013 alone was estimated at SGD23 billion, a value close to 5 times higher than in 2000.
- Similarly the volume of clinical research has close to doubled with a growing emphasis on complex early phase research. Nearly half of clinical trials in Singapore in 2014-15 were for more complex and cutting edge Phase I and II trials.
- Subsequent to Israel's 2010 IP reforms capital raised by the Israeli life sciences sector grew substantially, from just over USD300 million in total in 2010 to over USD800 million in total by 2014. This increase was almost completely driven by foreign investment. In 2010 the foreign share of capital raised was less than 20% of the total. By 2014 this had increased to close to 60%.
- Israel's generic sector (including its national champion Teva) were not adversely affected by the 2010 IP reforms. Since 2010 Teva's R&D expenditure on innovative activities has increased from 44% in 2009 to 55% in 2012, the number of Israeli employees has increased by 17%, and the company's added value has grown by 78%.



INTRODUCTION

Learning from the past – Addressing the major health challenge of the 21st century through IP incentives

It is worth introducing this paper with a look not at what IP incentives have achieved in the past but how they could potentially be used as tools in stimulating the discovery of new solutions for some of the major health challenges of the future. As the global population ages – in part due to medical and pharmaceutical advances one growing challenge we face is the burden of neurodegenerative diseases. Alzheimer's and neurodegenerative diseases are a growing disease challenge to not only the patients and families faced with this disease but also the health system charged with caring for them. The Global Burden of Disease health metrics project estimates that Alzheimer's disease and other dementias are the cause for close to 3.5% of global deaths and an estimated 0.97% of total disability adjusted life years.¹ These global figures are compounded when looking at high-income developed countries with ageing populations including Western Europe, the US and Asia Pacific. Looking only at these high income economies the figures are significantly higher. In these countries Alzheimer disease and other dementias account for almost 10% of deaths and 3.26% of total disability adjusted life years. This is likely to continue to increase as the populations of many high income economies age and economic dependency ratios increase. For example, for the EU Eurostat predicts that by 2040 the dependency ratio within the EU (that is the population primarily over 65 and thought to be outside the labor force) is set to rise to over 45% from less than 30% in 2015.² Looking at the US a 2014 estimate by the Alzheimer's Association suggested over 5 million Americas were currently living with the disease and that it was the sixth leading cause of death in the United States.³ Critically, the number of deaths caused by Alzheimer's increased by close to 70% between 2000 and 2010. The disease has been estimated to cost the US economy US\$200billion per year. And predictions for the coming decades is that as the baby boomer generation ages the disease will present an ever bigger burden costing an estimated USD1.1trillion by 2050 and affecting over 13 million Americans.⁴

Yet despite this growing disease burden the available treatment options for Alzheimer's and other dementias are limited. Despite significant R&D investment over the course of the last two-plus decades the availability of products that mitigate the effects of Alzheimer's is currently extremely limited.⁵ Given these challenges increasing number of research-based manufacturers are pulling out of this therapeutic space and relatively few companies (big or small) are investing resources in developing neurological treatments. The significant research challenge Alzheimer's poses is reflected by both the low number of new technologies under investigation and new products introduced onto the marketplace. Between 1998 and 2015 104 drugs were estimated to be under development for treating Alzheimer's.⁶ Only 3 of these drugs were subsequently approved into actual commercial products. But the most recent of these being in 2003; close to 15 years ago.

As this paper will show there is a blueprint in place to addressing the challenge of Alzheimer's and other disease areas. Building on the success IP based incentives have had in stimulating R&D of new products for rare diseases it is possible to create a similar incentive for research into Alzheimer's disease and other disease areas in which there has so far been limited success? Do the solutions to many of these health challenges lie in our past experiences?

Learning from the past: Case studies in how IP incentives have been critical in driving biopharmaceutical innovation

The purpose of this paper is to provide a drill-down analysis and two thematic case studies showing how IP based incentives have been absolutely key in spurring biopharmaceutical innovation and R&D.

Section 1 of the report focuses on case study analysis of concrete measurable biopharmaceutical outputs that IP incentives have produced. Whether it be the availability of special R&D incentives for rare diseases or incentives for new uses of existing biopharmaceutical products or progressive biotech patentability standards there is a wealth of example on how biopharmaceutical IP incentives have been critical in stimulating both new research and, most importantly, commercialized products helping patients all over the world.

Section 2 of the report broadens the lens looking at the economic impact the life sciences industry has. As a high-tech sector with significant growth potential, countries all over the world are competing to stimulate and grow their domestic life sciences industries and attract international investment. Examples from Israel and Singapore show how IP reforms were an integral part of these two countries' successful efforts to build and reform their biopharmaceutical sectors. In both countries the life sciences industries are now significant parts of their respective national economics contributing to high-tech job creation, economic growth and exports. Indeed, what is interesting about Israel is how a fundamental change in its relationship to biopharmaceutical IP rights beginning in the late 2000s have actually grown both research-based industry and Israel's world-leading generics sector.

Together both of these case studies show in concrete, measurable outputs how biopharmaceutical IP incentives have – and continue to – stimulate new clinical research and the creation and development of new products and technologies.







CASE STUDY 1 IP INCENTIVES AND BIOPHARMACEUTICAL OUTPUTS

I have seen with real alarm several recent attempts, in quarters carrying some authority, to impugn the principle of patents altogether; attempts which, if practically successful, would enthrone free stealing under the prostituted name of free trade, and make the men of brains, still more than at present, the needy retainers and dependents of the men of money-bags.

John Stuart Mill, Principles of Political Economy, 1848⁷

[patents are] injurious to the progress of production and to the common welfare and, thus, illegitimate in the light of the principle of property rights

John Prince-Smith, Über Patente für Erfindungen, 1867⁸

The debate over the role and value of IP rights to innovation is not new. Since the mid-1800s and the "Great Patent Controversy" much ink has been spilled on the role and value of intellectual property rights. This is particularly the case in the area of health care and access to medicines. A subject area which by its very nature is both unique in being highly emotive - this is fundamentally an issue of life and death - and also highly complex in that understanding what shapes health systems and the delivery of care and medicines to patients does not lend itself to simple explanations. And while the arguments, by and large, remain the same, the past few years have seen this debate reignite with real force. The UN High-level Panel's findings and recommendations on leveraging compulsory licensing and other TRIPS flexibilities are but one example.⁹ Looking more broadly a number of countries around the world have either introduced new restrictions on IP rights targeting biopharmaceuticals or amplified existing rules and regulations. 2016, for example, saw both Indonesia and Ecuador introduce new legislation that in effect banned the patenting of second uses of biopharmaceutical and biomedical products and technologies.

At the heart of these debates and policies is a deep skepticism of the value that IP rights bring to innovation and biopharmaceutical innovation in particular. It is argued that IP rights per definition limit access to medical products and technologies; lead to high prices; and instead of rewarding 'real' break-through innovation encourage 'evergreening' and, in effect, rent-seeking. Yet while on the surface credible, these arguments ignore some of the most basic and elemental facts of biopharmaceutical R&D, the nature of IP rights and access to medical technologies.

To begin with is the actual process, time required and cost of developing new biopharmaceutical products and technologies. Developing new medicines is not an easy process. The fixed costs in terms of laboratory, research facilities and researchers is high. Compared to many other high tech industries - for example, computer software - developing the next ground-breaking treatment for cancer or Alzheimer's disease requires more than just a laptop and a great idea. Furthermore, as medicines become more targeted and technically sophisticated the cost of development rises dramatically. In 1979, the total cost of developing and approving a new drug stood at USD138 million. Almost 25 years later, in 2003, this figure was estimated to have rocketed to USD802 million.¹⁰ A more recent estimate points to the total cost of drug development being approximately USD1.5 billion.¹¹ In addition to cost there is also the challenge of successfully developing new

medicines and technologies and the length of time spent on developing a drug. On average, only one to two of every 10,000 synthesized, examined and screened compounds in basic research will successfully pass through all stages of R&D and go on to become a marketable drug. It takes between 10 and 15 years from the filing of a new patent to the day when a new medicine finally becomes available for patients to use.¹² This high cost, high failure rate and complexity in creating new medical products and technologies necessitates that innovators have IP incentives to recoup their R&D investments.

Second, looking at the issue of access to medicines (to both new and older products) this is a complex subject that does not lend itself to generalizing. Access involves many different factors such as health system infrastructure, health financing, logistics, transportation networks, proper storage and distribution as well as regulatory capacity. Within this equation the protection of IP plays a relatively small role. For example, the vast majority - over 90% - of medicines viewed as essential (as compiled on essential drugs lists by the WHO and numerous individual countries) are off-patent.¹³ Yet patients in many countries - not just least developed countries, but richer middle income countries too - struggle to access these products. Given these are generic medicines IP rights are, per definition, not an influencing or limiting factor. India is a good example of this. This is a country which, in most respects, has an IP regime outside international standards with weak protection for biopharmaceutical IPRs. Indeed, in 1970 with the introduction of the Patent Act, India made a strategic decision to ban product patents on pharmaceuticals, among other inventions. Though (as part of the TRIPS Agreement) amendments to the Indian Patent Act in 2005 re-introduced product patents for pharmaceuticals, they also inserted new restrictions on what may be patented. Most notably Indian patent law has in place an additional requirement to patentability

FIGURE 1 Association between the International IP Index life sciences-related indicators' scores and clinical trial activity



IP Index 5th edition, life sciences-related indicators scores, standardized to 100
 Number of clinical trials registered in Clinicaltrials.gov to date per million population

that goes beyond the required novelty, inventive step, and industrial applicability requirements of TRIPS. Under Section 3(d) there is an additional "fourth hurdle" with regard to inventive step and enhanced efficacy that limits patentability for certain types of pharmaceutical inventions and chemical compounds.¹⁴ Moreover, a number of court cases have established a very narrow interpretation of Section 3(d), leading to several patent rejections and revocations of patents that have been granted by the largest patent offices in the world.¹⁵ On top of Section 3(d) Indian patent law also allows for compulsory licensing of biopharmaceuticals outside of public emergencies. Although the Indian Government has only issued one compulsory license (on the cancer drug Nexavar, on the grounds of cost and lack of sufficient local manufacturing of the product), it has maintained an ongoing discussion on issuing additional compulsory licenses for many more biopharmaceuticals.¹⁶ More broadly, India does not offer a term of patent restoration for delays caused

by the market approval process nor does it offer a term of regulatory data protection for submitted clinical test data; both IP rights which are becoming standard practice not only among developed OECD economies but also a growing number of middle-income countries. Yet despite these heavy restrictions on biopharmaceutical IP rights, the Indian health system does not provide its citizens with excellent access to medicines. Indeed, access to health care and pharmaceuticals remains limited for large parts of the population. For example, close to three quarters of Indians living in rural areas have limited or no access to basic care, including pharmaceuticals.¹⁷ This despite the fact that generic manufacturing dominates the domestic market and the considerable extent of the Indian generics industry has brought it the name "pharmacy of the developing world".¹⁸ India spends a very small amount – only around 4.2% – of its GDP on healthcare, and significant inequality exists among the services that are provided.¹⁹

FIGURE 2 Association between the International IP Index life sciences related indicators' scores and early-phase clinical trial activity²⁰



IP Index 5th edition, life sciences-related indicators scores, standardized to 100

Number of early phase (1+2) clinical trials registered to date, adjusted per million population



Finally, and most importantly, the track record to date shows quite clearly that the vast majority of new biopharmaceutical products developed since the early 1980s have been developed in countries with not only a strong technical R&D infrastructure and capacity, but also strong IP based protections and incentives. Data on global NCEs developed by firm nationality by Grabowski et al for the two decades between 1982-2003 show that out of the 919 NCEs analyzed only 20 (or just over 2%) were developed outside the US, EU and Japan; all jurisdictions with strong and clear IP incentives and protections in place.²¹ Indeed, looking at rates of biopharmaceutical R&D as captured by rates of clinical research there is a clear correlation between the availability of IP incentives and rates of clinical trials. Countries with strong IP incentives in place tend to also see higher levels of clinical research and biopharmaceutical R&D. Work done by the US Chamber of Commerce in their International IP Index have examined this relationship finding a statistically significant correlation between clinical research and IP incentives.²² On the preceding pages figures 1 and 2 show the results of this research.

As both figures show looking at both general gross levels of clinical research and more cutting edge, riskier early phase trials countries that have strong biopharmaceutical IP incentives in place have significant higher levels of clinical trial activity.

In this sense the bottom-line evidence is quite clear: biopharmaceutical innovation relies on the availability of IP incentives.

The following subsections will flesh out this finding. They will provide additional examples and details on how tailored biopharmaceutical IP incentives have stimulated new R&D and the development of new biopharmaceutical products and technologies. We begin with what is perhaps the most telling example of all: rare diseases.

1.1 A success story: How using IP rights and R&D incentives has sparked a sea-change in drug development for rare diseases

Introduction

Orphan drugs are niche treatments for diseases with small patient populations and commercial markets. Since the 1980s, a series of financial and regulatory incentives have managed to reverse the lack of commercial attractiveness and convince innovators to invest in these drugs. On the back of these schemes, as well as key pharmaco-genomics discoveries that fuelled interest in development of niche products,²³ the number of orphan drugs developed and authorised for rare diseases has increased exponentially. In 2016, orphan drugs generated revenues of \$114bn, roughly 12% of the total innovative biopharmaceutical market.²⁴ The segment is set to continue growing at a faster pace than non-orphan drugs, and are estimated to account for one out of five sales of prescription drugs in 2022.25

Developing new treatments for rare disease – a critical challenge

Nonetheless, substantial unmet medical and social needs persist. The number of rare diseases has risen to 6,000,²⁶ with around 250 new conditions described in the medical literature every year²⁷ and a growing quantity of disease genes identified.²⁸ Most of these conditions continue to lack a proper treatment. Approved drugs in the US and the EU currently cover only between 1-4% of known rare diseases,²⁹ although R&D efforts are ongoing for many more.³⁰

Commercial, clinical and regulatory challenges are associated with the development of treatments for rare diseases. The fundamental challenge is that these treatments are less likely to be developed by biopharmaceutical companies because their market is small and expected profits are too limited to cover the substantial R&D costs.³¹ In addition, the clinical development process is faced with difficulties linked to the unique characteristics of rare diseases, including the limited number of patients available for trials and few specialized investigators, but also scarce scientific literature and generally limited information on the natural history and mechanisms of the condition being investigated. These elements can translate into difficulties recruiting and retaining patients for trials, identifying comparators and endpoints and defining adequate pre-clinical models.³² Overall, knowledge gaps increase development risks and uncertainties, notably for those diseases for which no treatment has yet to be approved. What is more, clinical challenges make it difficult to create evidence for drug registration. Further regulatory difficulties are linked to changing or unclear treatment and monitoring guidelines.

Acknowledging these challenges, many countries have enacted laws and developed special programs to encourage orphan drug development through regulatory and financial incentives such as marketing exclusivity, tax credits, research grants, faster and cheaper drug approval, and scientific assistance. These wide-ranging measures shorten time to market by lowering development costs, accelerating review time and facilitating interactions with regulatory agencies. Critically, as will be discussed throughout this sub-section, the most successful of these policies include a significant market exclusivity or IP rights component.

1.1.1 The big 3: Orphan drug schemes in the US, EU and Japan

While the US was first in developing a set of initiatives and programs targeting the development of new treatments for rare diseases, both Japan and the EU have over the last two decades introduced similar policies. The below sub-section will compare the three schemes – their working methods, applicability and rewards offered. While other countries have also introduced orphan drug legislation and specific programs to spur innovation for rare diseases, it is worth beginning with a thorough review of the programs in the US, EU and Japan for two reasons. First, these incentive programs are the most comprehensive. And second, from a drug developmental perspective, these three jurisdictions are responsible for the vast majority of global biopharmaceutical innovation and development of new medical products and technologies both generally as well as for rare diseases.

Working arrangements

In addition to pursuing the same end-goal of incentivizing new research and new viable treatments for rare diseases, orphan drug schemes in the US, EU and Japan³³ are based on similar – but not identical – definitions, criteria and procedures, involving the facilitation for developers and early dialogue with regulatory institutions. In particular, two regulatory mechanisms are pertinent to orphan drugs: designation and marketing authorization.³⁴

Orphan drug designation

To benefit from existing incentives, proposed drugs and treatments in all three jurisdictions have to fulfill a series of criteria concerning disease prevalence, seriousness and existing treatments that allow them to be defined as "orphan".

First, orphan drugs have to treat rare diseases, defined with different prevalence criteria. In the US, rare conditions are those affecting less than 200,000 US citizens.³⁵ In Japan the threshold is set at 50,000, but was expanded in 2015 to cover also 'intractable diseases'³⁶ affecting up to 180,000 Japanese (0,1% of population) such as Parkinson's diseases.³⁷ In the EU, rare diseases are those occurring in a maximum of 5 out of 10,000 people. In addition to population prevalence based criteria, if it can be demonstrated that marketing of a treatment would not generate sufficient return of investment in the US and EU rare diseases can also be defined as those lacking profitability. This is meant to cover common diseases that are largely more prevalent in developing countries.

Japan does not include this criterion, but since 2006 orphan designation also to be granted for vaccines for infectious diseases rare in Japan or, if not affecting the Japanese population, whose indication targets travelers.³⁸ This difference in scope and targeting of vaccines explains much of the higher prevalence of vaccines among orphan drugs developed in Japan compared to the US and EU.³⁹

Second, to receive orphan designation, in all three jurisdictions drugs should constitute the first available treatment for that disease or, when a satisfactory treatment already exists, the sponsor should establish that the product will be "clinically superior" (US), provide a "significant benefit" (EU), or provide a major contribution to patient care in terms of "higher efficacy and/or safety" (Japan).⁴⁰ (Japan adds to these two criteria a further requirement whereby sponsors should provide a theoretical rationale for the use of the product for the target disease, and an "appropriate" development plan to prove feasibility of development. This higher threshold results in laterstage designations in Japan compared to the US and EU (see below).) Under all three frameworks,



designation can be requested at any stage of development prior to requesting marketing authorization. Around one out of four designations in the EU is based on preclinical data,⁴¹ and one out of three in the US (of which 2% are based on in vitro study data).⁴² Orphan drug designation is not exclusive, but can be granted to more than one sponsor applying for the same drug indicated for the same rare disease. Although not formally forbidden, the Japanese Ministry of Health, Labor and Welfare usually does not support development of two drugs with the same indications.⁴³ In the US and EU sponsors have to submit a yearly report on the status of development of the designated drug.⁴⁴ Of note is that both in the US and the EU sponsors will have to demonstrate upon approval that their drugs are clinically superior to similar products approved after they received orphan designation in order to benefit from the enhanced market exclusivity provisions.⁴⁵ However, only in the EU will orphan status be withdrawn if the disease prevalence of the conditions increased after designation was received.⁴⁶ No similar second check takes place in Japan.

Orphan drug marketing approval

Designated orphan drugs have to comply with the same high standards for marketing approval as any other submitted product. As concerns the EU, orphan drugs⁴⁷ can be authorized by the EMA only, not by national authorities.⁴⁸ Both the EU and US (since 2013⁴⁹) foresee the possibility to repurpose approved drugs for additional indications, and market exclusivity will run independently for each of them. In the EU orphan designation is reconsidered after 6 years, and in Japan orphan drug status gives right to extend by two years the marketing authorization re-examination period ie the Japanese equivalent to RDP. International liaison, including joint applications and cross reliance, has grown more and more common. In 2012, 62% of orphan drug applications were submitted in parallel in the US and EU.⁵⁰ FDA and EMA orphan drug designations are recognized by various other regulatory agencies such as Australia and Taiwan.⁵¹

Table 1 provides a summary overview of the key characteristics of orphan drug schemes in the US, EU and Japan.

TABLE 1 Comparison of orphan drug schemes in the US, EU and Japan

		US	EU	Japan	
Date introduced		1983	2000	1993	
Legislative basis		Orphan Drug Act; FDA implementing regulations at 21 CFR part 316 ⁵²	Regulation (EC) No 141/2000	Pharmaceutical Affairs Law, chapter 9 -3; Orphan Drug Regulation	
Institutions involved		FDA/Office of Orphan Products & Development (OOPD)	EMA /Committee for Orphan Medicinal Products (COMP)	Ministry of Health, Labour and Welfare/Pharmaceutical Affairs & Food Sanitation Council	
Orphan drug d	esignation criteria	a			
Treats a rare disease	Rarity: Prevalence of the disease per 10,000 inhabitants	Around 7,5 (<200K people in the US) OR no sufficient return on investment	5 (around 250,000 people) OR no sufficient return on investment	Around 4 (<50K people in Japan) and around 14 for 'intractable' diseases	
	OR: lack of profitability	Yes	Yes	No	
	Seriousness of the condition	No	Yes ("life-threatening or chronically debilitating condition")	Yes ("serious diseases, including difficult-to-treat diseases")	
Is the first drug for that disease or is clinically superior to an already available treatment		Yes ("clinical superiority")	Yes ("Significant benefit")	Yes ("Extremely higher efficacy and/or safety")	
Other criteria		-	-	High possibility of development	
Marketing app	roval				
Annual report marketing	prior to	Yes	Yes	No	
Re-evaluation of prevalence upo	evaluation of rare disease No valence upon marketing		Yes (re-evaluation report of orphan status)	No	
Re-evaluation of superiority' (if product was ap meantime)	of 'clinical a similar oproved in the	Yes	Yes (re-evaluation report of orphan status and, if needed, similarity report) ⁵³	No	
Post-marketing	approval				
Repurposing for rare diseases of approved products (with or without another indication for rare disease)		Yes	Yes	No	
Granting of de reconsidered	signation is	No	Yes (6 years)	No	

Source: FDA, EMA, MHLW; Pugatch Consilium analysis (2017)

1.1.2 Incentives

Orphan drug schemes provide different mixes of incentives. Of these, some are related to financing and are intended to allow sponsors to recover R&D costs, notably market exclusivity, subsidies, tax credits and fee waivers. Other incentives aim at accelerating or facilitating regulatory and administrative procedures, such as fast-track approval and scientific advice. As shown below in Table 2, market exclusivity constitutes the backbone of the incentives mix devised by the FDA, Japanese authorities and EMA, coupled with important tax credits in the US. Most direct R&D incentives are granted during the development phase, whereas market exclusivity follows approval of a designated orphan drug.

Exclusivity period

Orphan drug market exclusivity is widely regarded as key to the capacity of orphan drug schemes to foster more R&D into rare diseases. It ensures that regulators will not approve applications for generic products or secondary inventions based on the same active substance and same indications, even if the second application is based on independent data.⁵⁷ This is critical when comparing the exclusivity provided by orphan drug designation versus for example standard forms of regulatory data protection. Protection under RDP does not preclude the submission of independent clinical data in support for a market approval. Instead, RDP only provides protection during the specified term against the reliance by a follow-on applicant on the submitted clinical test data. While there are

	US	EU	Japan	
Exclusivity period	7 years	10 years (+2 for pediatric)	10 years	
Tax incentives	Tax Credits 50% of clinical trials costs	Provided by single member states	12% of study costs (excluding grant subsidies) for both clinical and non-clinical research	
Accelerated MA procedure	If qualifies for priority review	If qualifies for accelerated review	Yes (from 12 to 9 months)	
Waiver of MA fees	ver of MA fees Yes		25% discount	
Discounted scientific advice/ protocol assistance	No	Yes (free for SMEs, 70% discount for others)	Yes (discount granted from Drug Agency only)	
Grants	 Designation not a grant requirement⁵⁴ FDA Office of Orphan Products Development (OOPD) grant program; subsidizes development and pre-clinical studies since 2016 Annual budget: around USD 14 million 	 Designation not a grant requirement Over 0.9 billion from 1998 to 2014⁵⁵ Horizon 2020, national funds (coordinated in E-RARE) 	 Designation is a requirement⁵⁶ Up to 50% of development costs; Around half of designated drugs benefit from grant From National Institute of Biomedical Innovation; subsidizes development 	
	• Total: 261 million			
Parallel cumulative incentives	Priority Review Vouchers (neglected diseases and pediatric indications)	-	-	

TABLE 2 Comparison of orphan drug incentives in the US, EU and Japan

Source: FDA, EMA, MHLW; Pugatch Consilium analysis (2017)

TABLE 3 Main differences between patent andexclusivity protection

Exclusivity protection

- Regulatory measure
- Depends on market authorisation/linked to specific indication(s)
- Applies automatically (if statutory requirements are met)
- Can be revoked (orphan exclusivity)

Source: Pugatch Consilium (2017)

Patent protection

Property right

- Depends on fulfilment of patentability criteria/ can be issued anytime during the development of a drug, regardless of the drug's approva status
- Granted by Patent Office
- Can be attacked in court

important differences between jurisdictions, in this sense the type of market exclusivity provided by orphan drug designation is generally stronger (see below Table 3). Compared to patents, the protection ensured by market exclusivity for orphan drugs is generally shorter in time but much less uncertain. Also, while some products are not patentable they can obtain orphan designation.⁵⁸ Finally, orphan market exclusivity derives from a faster and cheaper regulatory procedure, whereas obtaining and protecting a patent is often a long and costly process. Both types of protections have vulnerabilities. Patents can be challenged in courts by competitors or revoked. Both in the EU and US, orphan drug marketing exclusivity can be revoked if a second similar drug targeting the same therapeutic indication can prove to be safer, more effective or otherwise clinically superior.⁵⁹ A second-in-time drug can be marketed also if the sponsor of the first product gives his consent or is unable to ensure a sufficient supply of the drug.⁶⁰

While the EU ensures first player advantage for a longer 10-year term (against 7 years in the US) orphan status can be withdrawn after 6 years if designation criteria are no longer met, including if the drug is sufficiently profitable.⁶¹ In addition, in the EU market exclusivity may be extended by two years if a pediatric investigation plan has been completed when requesting approval, even if results were negative.⁶² However, relatively few products are currently enjoying a 12-year market exclusivity term, as drug developers reportedly prefer to give up orphan designation and benefit from the 6-month patent term extension granted to reward paediatric studies of non-orphan drugs.⁶³ In the US, any drug for which a paediatric study is completed can benefit from six additional months added to all the terms of protection in place for that product (exclusivities, including for orphan drug, and/or patent protection).⁶⁴ Finally, in Japan orphan drugs benefit from an extended data exclusivity period (referred to as 're-examination' period).⁶⁵ of ten years, against eight years for NCEs and four years for new indications of drugs already approved..⁶⁶

Orphan exclusivity runs parallel to other rules on data exclusivity and market protection. As mentioned above, orphan drug exclusivity provide a broader protection than data exclusivity as it prevents competitors from entering the market even if they generated their own data (unless derogations apply⁶⁷). This is the case in both the US and EU, but not Japan where the protection granted to orphan drug is an extension of the data exclusivity term granted to other drugs.

A medicine that has several separate orphan designations for different indications can have several separate market exclusivities. Also, the exclusivity terms for various orphan indications could start at different moments. Hence, its duration can exceed the 12 years data exclusivity granted to biologics in the US, and the 10 (or 11) data and market exclusivity period granted in the EU, if the orphan designation was obtained after the reference product was licensed.⁶⁸

Finally, in the EU protection could be regarded as larger in scope as it covers "similar" products, intended as similar principal molecular structure, same mode of action and same indication.⁶⁹ It is also stronger than the 10-year market protection enjoyed by innovative drugs. Indeed, market protection holds generics and biosimilars from being marketed, but not from being approved by the EMA or national drug authorities.⁷⁰ In the case of orphan drugs, generic and biosimilar applications can be received after the 10-year term only. Finally, in 2015 the EU General Court confirmed the general strength of orphan drug exclusivity and its difference with the 8+2 protection scheme granted to all new drugs. The Court ruled that, when an orphan drug sponsors

TABLE 4 Orphan drug exclusivity in the US, EU and Japan, compared to other exclusivities available

	US	EU	Japan	
Orphan exclusivity	FDA will not approve another sponsor's marketing application for the same drug for the same use or indication for 7 years ⁷¹	A medicinal product which is similar to an orphan medicinal product cannot be validated, even if based on a full, complete dossier for 10 years	10 year data exclusivity (referred to as 're-examination period') during which follow- on applications are not accepted	
Other regulatory sanctioned exclusivities	 Biologics: 12 year reference product exclusivity. Filing for biosimilars based on innovator data cannot be accepted for 5 years, and approved for 7 additional years NCE RDP exclusivity: 5 years New use, dosage form, route of administration, strength: 3 years⁷² 	 New drugs: 8 years of data exclusivity 2 additional years of market protection: generic/ biosimilars applications can be accepted and even approved, but products cannot be placed on the market 1 additional year of data exclusivity for new indications (or market protection if the new indication is approved during the 8 year data exclusivity period)⁷³ 	 New drugs: 8 years New indications, formulations, dosages, or compositions: 4 years 	

Source: Pugatch Consilium (2017)

consent to a competitor entering the market during the exclusivity period, the competitor will benefit from an independent 10 year exclusivity protection for the same product.⁷⁴

Tax credits

Qualified costs incurred between designation and approval can benefits from orphan drug tax credits. The US framework provides subsidies of up to 50% of the cost of clinical testing, at an estimated cost of USD0.8 billion for 2015 expected to increase to US\$1.3 billion in 2019.⁷⁵ The focus on tax incentives is not as strong in other countries. In the EU designated orphan drugs are eligible for national incentives but – as reported by the European Commission⁷⁶ – only two of the 28 EU Member States have tax credits in place, and with a relatively limited scope.⁷⁷ In Japan, up to 12% of the expenses incurred during grant payments from NIBIO can be reported as tax credit.⁷⁸

Grant subsidies

Orphan drugs developers can receive funds to reduce their up-from costs. Japan's framework offers the most generous subsidies of up to half the actual development costs, including payroll costs.⁷⁹ From 1993 to 2013, roughly half of designated orphan drugs received a grant, at an amount between US\$35,000 (Y4m) to US\$630,000 USD (Y72m) per compound. On average the grants amounted to US\$140,000 (Y16m).⁸⁰ Payback clauses apply if the beneficiary makes a profit on the sales of the approved orphan drug exceeding US\$900,000 (Y100m) per year.⁸¹ Unlike the US and the EU orphan designation is a pre-requisite for grant eligibility in Japan.⁸²

EU funds are allocated within the Horizon 2020 Program and complemented by more limited national grants sometimes launched with supranational joint calls (E-RARE). Estimated funds in the area has almost tripled to EUR620 million from 2007 to 2013 compared to the previous five years.⁸³ The US framework finances the Orphan Products Clinical Trials Grants Program⁸⁴ to encourage orphan drug development by both academic and industry developers.⁸⁵ The program allocates roughly US\$15 million per year, with a maximum of US\$400,000 per project over four years for phase II and III trials and a lower threshold for early phase studies. As of 2015, around 10% of approved orphan drugs had benefited from grants.⁸⁶ The 21st Century Cures Act made pre-clinical, observational studies (i.e. human history studies aimed to provide insight on the biology of the disease and inform trial design and conduct) eligible for grant funding for neglected diseases. Enlarging the scope of subsidies to earlier research phases is expected to increase the focus on less investigated rare diseases.87

The US, EU and Japan have also all put in place programs to accelerate development of innovative products addressing serious unmet medical needs ("breakthrough" designation in the US, "PRIME" scheme in the EU and the Sakigake program in Japan)⁸⁸ that ensure early and closer engagement with regulators and submission efficiencies (such as the appointment of a rapporteur/concierge in the EU and Japan and rolling submission in the US) in addition to accelerated review (see below). However, these programs have a more limited scope compared to orphan designation, which, as already mentioned, can also be attributed to new indications and formulations of the same drug.

Accelerated approval

Although not automatically qualified for accelerated market approval procedures, orphan drugs in the US and EU tend to meet criteria for accelerated procedures based upon unmet needs or disease severity.⁸⁹ In 2016, 11 orphan products⁹⁰ benefitted from priority review in the US for drugs that significantly improve previous treatments; on average two months shorter than the standard review period.⁹¹ If eligible for an accelerated assessment for priority products as per Regulation EC/726/2004,⁹² orphan drugs in the EU can be approved in 150 days. Additionally, in the EU designated orphan drugs, as well as any drug treating life-threatening or seriously debilitating conditions, can request conditional approval, whereby the sponsor of the product commits

to complete clinical data within one year after receiving market authorization.⁹³

Only in Japan does orphan designation itself directly result in speedier review; nine months instead of 12.⁹⁴ The Sakigake strategy drafted in 2014 proposes more comprehensive regulatory facilitations to innovative products developed in Japan than the orphan designation. Sakigake designation gives the right to a six-month prioritized review (versus nine for orphan drugs); "substantial" consultation during development resulting in de facto review before application; and assignment of a PMDA manager as a "concierge" to assist all along the process.⁹⁵ Similarly to orphan drug designation, it also provides for an extension of the re-examination period.⁹⁶

Fee waivers

Since 1997 the US fully waives marketing application user fees for orphan drug developers. Japan provides a 25% discount, whereas in the EU fees are fully waived for SMEs and a 10% reduction applies to other companies.⁹⁷ Preauthorisation inspections are also free of charge for all drug companies,⁹⁸ while additional fees (post-authorization applications and annual fees for the first year after authorization) are set aside for SMEs only.⁹⁹

Discounted scientific advice

As developing orphan drugs can bring up complex scientific questions, countries offer scientific assistance on issues such as trial design or definition of "significant benefit". This helps sponsors bring development forward and adequately demonstrate their product's quality, safety and efficacy upon market authorization.¹⁰⁰ In the EU protocol assistance is provided for free to SMEs and with a 70% reduction for other developers,¹⁰¹ and accounted for more than half the value of total fee waivers for orphan drugs.¹⁰² In Japan sponsors also benefit from lower-fee consultation and guidance from the Ministry of Health, Labor and Welfare, the National Institute of Biomedical Innovation and the PMDA.¹⁰³

Related programs

Finally, orphan drugs in some therapeutic categories may be eligible for other incentives. This is the case of the US Priority Review Voucher programs, which grants developers of products for neglected diseases or pediatric formulations priority review. In 2015, almost one in four orphan drug approved also benefitted from a Priority Review Voucher.¹⁰⁴

1.1.3 The patchy status of rare disease incentives worldwide: Orphan drug schemes in other countries

Increasing awareness of the burden of rare conditions – assessed at around 4 to 8% of the world's population¹⁰⁵ – has put the issue higher up on public health agenda. Various countries around the world have made strides in improving access to treatments for rare diseases by adopting dedicated regulations or national plans,¹⁰⁶ and applying a broad perspective to related policy issues, such as in the Brazilian Rare Disease National Attention Policy adopted in 2014.¹⁰⁷ Some national plans rely on existing definitions of orphan drugs (such as Latin American countries including Mexico, Argentina and Colombia which rely on the EU definition), while others have devised their own definitions, which can vary considerably.¹⁰⁸ In Russia, for instance, rare diseases are those affecting less than 1/10,000 people,¹⁰⁹ and in Turkey a much stricter definition of 1/100,000 applies.¹¹⁰ In Singapore – the first country to draft orphan drug legislation after the US – the Medicine Orphan drugs Exemption Order (Medicines Act Chapter 176, Section 9) allows for compassionate use of unlicensed orphan drugs, defined as those treating serious disease affecting less than 20,000 people, corresponding to roughly 34/10,000 inhabitants.¹¹¹

Far fewer countries, however, have established orphan drug designation criteria and included in their policies incentives for the development of new products and technologies. Those countries that have put in place some incentive based mechanism have mainly focused on faster and/ or cheaper market approval timeframes. This is notably the case for Australia and Taiwan, as well as countries who have put in place independent regulatory pathways for orphan drug approval such as Switzerland and Korea. All these countries can rely on orphan drug designations made by other recognized regulatory agencies. With regards to IP based incentives Taiwan stands out as an exception and rewards the first entrant to the market with a 10-year exclusive license. Finally, Canada has drafted but not yet adopted a dedicated orphan drug policy.



	Rare disease definition (Prevalence 10,000 people)	Incentives	Scheme uptake		
Australia (1997)	Around 0.88 (less than 2,000 people) to become 5 after proposed reforms (+ seriousness criteria)	• Approval fee waiver	25 OD designated on average per year		
Taiwan (2000)	1112	 10-year exclusivity Exception from local trial requirement 	74 OD approved as of 2014		
Korea (2003)	4 (+ lack of appropriate existing treatment)	• Decided ad hoc by the MFDS	206 OD approved, 7 OD in development registered as of July 2015		
Switzerland (2006)	5	 Facilitated approval procedure 	239 OD approved as of March 2017		
Canada (2012)	5	Fast-track approvalScientific assistance	-		

TABLE 5 Overview of main orphan drug incentives in jurisdictions other than US, EU and Japan

Source: Pugatch Consilium (2017)

For most countries the primary focus is on accelerating market entrance and patient access to much needed and often life-saving treatments but not necessarily the development of new products and technologies.



Australia

Australia's orphan drug scheme was introduced in 1997 and is currently being reformed (in parallel to another reform that will introduce expedited pathways for drugs treating serious unmet medical needs).¹¹³ At present, the rare disease definition threshold is considerably lower than other countries, corresponding to less than 1/10,000 population.¹¹⁴ In 2016 the TGA proposed to increase this to 5/1,000 by adopting EMA's orphan drug criteria, which also includes disease severity and significant benefit over existing treatments (currently not applied in Australia).¹¹⁵ Importantly, the reform maintains the status quo with regard to the incentives stemming from orphan designation, with no other rewards than an authorization fee waiver.¹¹⁶ The measure is estimated as costing the government AD4 million per year.¹¹⁷ Since the

beginning of the program in 1998, the number of orphan designated products increased from an average of 17 to 25 per year in 2015.¹¹⁸ Out of a total of 287 designations granted up to 2015, half went on to enter the market, a larger share than in the EU and the US where fewer designated drugs reach the approval phase (see below). This points to the fact that designation takes place later in the development cycle, given the limited pulling force of rewards granted in Australia. Indeed, three out of four rejected orphan applications subsequently applied for standard marketing procedure, suggesting the prospect of orphan designation was not essential to their development.¹¹⁹ In this sense, the orphan drug regulatory framework in Australia is not geared at incentivizing R&D of new products and technologies for rare diseases. Rather, it is focused on improving patient access to existing developed products and technologies. The evaluation process to designate orphan drugs can rely on recent FDA designations.¹²⁰ TGA has also agreed to share with EMA the full assessment reports related to marketing authorization of orphan medicines.¹²¹ Orphan designation cannot be sought in Australia if previously refused by FDA, EMA and four other regulatory agencies (UK, Netherland, Sweden and Canada).¹²²



Korea

Since the end of 2015 Korea has significantly advanced and clarified the status of orphan drugs by adopting the 'Rare Disease Management Law" (Bill 1911253)¹²³ and revising a series of orphan drug-related regulations.¹²⁴ As of 2017 orphan drugs benefit from a rather comprehensive incentive package that notably includes a 10-year data exclusivity period (defined as "re-examination period"; similar to Japan's) plus one year for paediatric products, against a 6-year exclusivity for NCEs and 4 years for new indications.¹²⁵ Other rewards include priority review, scientific assistance and waivers of fees such as preliminary review fees.¹²⁶ The incentive package is expected to increase and accelerate market entrance of orphan drugs (as of 2016, 353 such products were licensed in Korea) as well as increase domestic production.¹²⁷ Orphan drugs are defined as those treating diseases affecting less than 20,000 people in Korea, with no appropriate treatment in place or that significantly improve the safety and efficiency of alternative drugs.¹²⁸ Drugs developed abroad can qualify for the orphan status incentives.¹²⁹ The revised definition removes the revenue cap previously applied under the 2003 Orphan Drug Guidelines, and according to which only drugs whose yearly revenue/value of import did not exceed 5 billion won (USD5 million) could be designed as orphan.¹³⁰ While a designation system was in place since 2003, no legal certainty about possible incentives was provided.¹³¹

* Taiwan

The Rare Diseases Control and Orphan Drugs Act of 2000¹³² protects patients of diseases classified as "rare" by rewarding new orphan drugs entering the Taiwanese market with a 10 year exclusivity period.¹³³ Other incentives include fast-track approval, protocol assistance and public reimbursement.¹³⁴ Once approved, the product is granted a 10-year license (against 5 years for other products)¹³⁵ which acts as a market exclusivity period. During these 10 years requests to register drugs "of the same kind" will not be accepted (art 17) unless – as in the US and the EU – the second drug complies with three conditions (it is clinically superior, insufficiently supplied or the first drug manufacturer agrees to allow market entry to a competing product). However, unlike the US and EU, Taiwan's regulatory framework also adds a fourth condition which allows for the approval of a similar product during the 10 year exclusivity period if the orphan drug price is deemed "unreasonable" (art 18). Rare diseases are defined as those with a prevalence of 1/10,000 inhabitants. However, any medicinal product approved by other countries for the treatment of rare diseases can be registered in Taiwan as an orphan drug (art 15). Authorities may, if necessary, require the conduct of domestic clinical trials (art 16).



Switzerland does not have in place a dedicated rare disease incentive scheme. Rare diseases are defined in the Drug Law (Therapeutic Product Act) that allows them to benefit from simplified authorization procedure.¹³⁶ As of March 2017, 309 products were registered as orphan drugs, defined as those treating diseases affecting less than 5 in 10,000 inhabitants, as well as those that obtained orphan status in a country with equivalent medicinal product control.¹³⁷



In October 2012 the Federal government announced the development of an orphan drug framework for Canada. The draft endorses the same rare disease definition as in the EU, i.e. an incidence of five in 10,000 inhabitants,¹³⁸ and rewards orphan drugs with discounted scientific assistance and prioritized market authorization, but no additional market exclusivity compared to other innovative drugs.¹³⁹ As the draft has yet to become law, Canada remains without a proper definition and approval framework for orphan drugs, which can discourage sponsors from entering the market.¹⁴⁰

1.1.4 Success of orphan drug schemes: assessing the evidence

Clinical trials

Over the last decades, rare diseases have gained increased focus in pharmaceutical R&D. An analysis of ClinicalTrials.gov data looking at trials conducted from 2005 to 2015 by key countries (US,

FIGURE 3 Clinical trials on rare diseases by phase, 2005-2015, all countries

UK, France, Germany, Italy, Spain, Switzerland, Japan, South Korea, Singapore, Taiwan, Canada and Australia)¹⁴¹ confirms a steady increase of research activities for rare conditions globally, notably in early stage Phase I and II trials.

Looking at the sample of countries individually the most R&D for rare diseases takes place in the US while major EU countries have steadily increased



FIGURE 4 Clinical trials on rare diseases by country/region, 2005-2015



Source: Pugatch Consilium (2017) based on clinicaltrials.gov

* The contribution of Switzerland – who unlike EU countries has no specific orphan drug incentives in place other than facilitated approval – to the overall Europe research activities for rare diseases is low, with an average of 3 trials carried out per year over the analyzed period.

FIGURE 5 CTs on rare diseases, by country/regional aggregate (annual number and % share of total), 2010



FIGURE 6 CTs on rare diseases, by country/regional aggregate (annual number and % share of total), 2015



Source: Pugatch Consilium (2017) based on clinicaltrials.gov

their R&D capacities for rare conditions (from 71 trials in 2005 to 130 in 2015), partially closing the gap with the US. Only Canada, who unlike most of the countries analysed lacks a specific orphan drug policy, shows a negative trend (from 25 trials in 2005 to 21 in 2015). The share of orphan drug clinical trials hosted by Asian Pacific countries remains limited, although increasing in Japan and South Korea.

Looking at evolution over time, the share of research carried out in the US and EU out of the total has increased, and accounted for more than 4 out of 5 clinical trials for rare diseases in 2015. As concerns research type, early phase research (Phase I trials) continues to constitute the lion's share of research in the US. What is noteworthy is the clear increase in the percentage of trials being early stage in both the EU sampled countries and Asia Pacific, suggesting that relatively new orphan drug schemes to attract resources to fill the research pipelines for rare diseases are having some effect.

Designation

The continuously increasing number of orphan drug applications and designations suggests that orphan drug incentives represent a key component of the drug development process, and have succeeded in attracting research resources and efforts to rare diseases. Indeed, ongoing R&D activities are resulting in a steady expansion of orphan drug applications. In 2016 applications reached a new high both with the FDA and EMA, with 582 and 329 applications respectively.¹⁴² Designations with both entities have consistently grown since the beginning of the century (with only a slight decrease in the US in 2016), with a notable upward trend registered in the last five years. As of end of 2016, 1,805 products had received orphan drug designation in the EU since orphan legislation was implemented, meeting various research needs for 487 conditions.¹⁴³ A recent study based on a sample of orphan medicines revealed that almost 50% of designations targeted rare conditions lacking any previously approved treatment in the EU.¹⁴⁴ A less consistent increase has been registered also in Japan, although at a considerably lower level than in the US and EU. The peak was reached in 2014 with 32 designations.

A recent study by Murakami and Narukawa on applicant type reveals a trend in the US and the EU, where smaller companies account for the majority – roughly two-thirds – of designation applicants.¹⁴⁵ A 2013 report by the EMA confirms a similar share of designated products as originating from SMEs.¹⁴⁶ Japan stands out for a bigger role played by large pharmaceutical companies, reflecting the limited role of SMEs in the country's drug development and the lack of designations granted to academic or research institutions. Indeed, in Japan the law stipulates that designation is granted to commercial entities that will engage in marketing a product.¹⁴⁷



FIGURE 7 Early-phase research on rare diseases (as % of country total CTs on rare diseases), 2005, 2010, 2015

Source: Pugatch Consilium (2017) based on clinicaltrials.gov



FIGURE 8 Designations per year in the US, EU and Japan, 2001-2016

Source: Pugatch Consilium (2017) based on data from FDA, EMA and Japan's NIBIO



FIGURE 9 Share of Orphan Drug Designation by Applicant Type and Revenue in the US, EU and Japan

Source: Pugatch Consilium based on M. Murakami and M. Narukawa, "Matched Analysis On Orphan Drug Designations And Approvals: Cross Regional Analysis In The United States, The European Union, And Japan", *Drug Discovery Today*, Volume 21, Number 4, April 2016 Because of its specific requirement that products demonstrate a 'high possibility of development' to be designed as orphans, the Japanese scheme results in later stage (and fewer) designations, with a higher probability of reaching approval stage and a shorter time lap between designation and approval.¹⁴⁸ Indeed, the percentage of successful marketing approvals to orphan drug designations was 13% in the US, 7% in the EU, and 51% in Japan,¹⁴⁹ indicating a greater capacity by US and EU schemes to incentivize riskier, early stage research.

Approvals

Annual numbers of orphan drug approvals has steadily increased in all three regions. The US continues to have the highest total number of approvals. The success of the US orphan scheme is measured by the dramatic increase in approved products for orphan drugs from 1983 onwards (estimated at more than 575 drugs and biologic products) compared to only 10 between 1973 and 1983, i.e. only one drug per year on average.¹⁵⁰ The US also shows the highest rate of orphan approvals out of total novel drug approvals, with almost one out of two new products targeting rare diseases (47% in 2015)¹⁵¹. Orphan drugs accounted for 43% of new approvals in the EU, and 37% in Japan.¹⁵² As of end 2016, 128 EU designations have resulted



FIGURE 10 Number of marketing authorizations granted to orphan drugs, 2001-2016

📕 EU 📕 US 📕 Japan

Source: Pugatch Consilium (2017) based on data from FDA, EMA and Japan's MHLW

* Data for Japan not available

in authorized medicinal products (including 12 extensions of indications) for 101 conditions.¹⁵³ Almost half of the products were approved for conditions with a prevalence level below 1 per 10,000 people.¹⁵⁴ As a recent example, in January 2017 FDA approved an orphan designated treatment for spinal muscular atrophy, a rare genetic and often lethal disease.¹⁵⁵

Finally, both in terms of designations and approvals, there's a relatively large overlap; approximately 50% of products designated and approved in the EU and Japan were also designated or approved in the US.¹⁵⁶

1.2 One step at a time: How incremental innovation and IP incentives drive biopharmaceutical innovation forward

Technological innovation is frequently thought of as consisting of two distinguishable modes or models: radical innovation and incremental innovation.¹⁵⁷ While there are some problems with thinking of innovation strictly in a binary fashion, the conceptual distinction between radical and incremental is useful as an analytical tool, particularly with regard to understanding the debates around what actually constitutes biopharmaceutical innovation.¹⁵⁸

Radical innovation, as the name suggests, is the introduction of completely new or revolutionary ideas or products. Frequently, such innovations wholly alter the way an industry or even an economy functions, fundamentally changing economic and social behaviour. Examples of radical innovations include the printing press, penicillin, electricity, personal computer and X-rays. Many scholars of technological innovation refer to radical innovations being a disruptive form of innovation.¹⁵⁹

In contrast to radical innovation, incremental innovation is a process of piecemeal improvement of existing technologies or techniques. Usually, incremental innovations follow on from revolutionary or radical innovations. That is, radical innovations are developed, changed and altered for either improved usage or different uses than its original intention.¹⁶⁰ Innovation that is incremental is by far the most common form of innovation. Indeed, biopharmaceutical innovation is in large part incremental. In fact incremental innovation is an essential part of the biopharmaceutical R&D process. Follow-on medications and incrementally improved or altered therapies frequently reduce side effects, improve upon existing delivery systems or the administration of a medicine, increase effectiveness and reduce dosages required.

Part of the wider debate on the value and role of IP incentives is this subsidiary debate over what the most effective forms of research are, what defines biopharmaceutical innovation and specifically what constitutes a 'new' drug or medical development. Broadly speaking critics argue that many incrementally improved drugs or medical devices developed are not as valuable as products developed through breakthrough or radical innovation.¹⁶¹ A quote from the *Financial Times* succinctly summarises this view:

The debate about pharmaceutical pricing and innovation should focus on how many companies provide real breakthrough benefit for consumers. The answer is: depressingly few. The vast majority of drugs are simply better or worse me-too copies of products that went before them.¹⁶²

Policymakers and governments have also been drawn into this debate. In 2006 the US CBO published a report on the state of R&D in the pharmaceutical industry. While the CBO did concede that incrementally improved drugs could provide "significant benefits to consumers" it also stated that "the higher prices that are charged for some drugs that are merely extensions of current product lines may not be commensurate with the additional value that those drugs provide."¹⁶³

Yet this binary view of radical innovation being good versus incremental innovation being insignificant is limited both in absolute terms as well as specifically within the context of the biopharmaceutical innovation process. For example, just under a decade ago there was a very serious debate in the US about the drop in biopharmaceutical innovation as exemplified by

Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
NMEs introduced	24	17	21	36	20	22	18	24	26	21

TABLE 6 NMEs introduced since 2001, FDA¹⁶⁴

the fall in the number of new products approved annually by the FDA. (Incidentally this debate has all been put to the rest by the record number of not only new NMEs approved by the FDA in recent years - with 45 new products approved in 2015 alone – but also by the break-through nature of many of these innovations.) Looking at figures from the mid to late 1990s there was a drop in the number of NMEs (defined by the FDA as drugs that contain an active substance not previously approved for marketing in the US) introduced. The number of NMEs introduced peaked in 1996 at 53 and declined markedly in the following period. Table 6 summarises the number of molecular entities introduced over this 10 year period 2001-2010

As Table 6 illustrates, the number of NMEs introduced averaged just under 23 (22.9) NMEs per year from 2001 to 2010. Based on these figures many concluded that pharmaceutical innovation had declined.¹⁶⁵ However, to being with if examining the figures from a longer historical perspective, it was not at all clear that biopharmaceutical innovation had actually decreased. Indeed, using the period 1996-1999 - when NMEs approved topped 35 every year - is misleading as this fouryear period was a historical aberration. In fact, from the mid-1960s to the early 1990s NMEs approved ranged around 20 per year hardly ever exceeding 30 NMEs.¹⁶⁶ In addition, rates of R&D expenditure were also much lower during this period. Between 1993 and 2003 industry wide investment by PhRMA members more than doubled with a substantial increase in R&D expenditure taking place after the peak period of approvals in 1996-1999.¹⁶⁷

Similarly, the *a priori* assumption that pharmaceutical innovation is best measured by the number of NMEs introduced is questionable. Cockburn has convincingly argued that focusing solely on NMEs as the primary measure of pharmaceutical innovativeness is fundamentally incorrect: Drugs vary significantly in their scientific significance, health impact and economic value. This heterogeneity in "quality" of drugs means that simple counts of NMEs may seriously mismeasure R&D performance. Blockbusters with more than \$1billion in annual U.S. sales, for example, are given equal weight to newly approved drugs that achieve only \$50million in annual U.S. sales, and drugs which represent a major advance in the treatment of disease are given the same weight as the "me-too" products that appear in their wake.¹⁸⁸

Others have agreed with this and find that postmarketing approval R&D expenditure can make up a substantial part of the total R&D costs if incremental innovations are expected to yield additional sales. For example DiMasi, Hansen and Grabowski have found that just over a quarter of total out-of-pocket R&D costs consisted of postmarketing R&D.¹⁶⁹

1.2.1 Incremental innovation is real innovation!

Incremental innovation encompasses a vast number of improvements to both pharmaceutical processes and products. These improvements can vary in complexity, economic value and patient benefit. For the purposes of analysis incremental innovation can be divided up into three different methods or ways a drug, medical device or treatment can be defined as being incrementally improved:

- new agents or drugs within the same therapeutic class for which a medicine or established treatment already exists;
- 2. incremental improvements in second or third generation drugs such as dosage, and delivery form; and
- 3. new indications or alternative uses for existing/ older drugs.¹⁷⁰

New agents or drugs within the same therapeutic class provide patients with a range of choices. For many drug classes the success rate of a given drug is sometimes at or below 50%. It is therefore vital that patients are able to access as wide a range of drugs within the same class. This can also save patients and payers substantial resources. For example, a 2005 study found that the use of torasemide instead of original loop diuretic furosemide in the treatment of cardiac heart failure created annual hospital savings of USD700,000 for admissions and USD1.3million for cardiac events.¹⁷¹ In fact, the consequences of incremental improvements in dosage and delivery form can actually be more akin to the results of radical innovation. This is particularly true for medical devices which rely on small incremental improvements to dramatically improve clinical effectiveness, patient comfort, as well as frequently reducing overall cost. For example, the economic benefit and value of the improvements to the CT scanner since the 1970s was quantified by Harvard economist M Trajtenberg in a 1990 study.¹⁷² Here Trajtenberg estimated that without the innovations that followed the original introduction of the CT scanner in 1974, only 7.4% of the total population would have benefited from CTs.¹⁷³ With the improvements and innovation that were made following the original radical innovation, by 1982 that population ceiling had actually increased to 49% of the total population.¹⁷⁴ Looking at biopharmaceuticals, new indications or alternative uses for older and existing drugs are an important and largely untapped source of innovation. Aronson has described the use of the antipsychotic thioridazine as a novel treatment for drug-resistant bacterial infections and used this as a case study example of how older treatments can be used in new ways.¹⁷⁵ Similarly in three large and medically significant therapeutic classes (ACE inhibitors, SSRI/SNRI antidepressants and anti-ulcer drugs), Berndt et al found that 70-80% of usage lies outside the drug's primary and initially approved indication.176

As the below case studies show there are a large number of examples of how incremental improvements, innovations and new uses for existing products are at the very heart of biopharmaceutical and medical progress. Many of the most heavily prescribed products on the market today – including beta-blockers, statins, insulin and oral contraceptives – are technologies that have over subsequent generations been incrementally improved and refined.

1.2.2 Case study analysis

Insulin

The development of insulin has largely followed an incremental trajectory.¹⁷⁷ The methods of precipitating insulin was first discovered by Eli Lilly scientists in the first half of the 20th century, yet through processes of incremental innovation new insulin products have and are continued to being developed.¹⁷⁸ This has taken place both in terms of how insulin is delivered as well as the actual design of the insulin product itself.¹⁷⁹ For example, the development and marketing of biosynthetic human insulin has led to the development of insulin analogs as well as biosimilar insulins; see for example the development of insulin lispor (Humalog) and Biocon's biosimilar insulin.¹⁸⁰ Similarly, the development of new delivery systems such as the pen injection device by NovoNordisk, Eli Lilly and others has been dependent on incremental improvements in both dosage and delivery method.¹⁸¹ This includes moving from needle to pen injection, to pre-filled pens requiring less injection force and now increasingly insulin pumps.¹⁸²

Beta-blockers

Beta-blockers (beta-adrenergic blocking agents) reduce blood pressure by blocking the effects of adrenaline.¹⁸³ They do so by inducing the heart to beat slower and with less force as well as opening up blood vessels for improved blood flow. There are three generations of beta-blockers which have successively been incrementally improved. For example, the first generation of beta-blockers were non-selective, meaning that they blocked both types of adrenoceptors (β 1 and β 2).¹⁸⁴ First generation beta-blockers include propranolol, nadolol and timolol. In contrast, second generation beta-blockers are more selective for which types of adernoceptors they block (cardioselective).¹⁸⁵ Second generation products include metoprolol, acebutolol, atenolol and bisoprolol. In addition to being more cardioselective, third generation beta-

	1st gen Nadolol	1st gen Propranolol	1st gen Timolol	2nd gen Acebutolol	2nd gen Atenolol	2nd gen Metoprolol	3rd gen Labetalol	3rd gen Pindolol
Preserves renal blood flow	х						x	x
Once- a-day dosing	х	х		Х	х	х		
Reduces mortality after heart attack		Х	х			х		
No change in serum lipid levels							х	x
β1 selectivity				Х	Х	Х		
Equal effectiveness in blacks and whites							х	
Intrinsic sympha- thomimetic activity				х				х
Very low central nervous system penetration	Х		х		Х			
Vasodilation							Х	Х

TABLE 7 Therapeutic characteristics of beta-blockers¹⁸⁶

blockers also have blood vessel relaxing properties ("vasodilator actions") through their blocking of vascular alpha-adrenoceptors.¹⁸⁷ Third generation blockers include carvedilol, labetalol and sotalol. Below Table 7 provides an overview of the different generations of beta-blockers and their respective therapeutic characteristics and the improvements made over time.

ACE inhibitors

ACE inhibitors treat blood pressure, scleroderma and migraines.¹⁸⁸ They do so by preventing the production of angiotensin II, a substance which can lead to the narrowing of blood vessels and higher blood pressure. Since the mid-1980s when breakthroughs were made in the scientific understanding of the pathobiology of cardiovascular diseases, the differences in effect of ACE inhibitors led to the development of new ACE applications.¹⁸⁹ Indeed, over the past 30 years and since the development of the third generation ACE inhibitor perindopril, ACE inhibitors have been used in the treatment of a number of diseases. For example, one major clinical study on the effectiveness of using perindopril in stroke prevention found that the patients in the active treatment group using this ACE inhibitor had significantly fewer strokes and major vascular events in the years following the trial.¹⁹⁰ Similarly, the EUROPA trials – which included over 12.000 patients - found that the primary end-point (cardiovascular mortality, nonfatal myocardial infarcation or resuscitated cardiac arrest) was reduced by 20% after four years of treatment with ACE versus patients taking a placebo.¹⁹¹ Perindopril has also been found to lower mortality and preserving left ventricular function in patients suffering from Duchenne muscular dystrophy.¹⁹² Finally, the incremental improvements that led to the development of second and third generation ACE inhibitors have also contributed to lowering the treatment cost of these inhibitors. For example, total median costs for newer ACE inhibitors in 1997 versus older ones were USD53 versus USD60, a saving of 11.6%.193

Oral contraceptives

First approved for market in 1960 oral contraceptives have evolved substantially through incremental improvements in both dosage and potency. Simply put, oral contraceptives have moved from being high-strength and high-potency drugs to lower strength, lower potency drugs.¹⁹⁴ The first contraceptives contained very high levels of both estrogen and progestogen which were found to raise the risk of blood clots.¹⁹⁵ Gradually, the concentration of estrogen has been reduced to the minimum amounts needed for safe and effective contraception; from a high of 150 µg with some pills today containing under 20 µg of estrogen.¹⁹⁶ Moreover, modern oral contraceptives have also introduced phased hormonal dosages through the contraceptive cycle.¹⁹⁷ The high number of products available on the market and variety in their respective hormonal levels and combinations allow physicians and prescribers to tailor the prescribed contraceptive to the specific circumstances of the patient. For instance, products with higher progestin levels may help limit breakthrough bleeding.¹⁹⁸ Similarly, patients suffering from acne could benefit from products with higher estrogen dosages.¹⁹⁹

Statins

Statins are one of the most important drug discoveries of the 20th century helping millions of patients around the world prevent the production of LDL cholesterol that promotes atheroscletoric

vascular disease and serious cardiovascular complications. First discovered in the mid to late 1970s statins were not commercialised and brought to market until 1987 when Merck received FDA approval for lovastatin.²⁰⁰ The product did not take off until the mid-1990s after a major clinical trial established the connection between the lowering of LDL cholesterol and the recurrence of heart attacks.²⁰¹ To date one of the highest selling statins and drugs of all time is atorvastatin (Lipitor); a type of statin that was not developed until several years after the first generation of statins. Through incremental innovation atorvastatin lowered levels of LDL cholesterol to a greater extent than its competitors and was used for a broader range of treatments. For instance, in both Phase I and Phase II clinical trials conducted as part of the FDA approval process in 1992 and 1994 respectively, atorvastatin reduced LD cholesterol by 50% and 60% respectively.²⁰² This was considerably higher than any other statin on the market. In fact, as part of the FDA review, atorvastatin was compared head-to-head against its competitors and found to reduce LDL cholesterol at a higher rate.²⁰³ During these clinical trials it was also discovered that atorvastatin was effective in treating familial hypercholesterolemia and led to the drug receiving the FDA's fast-track approval.²⁰⁴

Zoledronic acid

The compound zoledronic acid was first developed by Roche Diagnostics. It had a range of uses which included the treatment of bone metastases and urolithialis, the prevention of heterotopic ossification and the management of rheumatoid arthritis. This became a staple medicine for bone related ailments in the 1990s. It was sold as Zometa with its protection expiring in 2007.²⁰⁵ Fourteen years after the compound was first disclosed to the world, Novartis started funding research into its effects on bone resorption for osteoporosis patients. These trials found it to also reduce the effects on multiple myeloma. Novartis had no vested interest in doing this research without patent protection of its own, while Roche's protection would not have extended or lasted long enough to last beyond clinical trials. Novartis obtained protection of its own in 2001 for the new medical uses and started marketing the product under the name of Aclasta.²⁰⁶

Anti-retrovirals

The development of HIV/AIDS treatment is another example of how incremental improvements to existing technologies over time amount to what in effect becomes a radical innovation whereby the latest technology is barely recognizable compared to its first generation predecessor. The first generation of anti-retorvirals had both serious side effects and were combination therapies requiring the consumption of large volumes of medication several times per day.²⁰⁷ Side effects included explosive diarrhoea, severe nausea, the loss of sense of taste, skin problems and painful nerve injury. The development of the second generation of drugs, centring on the concept of highly active antiretroviral therapy, saw improved treatment options and reduced side effects. Still, treatment centred around the administration and consumption of a number of medicines. It is only in recent years that new therapies have been introduced based on incremental innovations that allow for combination pills. One such drug is Gilead's Stribild, which was approved by the FDA in 2012 and contains four different medications.²⁰⁸ Instead of an array of pills taken every few hours, Gilead requires that a single pill be taken once daily. This new ease of medication has led to increased adherence which has, in turn, increased efficacy significantly with little to no significant change in lifestyle. In the long term this has also caused a significant decrease in costs for treating side effects.

1.2.3 IP incentives and incremental innovation

IP incentives have played a key role in stimulating the development of the products described in the preceding sub-section. Without the ability to protect new uses or incremental improvements to existing products, innovators would not have an incentive to invest the time, effort and resources into continuing research into these existing products. This is particularly the case for second use patent claims; an area of patentability which has come under increasing attack the last few years.

Second medical use claims

One of the more common ways to incentivise incremental innovation in the biopharmaceutical industry is by allowing second medical use claims in patents. This practice is founded firmly in international agreements on patent law and is consistent with their wordings. The manner in which this can be done varies, and each way protects a different aspect of the discovery.

Legal basis

Most countries allow inventions to be patentable if they comply with certain criteria. Firstly, they must fall into the categories 'products' or 'processes'. They must furthermore be novel, inventive and capable of industrial application.²⁰⁹ There are a few exceptions to this rule, most notably the fact that countries are allowed to exclude treatments or diagnostics on the human or animal body.²¹⁰ This exception is frequently introduced into local patent law, which affects the manner in which biopharmaceuticals can be patented. Medicines are substances, which allows them to be patented as products. Secondly, there is the possibility of patenting the process of treating the patient using the medicine in question. The latter, however, is not permitted when treatments are excluded from patentability. Subsequently two distinct categories of second medical use claims exist: the 'use type claim' and the 'method of treatment' type claim.²¹¹

For use claims

Novelty remains a requirement for all patent requirements. Therefore the same product cannot *per se* be patented a second time. The Swiss-type claim was developed in the Swiss Patent Office in order to allow novelty to be preserved for second medical use claims. They used the following format²¹²:

'Use of compound X for manufacture of a medicament for treatment of disease Y'

This type of claim patented the process of the creation of a medical product using the substance in the prior art. Swiss type claims were used in the EPO from 1985 until the revision of the EPC in 2000. In similar fashion the German Patent Office created

a method of patenting which made the use of the compound the focus of the patent, rather than the product or medicament, using the form:²¹³

'Use of compound X for treatment of disease Y'

After the introduction of EPC 2000 the EPO created a new system where the substance was once again the topic of patentability, with the caveat that the compound is meant for the specific purpose of treating a given condition as follows:

'Compound X for use in treating disease Y'

For use claims are limited in their protection. They do not give the patent owner the right to prevent exploitation of the compound in general, since it is prior art and therefore either subject to a previous patent or public domain. However, it is important to remember that this second use claim is still subject to the same requirements of novelty and inventiveness. Therefore it must be a new product, albeit one that uses compounds existing in prior art. Therefore it is only the new products over which the patentee has a *de facto* monopoly.

Method of treatment claims

Treatment claims make the process of using the new product to treat a disease the subject matter of the patent as follows:

'A method of treating a patient suffering from disease Y comprising: administering compound X to the patient'

These types of claims are not permitted in most countries due to the restriction on patenting procedures on the human and animal body. However in the US and Australia these types of claims can be used.

1.2.4 Comparing international legal status

European Patent Organisation

Currently over 38 countries allow second medical use patents. This includes countries in the EPO region. The EPC allows for EPO style claims since the enlarged board of appeal approved it in 2008.²¹⁴ The EPO did not ban the use of the Swiss

type claim, but rather stated that it was no longer necessary. Since the EPO style claim protects the use rather than the method of production of a medicine, applicants tend to choose this type of claim when given the choice.²¹⁵



China

China in 2008 confirmed that the use of Swiss style claims for and second medical use patents were permitted.²¹⁶ The Guidelines for Patent Examination make a special allowance for Swiss type claims.²¹⁷ Without this allowance the claim would not be in accordance with the ban on methods of treatments and diagnosis.²¹⁸



The US requires novelty for patents entailing a new composition of matter.²¹⁹ As a result, second uses of known substances cannot be patented as such since there is a lack of novelty. However, no restrictions exist preventing patenting medical treatments or methods of diagnosis. Second medical uses therefore have to be made using method of treatment claims.



Australia

Australia allow for second use method claims. Biological patents processes are not patentable, but methods of treatment are not specifically excluded.²²⁰ Australia finally laid the question of patentability to rest in a 2013 judgement in which the judge stated:

Assuming that all other requirements for patentability are met, a method (or process) for medical treatment of the human body which is capable of satisfying the NRDC Case test, namely that it is a contribution to a useful art having economic utility, can be a manner of

manufacture and hence a patentable invention within the meaning of s 18(1)(a) of the 1990 Act²²¹

Australia also allows Swiss type claims, and the two types of claims are used interchangeably by applicants.



The Andean Community

Conversely, some countries have explicitly not allowed second use claims. This includes the Andean Community. Decision 486 in the Andean Pact notably states²²²:

Products or processes that are already patented and included in the state of the art within the meaning of Article 16223 of this Decision may not form the subject matter of a new patent owing to the fact of having a use ascribed to them different from that originally provided for in the first patent.

This decision is a renewal of the previous decision which outlawed the claims in 1993.²²⁴ These decisions were confirmed in the Andean Tribunal of Justice when Pfizer attempted to patent sildenafil for the secondary use for treatment of male impotency. In doing so the Tribunal dismissed claims that such provisions are not in keeping with article 27.3 of the TRIPS agreement.²²⁵



Ecuador

Although a member of the Andean Community Ecuador in 2016 outlawed the use of second use patents through the *Código Orgánico de Economía Social del Conocimiento, la Creatividad y la Innovación (Código Ingenios).* This is not found in the Intellectual Property Act, but a more recent amendment.²²⁶ Article 268 increases the number of non-patentable subject matter and article 274 eliminates any patentability of second use inventions. Paragraph 5 excludes second uses of known substances as described by the Andean Decision. Paragraph 3 excludes any "new form of a substance, including salts, esters, ethers, complexes, combinations and other derivatives". This precludes the patentability of new products wherein known substances are combined to increase effectivity or safety of treatment, which is a key part of incremental medical innovation.



Indonesia

Like Ecuador Indonesia is one of the latest countries to outlaw second use patents. This is a clear break from its previous patent examination guidelines which made a special allowance for Swiss-type patents.²²⁷ The previous allowance of second use patents was not based on law but on the accepted practises promulgated by the patent office. Article 4(f) of the Patent Act now precludes patentability of new uses for known substances. The same paragraph allows the patenting of new forms of known compounds only if there is a significant increase in efficacy and there is a meaningful difference in the chemical structure. To illustrate the meaning of "meaningful", the explanation accompanying the law uses the example of amoxicillin. It states that the Hydrogen and Hydroxide clusters' new repellent properties create a greater stability to the product ampicillin, making the difference meaningful. This undoubtedly makes the threshold for patentability far greater than mere inventiveness, and leaves patents of incremental innovation far more vulnerable to the risk of revocation.



India

India added section 3 into its patentability requirements which includes a list of nonpatentable inventions.²²⁸ This list includes the "mere new use of a substance" and "new form of a known substance unless there is a significant increase in efficacy". Second use patents are therefore no longer allowed. Patents of new products made of known substances are still possible, but the further exclusion of "simple admixtures" has meant that the threshold for inventiveness has been raised significantly. Many types of incremental innovation can therefore no longer be patented.



Argentinian patent examination guidelines equate second use claims with method of treatment claims.²²⁹ The law prohibits treatment claims from being made.²³⁰ Subsequently second use patents fall wholly outside the scope of patentability in Argentine law.



Brazil does not have any provisions explaining whether or not second medical use patents are permitted. However resolution 124/2013, which provides examination guidelines to the patent office, makes an allowance for Swiss type patent claims. Second use claims are generally found to be equivalent to process claims. This would make the Swiss type claim in violation with the ban on patenting medical procedures.²³³ However a special exception is made for the pharmaceutical field.²³⁴ Accordingly, the use of a substance for the creation of a medicine can be afforded patent protection.

A short summary of patentability of second medical uses is shown in Table 8 below.



In Egypt no specific provision is made for second medical use claims. The Egyptian Patent Office interprets second use claims as discoveries rather than inventions. Under Egyptian law these are not patentable.²³¹ Method of treatment claims are further banned under the same provision.²³²

TABLE 8 Second use patents, Country comparison

Country/ region	2nd use patents	Swiss type	EPC type	Method of treatment	
US	Yes	No	No	Yes	
EPC	Yes	Yes	Yes	No	
Australia	Yes	Yes	No	Yes	
China	Yes	Yes	No	No	
Brazil	Yes	Yes	No	No	
Andean Community	No				
Ecuador	No				
India	No				
Argentina	No				
Egypt	No				

1.3 How pro-innovation policies on biotech patentability standards and the introduction of technology transfer frameworks in the 1980s have enabled the building of the modern American life sciences industry

Diamond v. Chakrabarty

While James Watson and Francis Crick's discovery in 1953 of the double helix structure of human DNA provided the scientific basis on which modern medical biotechnologies are developed and used, arguably as important a development in spurring the full potential of this within the field of human health came forty-seven years later in a United States Supreme Court Decision in 1980. On its thirtieth year anniversary the Court's decision in Diamond v. Chakrabarty holding that living matter is patentable when created by human ingenuity was described by than USPTO Director David Kappos as unleashing "the opportunity to leverage the life sciences into new industries, new jobs, and new solutions".²³⁵ Indeed, looking at the history of medical biotechnology it is hard to argue with this assessment. After the Court's decision activity and research into biotechnologies surged with the US the leading nation with regards to both patenting activity and generation of new products and technologies. Indeed, looking at rates of international patenting activity it is clear that with respect to biotechnology the US has been the predominant source of global innovation. Below

FIGURE 11 Total triadic biotechnology patenting 1985-2013, % share select economies



Figure 11 shows the percentage share of total triadic biotechnology patenting from 1985 to 2013 comparing the US, Japan, and EU28.²³⁶ Throughout the period the US has maintained its leadership accounting for the largest share of triadic biotechnology patenting activity in the world at just over 43% during this time period.

The result of this patenting activity can be seen in the growth in the number of new medicines and biologic based products commercialized in the 30 year period since the Supreme Court Decision. Indeed, the first biologic product to be FDA approved was Elil Lilly's and Genentech's Humulin insulin in 1983.²³⁷ The application for Humulin was not submitted to the FDA until 1982; two years after patent protection had been obtained following the Diamond v. Chakrabarty decision. Looking at FDA approvals data for biologic products the share of total NMEs approved has risen steadily since the mid-1980s.²³⁸ In total between 1982 and 2013 91 biologic products were approved by the FDA compared to 777 small molecule drugs.²³⁹ Significantly the percentage share of new products approved by the FDA that were biologics has increased steadily from less than 5% in the mid-1980s to close to 30% since 2010. The latest available data from the FDA shows that, with the exception of 2012 and 2013, since 2009 the percentage of NMEs approved by the FDA being biologics has never been lower than 20% and has averaged 25.8%.²⁴⁰

Moving in a different direction?

Despite the demonstrated American leadership on biotechnology the last few years has seen the US diverge from this path. Indeed, the USPTO and US Supreme Court have in the past three years begun to take a somewhat stricter stance on patenting of naturally occurring substances and level of inventive step required. Recent court decisions, namely Association for Molecular Pathology v. Myriad Genetics, Inc., 2013, and Mayo Collaborative Services v. Prometheus Laboratories, Inc., 2012 and subsequent USPTO guidance introduce restrictions on patenting of naturally occurring substances, even if isolated and purified, if there is not sufficient distinction shown between a claim and the substance as found in nature.²⁴¹ In particular, in relation to inventive step,



a biotechnology claim must demonstrate that something "significantly more" than a generic process and/or a material change from a naturally occurring substance has taken place, while also not limiting other research into the natural phenomena in question. These issues have not been resolved in 2016/17. Instead, there remains deep uncertainty as to USPTO's and courts' standard for patenting of biotech inventions, continued low rate of life sciences patents found to be eligible by PTO, and an ongoing feeling from innovators and legal analysts that American patentability standard are falling behind other developed countries and from its long-standing pro-innovation approach.²⁴² Guidance issued over the past year is relatively limited in its utility and has not provided adequate clarity. Furthermore, the Supreme Court decided in late 2016 to decline to review a number of Federal Circuit cases that held biotech and other inventions were not patentable.²⁴³

"[Bayh-Dole]...The most inspired piece of legislation to be enacted in America in the last half-century"²⁴⁴

Subsequent to the Supreme Court's Decision on biotech patentability the US Congress passed two path-breaking pieces of legislation: the Patent and Trademark Law Amendments Act of 1984

and 1986 (the Bayh-Dole Act) and the Stevenson-Wydler Technology Innovation Act, which was later amended by the Federal Technology Transfer Act of 1986 and the Technology Transfer Commercialization Act in 2003. This legislation attempted to supply federal laboratories (including the NIH) and universities using federal funds with the incentives needed to work with industry for the purpose of translating early stage research into usable products in the marketplace for the benefit of the wider public. The legislation sought to secure the above goals through three major changes to the IP system. First, they allowed universities and federally funded bodies to retain ownership of the proprietary knowledge stemming from the research and daily activities of these institutions, including the ability to own patents on their inventions. Second, they encouraged these institutions to become much more proactive and professional in the management and exploitation of their IPRs by creating professional technology transfer offices. Finally, the legislation sought to stimulate the commercial and financial aspects of public-private collaboration, with the intention of creating new businesses (such as spin-off companies) and generating income for the institutions, as well as for the researchers.245 The importance of the Bayh Dole framework to US innovation - and especially for the life sciences

sector – cannot be overstated. The above quote from the *Economist* aptly sums up the positive impact the legislation had, and continues to have, on innovation in the US.

Looking at general rates of innovation and commercialization activities this can be seen in terms of both patenting activity and actual economic impact and output. To begin with academic research into the effects of the Bayh-Dole framework have found a significant correlation between increased patenting activities at US universities and the Act. For example, a 2004 study found that university share of total patenting in the US increased from 0.69% of total patents at the time of legislation to just under 5% in 1996. Moreover, in a range of 117 industries (including biopharmaceuticals) the increase was from a decrease of 87% in 1969 to an increase of 1,648% in 1996.²⁴⁶

The positive impact of Bayh Dole can also be seen in terms of direct and significant contributions to economic output and employment. For instance, using eighteen years of data from the annual AUTM survey a 2015 study estimating the economic contribution of licensing activity by academic institutions found that in the US the contribution of academic licensing to gross industry output ranged from USD282-1,180 billion (measured in 2009 USD).²⁴⁷ Contributions to GDP were equally significant estimated at between USD130-518 billion (measured in 2009 USD).248 In addition, this study found that this licensing activity was also a major contributor to the American jobs market, responsible for between 1.1million-3.8 million person years of employment.

With regards to the life sciences sector the combination of the Bayh Dole framework, the Diamond v. Chakrabarty decision and the scientific breakthroughs of the 1980s and 1990s laid the foundation for the biotechnology revolution and today's life sciences sector. Perhaps the most telling statistic is the strong growth in industryuniversity collaboration and the, in effect, institutionalization of this partnership as the foundation of modern drug development. For example, a decade after Bayh-Dole was passed the combined campuses of the University of California became the top recipient in the US of biotechnology patents; a position formally held by Merck.²⁴⁹ Similarly, looking at licensing income for US universities, not only has this grown exponentially since the mid-1980s but the life sciences sector is the predominant source of this income. For example, *Nature Biotechnology* in 2013 examined licensing income and sectorspecific sources of this income for top US universities and research institutes and found that of the USD1billion in total gross licensing income in 2013, over USD977million (97%) came from the life sciences sector.²⁵⁰ The number was similar with regards to the number of start-ups and licenses executed with the vast majority being in the life sciences sector.

1.4 Section summary

As the examples examined in this section show, IP incentives are at the heart of biopharmaceutical innovation.

Whether it be looking broadly at the evidence on products developed and rates of clinical trials or more tailored IP incentives including for rare diseases, biotechnology patentability or second use claims for incrementally improved products and technologies this section finds that IP incentives have stimulated new research and the development of new biopharmaceutical products.

The following case study changes focus. It zooms out from the micro, product perspective and looks at the role IP incentives play at a national level and how different countries have used IP incentives to build and develop their biopharmaceutical sectors.





2

CASE STUDY 2: FROM THE MICRO TO THE MACRO – HOW INTRODUCING TAILORED BIOPHARMACEUTICAL IP RIGHTS HELPED (AND IS HELPING) COUNTRIES AROUND THE WORLD BUILD STRATEGIC LIFE SCIENCES SECTORS

The preceding section examined the positive impact biopharmaceutical IP incentives have had on a micro basis, that is, on actual tangible medicines and biopharmaceutical products developed.

This section shifts the focus from the micro to the macro. It examines how IP based incentives have been used strategically by a growing number of countries as part of their national innovation and development reform efforts to build a thriving, high-tech biopharmaceutical/ medical sector. From Latin America, to Asia Pacific to the Mediterranean increasingly countries are recognizing the need for reforming their biopharmaceutical IP environments in order to reap the maximum positive impact of wider efforts to build thriving, R&D based life sciences sectors. This section examines two such cases: Israel and Singapore. These first two examples tell the story of the reform efforts of two relatively small economies not blessed with an abundance of natural resources or the magnetism of being a large market. Instead, to build their respective life sciences sectors both Israel and Singapore had to focus on getting their policies right and making their economies and environments as competitive as possible. Singapore is an example of how a country over a period of 10-15 years can move from having a relatively limited technical biopharmaceutical capacity to over time becoming both a leading high-end manufacturer and exporter of biopharmaceutical products as well as preeminent destination for advanced clinical research. Critically, biopharmaceutical IP reforms were an elemental part of Singapore's transformation. The Israeli story is slightly different in that Israel's biopharmaceutical capacity has always been quite advanced. Israel has for decades been a leader in the biomedical sciences and a destination for biomedical research. However, unlike most high-income OECD economies Israel for many years was an outlier with regards to international biopharmaceutical IP standards. Neither RDP nor patent term restoration were offered. Instead public policies were largely geared towards supporting the domestic generic industry and in particular national champions including Teva Pharmaceuticals. Yet over time the Israeli Government realized that its life sciences sector was being held back by low IP standards and by strengthening its biopharmaceutical IP environment in 2010 Israel became even more competitive.

2.1 Israel

Twenty years ago the innovative research-based biopharmaceutical sector in Israel consisted mainly of research organizations and early stage companies focused on licensing out technologies, with little development and commercialization of biopharmaceuticals and biomedical technologies in Israel. Yet over the past two decades Israel has seen a surge in enabling policies and incentives for biopharmaceutical innovation. According to the Office of the Chief Scientist's 2015 Innovation Report, the number of life sciences companies in Israel has increased by more than five times in the past 15 years (from 200 in the late 1990s to around 1,100 in 2015) and the sector represents around 18% of total exports.²⁵¹ Today at least 40%



of the total biopharmaceutical sector includes companies involved in biopharmaceutical discovery, development and delivery (with 22% engaged in drug discovery).²⁵² Despite the small size of the Israel domestic market. Israel hosts 19 local subsidiaries of research-based multinational biopharmaceutical companies and attracts a high level of R&D investment from PhRMA member companies. In 2012 they invested USD8.8 million per million population – a level comparable with Japan and leading EU markets. The Israeli innovative sector not only continues to play a role in many new biopharmaceuticals (with contributions from Israeli-developed technologies to a number of recent "blockbuster" biopharmaceuticals estimated at around 25%), but is also leading the development and marketing of cutting edge treatments, such as the Israeli company Protalix's BioTherapeutics plant cellbased enzyme replacement therapy for Gaucher disease.²⁵³ Yet it was only a few years ago that Israel was one of the few developed OECD economies to be included on the USTR's Special 301 Report. What happened?

Israel and biopharmaceutical IPRs – A checkered history

Israel has historically had a challenging IP environment, particularly in relation to biopharmaceuticals. The main reason originates in the longstanding Arab boycott initiated with the establishment of the State of Israel in 1948, which deterred foreign companies from commercial ties with Israel. Developing a strong, self-sufficient generic pharmaceutical industry to meet security and public health needs was a national interest.²⁵⁴ For example, in 1967 Israel modified its Patent Law to permit the domestic manufacturing of generic versions of patentprotected pharmaceutical products that were not marketed in Israel – a major driver for the sector's growth. As a result, the interests of the domestic generic pharmaceutical industry became embedded in Israel's governmental structures and policies (interestingly, to date Teva's stock is commonly referred to as "the people's stock").²⁵⁵ Perceptions began to shift during the mid-1990s, as Israel became a member of the WTO and a signatory to the TRIPS agreement. Nevertheless, until 2010 Israel's IP regime did not fully develop in-line with international standards. In 1998 the USTR moved Israel to the Priority Watch list within its annual 301 report following, among other issues, an amendment to the Patent Law permitting the use of innovators' confidential test data for commercial purposes without being accused of violating the patent (known as the 'Teva exemption').²⁵⁶ In 2005 an additional amendment to the Patent Law added burdensome conditions that rendered the option of receiving a period of patent term restoration nearly impossible.²⁵⁷ Earlier that year a different amendment to the Pharmacists Ordinance allowed the Israeli MoH to rely on innovative companies' confidential test data in approving follow-on products for local marketing and export.²⁵⁸ In addition, the regulatory environment, especially with regards to pharmaceutical patents and products approval, suffered from substantial backlogs due to a shortage of qualified personnel and red tape: the pharmaceutical patents review process took 4 years on average, and the regulatory approval by the MoH took between 12 and 24 months.²⁵⁹

Following the completion and signing of a MoU between the US and the Israeli Government the year 2010 marked a shift in Israel's IP framework, particularly in key areas of biopharmaceutical IP protection. A formal letter sent by the Israeli Minister of Industry, Trade and Labor to the US Trade Representative on February 18th, 2010, details the steps taken by the Israeli Government in improving its IP framework in three distinct areas: data protection, patent term extension and publication of patent applications.

Regulatory Data Protection

Prior to 2010 Israel did not provide adequate data protection for submitted biopharmaceutical test data as part of a marketing authorization application, mainly intending to strengthen domestic generic drugs manufacturers' exports.²⁶⁰ In 2011 the RDP term for new chemical drugs was increased to 6 years from the date of registration in Israel or 6.5 years from the date of registration in one of the recognized drug regulatory authorities (primarily the FDA and EMA).²⁶¹ Article 47(D) of the Pharmacists Ordinance provides a term of protection for submitted clinical research data of 6.5 years if the first marketing approval of the product was received in any recognized economy, or 6 years in case the first marketing approval of

FIGURE 12 Capital raised by Israeli life sciences companies, domestic v. foreign investors, 2010-2014 (in million USD)



Capital invested by domestic investors Capital invested by foreign investors Source: IATI, 2016; analysis: Pugatch Consilium said product was received in Israel.²⁶² To date, however, this term of protection has not been afforded to biologic drugs. And this remains a significant hole in Israel's IP framework.

Patent term restoration

Due to regulatory delays in marketing approval, a 2005 amendment to the Israeli Patent Law introduced certain provisions that rendered the option of obtaining this type of protection in Israel extremely difficult. For example, the amendment required that the restoration period would align to the shortest extension period granted within one of a basket of "recognized countries".²⁶³ Furthermore, the legislation stipulated that a similar PTE application must have been obtained in the US and at least one EU Member States prior to the submission of the application in Israel.²⁶⁴ In 2014 the Knesset amended the Patent Act and introduced a 5-year maximum term of restoration in line with prevailing international best practices. In addition, the number of recognized countries was substantially reduced and the condition of an approval of a PTE in the US and EU prior to its application in Israel was removed.²⁶⁵

Administrative and legal process improvements

The 2012 and 2014 patent amendments also introduced several additional improvements, including early publication of patent applications after 18 months from the date of application, and legal remedies in case of infringement cases during the early publication period.²⁶⁶ The Israeli Government also addressed the concerns raised by the USTR regarding backlogs and inefficiency of the regulatory approval process for pharmaceuticals. Under Government Decision No.183 of 2009 (implemented March 2010) amending the Pharmacists Regulations, marketing approvals are to be issued within 270 days from their submission.²⁶⁷ In 2014 the Government authorized a five-year plan aimed at decreasing the regulatory burden across the board.²⁶⁸ Among other elements, the plan set the objective of decreasing administrative costs by 25% through new requirements for regulatory agencies to opt for measures that bear the least regulatory burden.²⁶⁹ In addition, substantial resources were invested in improving the Israeli Patent Office.

Since 2012 the Patent Office began functioning as an International Searching Authority for Patent Cooperation Treaty applications and since 2014 as an International Searching & Examining Authority for PCT applications filed at the USPTO. In 2011 the Israeli Patent Office and USPTO initiated a Patent Prosecution Highway program whereby a special status may be granted to a patent application pending in one office based on positive examination results of the application in the other office.²⁷⁰

IP Reforms = real world results

What have been the results of Israel's IP reform efforts? Interestingly the positive impact these biopharmaceutical IP reforms have had can be seen almost immediately following their announcement in 2010. This is especially the case for levels of financial investment (especially by foreign companies) and economic activity within Israel's life sciences sector. The data is quite clear: since the IP policy reform efforts biopharmaceutical foreign direct investment into Israel has surged. Below Figure 12 shows the level of capital raised by Israeli life sciences companies annually between 2010 and 2014.

Two things stand out from the above figure. First, the substantial sustained increase in capital raised, growing from just over USD300 million in total in 2010 to over USD800 million in total by 2014. Second, the fact that this increase is almost completely driven by <u>foreign</u> investment. In 2010 the foreign share of capital raised was less than 20% of the total. By 2014 this had increased to close to 60%. While the protection of IP is only one of many factors that affect FDI, it is noteworthy that the improvement in Israel's IP environment was followed by such a marked rise in foreign-sourced investment.

No longer mutually exclusive: Strong IP rights and generic manufacturing

Perhaps the most interesting aspect of Israel's story is how its IP reform efforts have not hurt the position of the world's largest manufacturer of generic medicine and one of Israel's true national champions: Teva. Teva Pharmaceuticals is the world's largest generic drugs company owning subsidiaries and plants in 60 countries and employing over 46,000 people.²⁷¹ Indeed, a recent study estimating Teva's contribution to the Israeli economy suggests that under a scenario of Teva moving its activities out of Israel, the Israeli economy stands to lose 50.5 billion ILS in production terms and 22.7 billion ILS from its GDP.²⁷² It is therefore no surprise that in terms of public perception Teva is one of the most valued companies in Israel, and that its interests are at times viewed as being one and the same as that of the broader Israeli economy.²⁷³ Yet far from being hurt by the IP reforms of 2010, Teva has actually thrived. Since 2010 Teva's R&D expenditure on innovative activities has increased from 44% in 2009 to 55% in 2012, suggesting a positive link with the broader policy measures taken to strengthen Israel's IP regime. At the same time, the number of Israeli employees has increased by 17%, and the company's added value has grown by 78%.²⁷⁴

In sum, the Israeli experience suggests that, contrary to common perceptions and received wisdom, providing a supportive environment for innovative activities in the life sciences (including a robust IP regime) does not necessarily hurt the generic drugs industry. In fact, the R&D-based and the generic industries – often perceived as being mutually exclusive – in the Israeli case have turned out to be mutually beneficial.

2.2 Singapore

Today the success of Singapore as a high-tech economic powerhouse is largely taken for granted. The island-state has one of the highest per capita incomes in the world at an estimated USD 52,000 for 2015.²⁷⁵ This is higher than the UK, Germany, and just under that of the US. Yet only a generation ago, in 1990, Singapore was for all intents and purposes a developing world country with a per capita income about half of the Netherlands and just over a third of Sweden's.²⁷⁶ Its high-tech capacity was a Government aspiration and the future of the biopharmaceutical industry was a building site in Tuas.

Yet today Singapore remains the preeminent example of what can be achieved with the right policy mix over time. Singapore is a regional and global leader both in biopharmaceutical manufacturing and R&D. Of the top ten researchbased biopharmaceutical companies worldwide in 2014, seven manufactured a portion of their products in Singapore and eight had regional headquarters there with some choosing Singapore as a global manufacturing base.²⁷⁷ Manufacturing in 2013 alone was estimated at SGD23 billion, a value close to 5 times higher than in 2000.278 And for R&D capabilities there is a similar story. In 2013 around 50 biopharmaceutical companies carried out R&D activities in the country, including more than 30 top global biomedical companies.²⁷⁹ In addition, at least 40 corporate research laboratories were based in Biopolis together with A*STAR research institutes.²⁸⁰ Spending on biomedical research makes up a substantial part of the overall R&D expenditure in Singapore (which is about 2% of GDP).²⁸¹ In 2011 biomedical sciences R&D accounted for SGD1.509 million of which SGD573.8 million came from the private sector and SGD 935.2 million from the public sector.²⁸² Moreover, a relatively high number of researchers and scientists are employed in the biomedical sector. In 2011, biomedical researchers and scientists (including both private and public sectors) made up 22% of the overall number of researchers and scientists in the country.²⁸³ Looking at R&D investment from the angle of clinical research, Singapore has a high rate of clinical trials per capita, among the highest globally at around 300 clinical trials per million population to date.²⁸⁴ And nearly half of clinical trials in Singapore in recent years are for the more complex and cutting edge Phase I and II trials suggesting a strong technical R&D capacity.²⁸⁵ Indeed, many of the top global research-based companies have established their regional clinical trial center in there.²⁸⁶ Figure 13 below shows how since 2008 a large proportion of Singapore's clinical trials is in early phase complex research.

A key driver of Singapore's success: The 2003 US-Singapore FTA

Combined with the heavy and sustained emphasis on building technical, physical and educational capacity was Singapore's efforts in improving its regulatory and IP environment. What is instructive about Singapore is that the focus of the Government's reform efforts was not only on building physical infrastructure or investing in improving the technical R&D capabilities of R&D staff or companies. Singapore also fundamentally reformed its IP environment, strengthening and



FIGURE 13 Clinical trials in Singapore, by phase, 2005-2015

Source: Clinicaltrials.gov, 2016; analysis: Pugatch Consilium

introducing a number of new biopharmaceutical specific IP rights through the 2003 US-Singapore FTA. The final agreement signed and ratified in 2003 (negotiations began in 2000) included provisions relating to the following key areas:

- a 5-year term of regulatory data protection for submitted biopharmaceutical clinical test data;
- a 5-year term of patent restoration for undue delays caused during the patent and/or marketing approval process; and
- a linkage mechanism whereby a rights-holder is required to be notified by relevant authorities of any follow-on application for marketing approval during an existing patent term of protection.²⁸⁷

Showing the positive impact of these reform efforts and the implementation of the provisions of the FTA is the strong overall growth in levels of recorded biomedical investment post 2003 and the implementation of the agreement. In a 2010 Journal of Commercial Biotechnology article Pugatch and Chu examined this relationship showing how Singapore's strengthening of its biopharmaceutical IP environment coincided with a strong rise in biomedical investment levels.²⁸⁸ With the improvement to its biopharmaceutical IP environment (measured by its Pharmaceutical IP Index score which rose from 3.3 in 1998 to 4.4 in 2004, following the FTA) they found the volume and value of FDI in biomedical research, including in clinical trials, increased exponentially. Below Figure 14 displays the relationship between the improvement in the Pharmaceutical IP Index and levels of biomedical investment.

Close to fifteen years on from its reform efforts Singapore continues to be considered a top performer and destination for biopharmaceutical companies and executives. In the 2016 Biopharmaceutical Competitiveness Index executive opinion survey Singapore was ranked number 1 with particular strengths in its biopharmaceutical IP environment.²⁸⁹

FIGURE 14 FDI in Biomedical R&D in Singapore (calculations based on A*STAR R&D Survey Statistics 2000-2008)²⁹⁰







3

CONCLUSIONS AND FINAL THOUGHTS

The purpose of this report has been to discuss and describe the positive and critical manner in which IP incentives and rights have played in stimulating biopharmaceutical innovation. Debates over the value if IP rights to innovation are not new.

As was noted above some of the fiercest – and also most sophisticated – debates about the costs and benefits of IP rights actually took place in the mid to late 1800s. An IP right is per definition a right of monopoly granted by society in order not only to make that particular innovation or product of creativity available to society but also as a tool to further incentivize the creation of future ideas and commercial products. The basic premise being that the cost of the monopoly today is worth the return in terms of the generation of new products and ideas. This is particularly the case for the biopharmaceutical sector where the cost of innovation is both high and the returns are highly uncertain.

Whether it be targeting specific medical areas, such as rare diseases; types of innovation; as a means of developing the life sciences sector as an engine of economic development and growth; or incentivizing the commercialization of publicly funded research; this paper has found a comprehensive body of evidence that IP incentives are an effective mechanisms in stimulating biopharmaceutical innovation.

Key findings

The main conclusions of the report can be grouped around four key findings.

Key finding 1: Orphan drug laws and their provision of market exclusivity incentives have led to significant new research, clinical trials and the development of new drugs for rare diseases

First developed in the US in the mid-1980s, IP based market exclusivity provisions have been at the core of the most successful schemes used to stimulate research into rare diseases globally. The most successful orphan drug schemes are the ones that include a clear and strong IP/market exclusivity incentive. The EU and the US are the leaders in developing new products and technologies for rare diseases and critically both have in place a strong and pronounced IP incentive. Other countries with strong IP incentives (e.g. Japan) have other regulatory barriers in place. Looking at concrete outputs orphan drug schemes in the US and EU have led to sustained and increased number of designations, clinical trials and the approval of new products:

- The number of orphan drug designations in the US, EU and Japan has grown from 150 in 2001 to 557 in 2016.
- A significant and sustained increase in new clinical trials for drugs treating rare diseases has been registered since the introduction of orphan drugs schemes; particularly in Europe. In the EU, orphan drug clinical trials grew by 84% from 2005 to 2015.
- The annual numbers of orphan drug product approvals has also steadily increased. The US continues to have the highest total number of approvals. Only 10 products were approved between 1973 and 1983 compared to more than 575 since then.
- As of end 2016, EU designations have resulted in authorized medicinal products for 101 conditions.

Key finding 2: IP incentives are a key driver in incremental improvements in some of the most heavily prescribed medicines (including insulin, statins, oral contraceptives and beta-blockers) that over time have resulted in radically improved and effective products that are safer and easier to use for patients

Second and new uses for existing drugs and treatments are an essential part of

biopharmaceutical innovation. Incentives, such as the ability to patent second and new uses of existing products, are fundamental to continue encouraging investment into continuous improvement and R&D. First generation products are barely comparable to later generation technologies with improvements in delivery, efficacy and a reduction in unwanted side effects some of the most common innovations. Examples of incrementally improved products include:

- Beta-blockers: The first generation of betablockers were non-selective, meaning that they blocked both types of adrenoceptors (β1 and β2). In contrast, second generation beta-blockers are more selective for which types of adernoceptors they block (cardioselective). Third generation beta-blockers also have blood vessel relaxing properties ("vasodilator actions") through their blocking of vascular alpha-adrenoceptors.
- Oral contraceptives: The first generation of oral contraceptives contained very high levels of both estrogen and progestogen which were found to raise the risk of blood clots. Gradually, the concentration of estrogen has been reduced to the minimum amounts needed for safe and effective contraception; from a high of 150 µg with some pills today containing under 20 µg of estrogen. Moreover, modern contraceptives have also introduced phased hormonal dosages through the contraceptive cycle.
- Anti-retrovirals: The first generation of antiretroviral drugs had both serious side effects and were combination therapies requiring the consumption of large volumes of medication several times per day. New therapies have been introduced based on incremental innovations that allow for combination pills. Instead of an array of pills taken every few hours, the most recent products only require a single pill be taken once daily.

Key finding 3: Targeted IP incentives on biotech patentability standards and technology transfer laws introduced in the 1980s are key drivers of the American biotechnology innovation revolution

The US Supreme Court's 1980 decision *Diamond v. Chakrabarty* holding that living matter is

patentable when created by human ingenuity put the conditions in place for the development of new biotech based products and technologies. Since 1985 the US has accounted for the largest share of triadic biotechnology patenting activity in the world at just over 43%. Equally the Bayh Dole technology transfer framework and accompanying IP regulations for publicly funded research has had a dramatic impact on the American economy and the life sciences sector. Since the mid-1990s the contribution of academic licensing to gross industry output was estimated at USD282-1,180 billion (measured in 2009 USD), contributions to GDP at USD130-518 billion creation of 1.1million-3.8million person years of employment. Looking at licensing income for the top US universities and research institutes over USD977million (over 97%) of the USD1billion in total gross licensing income in 2013 came from the life sciences sector.

Key finding 4: IP incentives have been a critical part of national high-tech economic development and the building of cutting-edge biopharmaceutical sectors

Singapore and Israel have relied on IP reforms to build and improve their national life sciences sectors:

- The 2003 implementation of the US-Singapore FTA (negotiations began in 2000) and biopharmaceutical IP reform coincided with a strong rise in biomedical investment levels which grew 10-fold between 2000-2008.
- During this time Singapore grew from a limited manufacturing base to a regional and global biopharmaceutical manufacturing hub – manufacturing in 2013 alone was estimated at SGD23 billion, a value close to 5 times higher than in 2000.
- Similarly the volume of clinical research has close to doubled with a growing emphasis on complex early phase research. Nearly half of clinical trials in Singapore in 2014-15 were for more complex and cutting edge Phase I and II trials.
- Subsequent to Israel's 2010 IP reforms capital raised by the Israeli life sciences sector grew substantially, from just over USD300 million in

total in 2010 to over USD800 million in total by 2014. This increase was almost completely driven by foreign investment. In 2010 the foreign share of capital raised was less than 20% of the total. By 2014 this had increased to close to 60%.

 Israel's generic sector (including its national champion Teva) were not adversely affected by the 2010 IP reforms. Since 2010 Teva's R&D expenditure on innovative activities has increased from 44% in 2009 to 55% in 2012, the number of Israeli employees has increased by 17%, and the company's added value has grown by 78%.

Closing thoughts

This paper began by looking at one of the major global health challenges of the 21st century: Alzheimer's and neurodegenerative diseases. Having spent the preceding two sections detailing the concrete, measurable benefits IP incentives have had on biopharmaceutical innovation and new product development this paper will close with an idea on the potential a tailored IP incentive could have for the development of a new generation of treatments for Alzheimer's and related diseases.

Designing a targeted IP incentive for Alzheimer's and related dementias

Examining the experience with rare disease and the types of frameworks and incentives in place globally, section 1 of this paper found that the EU and US have had the most success in stimulating both R&D into rare diseases and actual product development and dissemination. In other countries that have special rare disease incentives in place these tend to be either not very generous or hampered by other regulations. For example, Australia's regulatory incentives are relatively limited and primarily target market authorization fee waivers. Japan has a framework similar to the US that includes both a strong exclusivity period of 10 years and potential for research grants to cover development costs, yet because of its specific requirement that products demonstrate a 'high possibility of development' to be designed as orphans, the Japanese scheme results in later stage (and fewer) designations.

Comparing the EU and US the biggest differences are in the length of potential market exclusivity periods and availability of other incentives, such as tax credits or research grants. The EU provides the potential for a 12 year exclusivity period (10+2) whereas the American term is a maximum of 7 years. Unlike the US, the EU does not provide any R&D tax incentives (these exist only at the Member State level and are relatively limited) and small, but growing, support through research grants. Yet the focus on a long and relatively strong exclusivity period has had a pronounced and sustained impact on R&D on rare diseases and innovation in the EU. Indeed, despite the fact that the EU's framework was introduced half- a generation after the US, since the mid-2000s major EU countries have steadily increased their R&D capacities for rare conditions (from 71 trials in 2005 to 130 in 2015) and the number of orphan drug designations has increased.

In sum, while the exact length of any proposed exclusivity period and the interaction with other incentives (such as R&D grants and tax incentives) is unclear and will largely depend on the preexisting IP incentives and frameworks in place in a given country/jurisdiction, <u>what is clear is that</u> a clearly defined statutory market exclusivity period would have the potential of stimulating significant R&D and resources into what is likely to be one of the key health challenge of the 21st century.

In fact, perhaps the primary finding or lesson from this report is not on how IP based incentives have acted and impacted biopharmaceutical innovation in the past, but simply how, despite their age and inherent flaws, they are one of the most effective and proven tools in the battle against disease and illness. Perhaps the answer to the Alzheimer's riddle and other major health challenges lay in our experiences from what was perceived over two decades ago as an impossible challenge, that is, that of rare diseases.

NOTES

- Institute for Health Metrics and Evaluation (2016) "GBD Compare", data visualization
- Eurostat (2016) "Population structure and ageing". Statistics explained. June 2016
- Testimony of Harry Johns, President and CEO of the Alzheimer's Association Fiscal Year 2014 Appropriations for Alzheimer's-related Activities at the U.S. Department of Health and Human Services Subcommittee on Labor, Health and Human Services, Education and Related Agencies Committee on Appropriations United States House of Representatives March 13, 2013
- Alzheimer's Association (2015) Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars, pp. 4-6. One estimate suggests that the failure rate for Alzheimer's drugs in
- Phases II and III of clinical testing has been virtually 100% (99.6%). See: R Wright (2016) "Convince Me Why Investing In Alzheimer's R&D Is A Good Idea", Life Science Leader, May 1 2016
- PhRMA (2012) Researching Alzheimer's Medicines: Setbacks and Stepping Stones, pp. 12-13. Quoted in F Machlup & E Penrose (1950) "The Patent Controversy in
- the Nineteenth Century", Journal of Economic History, Vol 10, No 1, May 1950
- UN High-level Panel on access to medicines (2016), PROMOTING INNOVATION AND ACCESS TO HEALTH TECHNOLOGIES, September 2016, pp.9-10.
- UN High-level Panel on access to medicines (2016), PROMOTING INNOVATION AND ACCESS TO HEALTH TECHNOLOGIES, September 2016, pp.9-10.
- JA DiMasi et al (2003). "The price of innovation: new estimates of drug development costs." Journal of health economics 22.2 (2003): 151-185.
- D Mestre-Ferrandiz et al (2012), "The R&D cost of a new medicine." London: Office of Health Economics p. v.
- WHO (2006), "The pharmaceutical industry in Europe, key data", PowerPoint
- 13 A Attaran (2004), How Do Patents and Economic Policies Affect Access to Essential Medicines in Developing Countries? Health Affairs, Vol.23, No.3, pp.155-66
- The Patent Act (1970), Section 3, "Inventions not Patentable". Text available at http://ipindia.nic.in/ipr/patent/eVersion_ActRules/ sections/ps3.html; See OPPI (2015), "Position on Narrow Patentability Criteria", 05/2015, www.indiaoppi.com/sites/default/files/PDF%20 files/Position%20on%20Narrow%20Patentability%20Criteria%20-%20 May%202015_0.pdf
- Pharma Times, "India rejects Astraz Zeneca patent appeal on Iressa", 2012, www.pharmatimes.com/Article/12-11-29/India_rejects_ AstraZeneca_patent_appeal_on_Iressa.aspx Economic Times (2015), "Commerce and Industry Ministry
- Considering Proposal for Compulsory License to Anti-Cancer Drug' 07/24/2015. http://articles.economictimes.indiatimes.com/20150724/ news/6417507_1_compulsorylicencedasatinibanticancerdrug; Business Insider, "India defends right to issue drug 'compulsory licenses'", 3/23/2016, www.businessinsider.com/r-india-defends-right-
- to-issue-drug-compulsory-licenses-2016-3 K. Srinath Reddy (2015), "India's Aspirations for Universal Health Coverage", The New England Journal of Medicines, 07/02/2015, www. nejm.org/doi/full/10.1056/NEJMp1414214?af=R&rss=currentIssue
- Lanjouw, J. (1997), The Introduction of Pharmaceutical Product Patents in India: Heartless Exploitation of the Poor and Suffering, Center Discussion Paper, No.775; Kapczynski, A. (2013), "Engineered in India – Patent Law 2.0", New England Journal of Medicine, Vol.369, pp.497-99
- Forbes (2014), "Five Things to Know about India's Healthcare System" 09/2014, http://forbesindia.com/blog/health/5-things-to-know-aboutthe-indias-healthcare-system/
- Early-phase clinical trial activity is measured as the gross number of phase I and phase II clinical trials to date per economy, as registered in clinicaltrials.gov database, standardized per million population; Source: Clinicaltrials.gov, (2016); The World Bank, (2016). A more detailed discussion on the components of the biopharmaceutical R&D process is provided at: Pugatch Consilium, (2014). Scaling up global clinical trial activity: Key trends and policy lessons, pp. 14-18. Life sciences-related indicators consist of indicators falling under the Patent category of the GIPC Index (excluding patentability of computer-implemented inventions), as well as indicators in Trademarks and Market Access, Enforcement and International Treaties categories that are relevant to life sciences (specifically: 1-2, 4-8, 15-21, 22-24, 25, 27-31, 33-35).
- 21 HG Grabowski and YR Wang (2006) "The Quantity And Quality Of Worldwide New Drug Introductions, 1982-2003", Health Affairs, Vol. 25, No. 2
- 22 US Chamber of Commerce GIPC (2017) IP - A GLOBAL NAVIGATION SYSTEM FOR THE KNOWLEDGE ECONOMY, Supplemental Statistical Analysis to the U.S. Chamber International IP Index, 2017.

- ²³ Paul D. Maher & Marlene Haffner (2006), "Orphan Drug Designation And Pharmacogenomics: Options And Opportunities", BioDrugs 20:71, http://link.springer.com/article/10.2165/00063030-200620020-00001?no-access=true
- 24 Evaluate Pharma (2017), "Orphan Drug Report 2017", February 2017, p.8.
- 25 Ibid
- 26 EURORDIS (2007), "What Is A Rare Disease?", 4/17/2007, http://www. eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf
- Stephen C. Groft (2016) "Global View of the Rare Diseases Field", ICORD 11th Annual Conference, October 2016. www.ema.europa.eu/docs/en_GB/document_library/ Presentation/2014/03/WC500164162.pdf
- EC/IRDIRC (2014), "EU Research Funding for Rare Disease Research", March 2014, www.ema.europa.eu/docs/en_GB/document_library/ Presentation/2014/03/WC500164162.pdf
- EY (2015), "Impact of the Orphan Drug Tax Credit on Treatments for rare diseases", June 2015. EC/IRDIRC (2014).
- 30
- 31 Philip J. Vickers (2013), "Challenges And Opportunities In The Treatment Of Rare Diseases", Spring 2013, www.ddw-online.com/ therapeutics/p211490-challenges-and-opportunities-in-the-treatmentof-rare-diseases-spring-13.html Ibid.
- 33 Japan alone designates also medical devices as orphan products. Drusilla Scott (2001), "Orphan Drug Programs/Policies in Australia, Japan, and Canada", Therapeutic Innovation and Regulatory Science, www.researchgate.net/publication/254087308_Orphan_Drug_ ProgramsPolicies_in_Australia_Japan_and_Canada
- Referred in the US as New Drug Application (NDA)/Biological Licensing Application (BLA) Approval.
- Sec. 526 Of The Federal Food, Drug, And Cosmetic Act, www.fda. gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ HowtoapplyforOrphanProductDesignation/ucm364750.htm
- Intractable ('Nambyo') diseases are those. Intractable (referred to in Japanese as 'Nambyo') diseases are conditions without clear cause and treatment that develops into chronic disability and whose diagnosis may depend on the level of healthcare and the social state of affairs of a country at that time. For the full definition see the Japan Intractable Disease Information Center, "What is an Intractable Disease?" (accessed March 2017), www.nanbyou.or.jp/english/index. htm
- Pacific Bridge Medical (2015), "Japan Expands Orphan Drug Designation Criterion", 5/1/2015, www.pacificbridgemedical.com/ news-brief/japan-expands-orphan-drug-designation-criterion/
- 38 As well as vaccines against emerging or re-emerging infectious disease associated with genetic mutation susceptible to have high impact or Japanese population www.mhlw.go.jp/english/policy/health-medical/ pharmaceuticals/orphan_drug.html
- Manabu Murakami & Mamoru Narukawa (2016), "Matched Analysis On Orphan Drug Designations And Approvals: Cross Regional Analysis In The United States, The European Union, And Japan", Drug Discovery Today, Volume 21, Issue 4, April 2016, Pages 544–549. Ministry of Health, Labor and Welfare, "Overview of Orphan Drug/
- Medical Device Designation System" (accessed March 2017), www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/ orphan_drug.html
- James Reese (2014)," FDA Orphan Drug Designation 101", www.ema. 42 europa.eu/docs/en_GB/document_library/Presentation/2014/03/ WC500164160.pdf
- Pacific Bridge Medical (2014), "Guidelines and Regulatory Requirements To Help Orphan Drug Products Enter the Asian Market", p.34, www.pacificbridgemedical.com/wp-content/uploads/2015/04/ Orphan-Drugs-in-Asia-2014.pdf
- EMA website, "Annual Report on Development" (accessed March 2017), www.ema.europa.eu/ema/index.jsp?curl=pages/ regulation/document_listing/document_listing_000343. jsp&mid=WC0b01ac058061f018
- See for the US the Orphan Drug Final Rule (2013), Federal Register/Vol. 78, No. 113 www.gpo.gov/fdsys/pkg/FR-2013-06-12/pdf/2013-13930. pdf and for the EU the EMA website, "Marketing Authorisation and Market Exclusivity" (accessed March 2017), www.ema.europa.eu/ema/ index.jsp?curl=pages/regulation/general/general_content_000392. jsp&mid=WC0b01ac058061f019
- Ibid.; For the US see Code of Federal Regulations, 21 CFR Ch. I (4–1–12 Edition), Sub-part D, www.gpo.gov/fdsys/pkg/CFR-2012-title21-vol5/ pdf/CFR-2012-title21-vol5-sec316-30.pdf As well as drugs with NCE for serious conditions
- Regulation EC/726/2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicine Agency,

http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/ reg_2004_726/reg_2004_726_en.pdf; EMA website, "Authorization of Medicines" (accessed March 2017),

www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/

- www.ema.europa.eu/ema/index.jsp/curi=pages/about_us/general/ general_content_000109.jsp&mid=WC0b01ac0580028a47 Orphan Drug Final Rule (2013), Federal Register/Vol. 78, No. 113, www.gpo.gov/fdsys/pkg/FR-2013-06-12/pdf/2013-13930.pdf; Arnall Golden Gregory LLP/Lexology (2013), "FDA Publishes Final Rule on Orphan Drug Exclusivity", 7/5/2013, www.lexology.com/library/detail. aspx?g=7687103b-6739-48e1-9172-25ee21143aef
- EMA website, "Committee for Orphan Medicinal Products Strengthened Interactions With Patients And International Partners" (accessed March 2017), 2/14/2013, www.ema.europa.eu/ema/index. jsp?curl=pages/news_and_events/news/2013/02/news_detail_001718. jsp&mid=WC0b01ac058004d5c1 CADTH (2016), "Drugs for Rare Diseases: Evolving Trends in Regulatory
- and Health Technology Assessment Perspectives", 2/11/2016, www.cadth.ca/drugs-rare-diseases-evolving-trends-regulatory-andhealth-technology-assessment-perspectives
- 52 See the US Code of Federal Regulations, Part 316 "Orphan Drugs www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=0e737d105ef9a1632b19a 1e713b93cc4&mc=true&n=pt21.5.316&r=PART&ty=HTML EMA website, "Marketing Authorization and Market Exclusivity"
- 53 (accessed March 2017), www.ema.europa.eu/ema/index jsp?curl=pages/regulation/general/general_content_000392.
- jsp&mid=WC0b01ac05806ff019 Matthew Thomas/FDA, "The Orphan Drug Act and the Development of Products for Rare Diseases", https://rarediseases.info.nih.gov/files/ fda%20orphan%20drugs.pdf
- 55 Irene Nordstedt/EC (2014), "International Rare Diseases Research Consortium - EU Research Funding For Rare Disease Research 3/10/2014, www.ema.europa.eu/docs/en_GB/document_library/ Presentation/2014/03/WC500164162.pdf
- Hirofumi Kusunoki/NIBIO (2014), "Grant Frameworks: Japan" 3/10/2014, www.ema.europa.eu/docs/en_GB/document_library/ Presentation/2014/03/WC500164163.pdf
- Carolyne Hathaway, John Manthei and Cassie Scherer (2009), "Exclusivity Strategies in the United States and European Union", May/ June 2009, www.lw.com/upload/pubcontent/_pdf/pub2655_1.pdf
- 58 Sumin Kim (2013), "The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity", Northwest Journal of Technology and Intellectual Property", Volume 11, Issue 6, http://scholarlycommons. law.northwestern.edu/cgi/viewcontent.cgi?article=1200&context=njtip
- EMA website, "Marketing Authorisation and Market Exclusivity" (accessed March 2017), www.ema.europa.eu/ema/index sp?curl=pages/regulation/general/general_content_000392. jsp&mid=WC0b01ac058061f019 Sumin Kim (2013), "The Orphan Drug Act: How the FDA Unlawfully
- Usurped Market Exclusivity", North western Journal of Technology and Intellectual Property, Issue 11, Vol.6, Art.3, http://scholarlycommons. law.northwestern.edu/cgi/viewcontent.cgi?article=1200&context=njtip
- Jenkins (2013), "Developing Orphan Drugs in Europe", Patent Issues Jenkins Information Sheet 02/2013, www.maucherjenkins.com/assets/ Publications/Fact%20Cards%20and%20Guides/Orphan%20Drugs_ aligned-3.pdf
- Article 37 of the Regulation on medicinal products for paediatric use.
- Article 37 of the Regulation on medicinal products for pediatric use and See EMA (2013). EC (2006), "Regulation on medicinal products for pediatric use and amending Regulation", art.t 36-37, 12/12/2006, http://ec.europa. eu/health//sites/health/files/files/euralex/vol-1/reg_2006_1901/ reg_2006_1901_en.pdfEC (2013), "Better Medicines for Children — From Concept to Reality General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use", 6/24/2013, p.8, http://eur-lex.europa.eu/ legal-content/EN/TXT/PDF/?uri=CELEX:52013DC0443&from=EN
- US FDA website, "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A)" (Accessed March 2017), www.fda.gov/Drugs/DevelopmentApprovalProcess/ DevelopmentResources/ucm077915.htm
- Hiroshi Takeda/MHLW (2014), "Incentives and Regulatory Considerations in Orphan Drug/Medical Device Development-Situation in Japan", www.ema.europa.eu/docs/en_GB/document library/Presentation/2014/03/WC500164166.pdf; Vishva V. Ramlall (2004), "The Pharmaceutical Industry in The Great White North and Land of the Rising Sun: A Comparison of Regulatory Data Protection in Canada and Japan", www.iip.or.jp/e/e_summary/pdf/detail2003/ e15 12.pdf
- Morrison & Foerster LLP (2012), "Patent Term Extensions And Regulatory Exclusivities For Pharmaceuticals In Asia And South America", 6/27/2012, www.lexology.com/library/detail. aspx?g=0a295b70-e577-461b-99e5-48e0eeeac512;
- Both in the US and EU orphan exclusivity can be revoked if the second drugs proves to be clinically superior, the orphan drug is not adequately supplied on the market or its sponsor consent to the competitor entering the market.
- FDA website "Background Information: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple

Book)", www.fda.gov/Drugs/DevelopmentApprovalProcess/ HowDrugsareDevelopedandApproved/ApprovalApplications/ TherapeuticBiologicApplications/Biosimilars/ucm411424.htm; Guidance for Industry Reference Product Exclusivity For Biological Products Filed Under Section 351(a) of the PHS Act", www.fda.gov/

- downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/UCM407844.pdf EMA (2013), "An Agency Of The European Union Data Exclusivity, Market Protection and Pediatric Rewards", Workshop for Micro, Small and Medium Sized Enterprises, 4/26/2013, www.ema.europa.eu/docs/ en_GB/document_library/Presentation/2013/05/WC500143122.pdf Ibid
- CFR Title 21, Part 36, www.accessdata.fda.gov/scripts/cdrh/cfdocs/ cfcfr/cfrsearch.cfm?cfrpart=316&showfr=1&source=govdeliver y&subpartnode=21%3A5.0.1.1.6.4&utm_medium=email&utm_ source=govdelivery
- www.fda.gov/Drugs/DevelopmentApprovalProcess/
- SmallBusinessAssistance/ucm069962.htm
- Zaida Fries (2013), "An Agency Of The European Union Data Exclusivity, Market Protection And Pediatric Rewards", 4/26/2013, www. ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/ WC500143122.pdf
- Hogan Lovells?Lexology (2015), "EU Orphan Drug Exclusivity", 1/26/2015, www.lexology.com/library/detail.aspx?g=ec701168-35a3-41e6-a79f-b14cd3ce0594
- Office of the Assistant Secretary for Planning and Evaluation (ASPE)/ US Ministry of Health (2016), "Report to Congress: Prescription Drugs: Innovation, Spending, and Patient Access", p.33, http://delauro.house. gov/sites/delauro.house.gov/files/Prescription-Drugs-Innovation-Spending-and-Patient-Access-12-07-16, pdf European Commission (2016), "Inventory of Union and Member
- State incentives to support research into, and the development and availability of, orphan medicinal products State of Play 2015"
- Many countries have national orphan drug plans with complementary incentives to promote R&D into and accessibility of orphan drugs, including reduced fees for registration and academic clinical trials, grants, compassionate programs and special reimbursement onditions.
- Ministry of Health, Labor and Welfare website, "Overview of Orphan Drug/Medical Device Designation System" (accessed March 2017), www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/ orphan_drug.html
- Hirofumi Kusunoki (2013).
- 80 Orphanet website, "Orphan Drugs in Japan" (accessed March 2017), www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs. php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ ABOUTORPHANDRUGS_JAP Michael Mehzer (2015), "Johns Hopkins Researchers Call for Orphan
- Drug Reform", 11/20/2015, www.raps.org/Regulatory-Focus/ News/2015/11/20/23651/Johns-Hopkins-Researchers-Call-for-Orphan-Drug-Reform/#sthash.FXTg6jmv.VWlcjUpL.dpuf www.raps org/Regulatory-Focus/News/2015/11/20/23651/Johns-Hopkins-Researchers-Call-for-Orphan-Drug-Reform/#sthash.FXTg6jmv.dpuf
- EMA (2013), "Japanese Orphan Drug Designation", www.ema europa.eu/docs/en_GB/document_library/Presentation/2013/10/ WC500152531.pdf
- Irene Norstedt/EC (2014). US FDA website, "Orphan Products Clinical Trials Grants Program" (accessed March 2017), www.fda.gov/ForIndustry/ DevelopingProductsforRareDiseasesConditions/
- WhomtoContactaboutOrphanProductDevelopment/default.htm Erika McNelly/FDA (2014), "Orphan Products Grants Program Overview", www.ema.europa.eu/docs/en_GB/document_library/ Presentation/2014/03/WC500164161.pdf
- Office of Orphan Product Development/FDA, "Budget Report 2016", www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/
- BudgetReports/UCM438013.pdf JDSupra (2016), "Thanks to 21st Century Cures, the Sun is Coming out Tomorrow for Orphan Drugs and Pediatric Priority Review Vouchers", 16/12/2016, www.jdsupra.com/legalnews/thanks-to-21st-centurycures-the-sun-is-44718/
- Susan Forda/EFPIA (2016), "EMA's PRIME can help speed delivery of new medicines to patients", 3/1/2016, http://efpiamapps.eu/emasprime-can-help-speed-delivery-of-new-medicines-to-patients-bysusan-forda/
- Todd Gammie & Christine Lu (2015), "Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries", 10/9/2015, http://journals.plos.org/plosone/ article?id=10.1371/journal.pone.0140002 FDA website, "Priority Review" (March 2017), www.fda.gov/ForPatients/ Approvals/Fast/ucm405405.htm; FDA (2016), "CY 2016 CDER Drug and Diche ic Calcada Vace Priority Approvals (2016), "CY 2016 CDER Drug
- and Biologic Calendar Year Priority Approvals As of December 31, 2016," www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/ HowDrugsareDevelopedandApproved/ DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ UCM540570.pdf

- ⁹¹ FDA (2016), "CY 2016 CDER Drug and Biologic Calendar Year Priority Approvals As of December 31, 2016", www. fda.gov/downloads/Drugs/DevelopmentApprovalProcess/ HowDrugsareDevelopedandApproved/ DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ UCM540570.pdf
- Drugs with major therapeutic advantage over existing treatments, or which benefit patients without treatment options.
- Commission Regulation EC/507/2006 of 29 March 2006 On The Conditional Marketing Authorization For Medicinal Products Fo Human Use Falling Within The Scope Of Regulation (EC) No 726/2004 of the European Parliament and of the Council, http://ec.europa. eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_507/ reg_2006_507_en.pdf
- Hiroshi Takeda (2014).
- Ministry of Health, Labor, Welfare (2014), "Strategy of SAKIGAKE", www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/ dl/140729-01-01.pdf; IDA website, "SAKIGAKE (Forerunner) Initiative" (accessed March 2017), https://www.i-d-a.com/japans-regulatoryenvironment/sakigake-forerunner-initiative/
- libid.
- In 2016, fee reductions for designated orphan products cost the EU EUR12.7 million, of which more than half for protocol assistance; Thomas Meek/PMLive (2013), "EMA – more fee reduction for Orphan Drugs", www.pmlive.com/pharma_news/ema_more_fee_reductions_ for_orphan_drugs_523882; EMA (2017), "Annual Report On The Use Of The Special Contribution For Orphan Medicinal Products Year 2016", 1/25/2017, www.ema.europa.eu/docs/en_GB/document_library/ Report/2017/02/WC500221159.pdf
- Alexander Gaffney/RAPS (2013), "EMA Announces User Fee Reductions for Orphan Drugs", 12/3/2013, www.raps.org/focus-online/
- news/news-article-view/article/4376/ EMA (2014), "European Medicines Agency Applies Greater Fee-Reduction Rates For Orphan Medicines In 2014", www.ema.europa. eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/ news_detail_001984.jsp&mid=WC0b01ac058004d5c1
- Guidance is also provided to establish the need of a Pediatric Investigational Plan and advices on compassionate use.
- Thomas Meek/PMLive (2013). 101
- 102 EMA (2017).
- ¹⁰³ Japanese Ministry of Health, Labor and Welfare website, "Overview of Orphan Drug/Medical Device Legislation" (accessed March 2017), www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/ orphan_drug.html
- Office of the Assistant Secretary for Planning and Evaluation (ASPE)/ US Ministry of Health (2016), "Report to Congress: Prescription Drugs: Innovation, Spending, and Patient Access", p.33, http://delauro.house. 104 gov/sites/delauro.house.gov/files/Prescription-Drugs-Innovation-Spending-and-Patient-Access-12-07-16.pdf
- ¹⁰⁵ Stephen C. Groft (2016) "Global View of the Rare Diseases Field", ICORD 11th Annual Conference, October 2016. www.ema.europa.eu/docs/en_GB/document_library/ Presentation/2014/03/WC500164162.pdf www.thomsonreuters.com/ content/dam/openweb/documents/pdf/pharma-life-sciences/whitepaper/1001450.pdf
- Todd Gammie & Christine Lu (2015), Brazilian Ministry of Health Ordinance N. 199, http://bvsms.saude.gov. br/bvs/saudelegis/gm/2014/prt0199_30_01_2014.html Renee J.G.Arnold et al/F1000Research (2015), "The Role Of 107 108
- Globalization In Drug Development And Access To Orphan Drugs: Orphan Drug Legislation In The US/EU And In Latin America", https:// f1000research.com/articles/4-57/v1
- ¹⁰⁹ Federal Law N.323 FZ.

60

- Gulce Belcin/PharmExec (2016), "Access to Orphan Drugs in Turkey", 1/6/2016, www.pharmexec.com/access-orphan-drugs-turkey
- ¹¹¹ Any doctor or dentist identifies and requests the use of orphan drugs to treat their patients without any formal designation process (art 2) Life saving orphan drugs – as any other drug – can benefit from priority review if there is unmet medical need. See text of the Medicines Act at www.hsa.gov.sg/content/dam/HSA/HPRG/Useful_Information_for_ Applicants/Legislation/MEDICINES%20(ORPHAN%20DRUGS)%20
- (EXEMPTION)%20ORDER.pdf ¹¹² Aarti Sharma et al (2010), "Orphan drug: Development Trends and Strategies", Journal of Pharmacy and BioAllied Sciences, Vol.2, Issue 4, /www.jpbsonline.org/article.asp?issn=0975-7406;year=2010;volume=2;i sue=4;spage=290;epage=299;aulast=Sharma
- SSUE=4;Spage=270;epage=277;auast=anama
 ¹¹³ Adrian Bootes/Department of Health (2016), "Prescription Medicines MMDR Reforms Overview and Designation Process: Expedited Pathways for Prescription Medicines", 10/14/2016, www.tga.gov. au/sites/default/files/tga-presentation-prescription-medicinesmmdr-reforms-targeted-stakeholder-information-meeting-14october-2016-161014.pdf
- ¹¹⁴ Although according to the procedure only vaccines and in vitro diagnostic products have to state they comply with this requirement when requesting registration See Australian TGA website, "How to Apply for Orphan Designation" (accessed March 2017), www.tga.gov au/book-page/how-apply-orphan-drug-designation; Cancer Council of Australia (2015), "Therapeutic Goods Administration: Orphan Drugs Program: Discussion paper", March 2015, www.cancer.org.au/ content/pdf/CancerControlPolicy/Submissions/Orphan%20Drugs%20 submission%20FINAL.pdf

- ¹¹⁵ Australian TGA website, "What is Eligible to Be Designed as Orphan Drug" (accessed March 2017), www.tga.gov.au/book-page/whateligible-be-designated-orphan-drug
- Australian TGA (2016), "Consultation: Orphan Drug Program 2015 Consultation Outcomes And 2016 Orphan Drug Program Proposal", October 2016, www.tga.gov.au/sites/default/files/consultationorphan-drug-program.pdf www.tga.gov.au/sites/default/files/ tga-presentation-prescription-medicines-mmdr-reforms-targetedstakeholder-information-meeting-14-october-2016-161014.pdf
- ¹¹⁷ Ibid.
- Adrian Bootes/TGA (2016).
 Australian TGA (2015), "Orphan Drug Program Discussion Paper", May 2015, www.tga.gov.au/sites/default/files/consultation-orphandrugs-program.pdf
- 120 Australian TGA website, "How to Apply for Orphan Designation"
- (accessed March 2017), www.tga.gov.au/book/export/html/190328 Australian TGA (2014), "EMA And Australian Regulatory Authority Strengthen Collaboration In The Area Of Orphan Medicines", 4/7/2014, www.tga.gov.au/media-release/ema-and-australian-regulatoryauthority-strengthen-collaboration-area-orphan-medicines
- ¹²² Ibid.
- 123 See notably Chapter 4. Text available (in Korean) at http://ko.pokr.kr/ bill/1911253/text
- Korea Pharmaceutical Association News (2016), "Approximately 14 rare ingredients such as 'Erotouzim' were newly designated", 5/12/2016,
- www.kpanews.co.kr/article/show.asp?idx=173583
 ¹²⁵ Aslan Pharmaceuticals (2017), "Aslan Receives Orphan Designation in Korea", January 2017, http://aslanpharma.com/2017/02/19/aslanpharmaceuticals-receives-orphan-drug-designation-in-korea-for-
- varlitinib-aslan001-in-biliary-tract-cancer/ Daily Pharm (2015), "Priority Clearance Of Rare Medicines Renewal 126 Period To 10 Years" (translated), 12/11/2015. www.dailypharm.com/ News/206568
- 127 Chosun Media (2016), "Development And Release Of 'Rare Medicine Elimination Of Designation Requirements For Medicines And Rare Drugs, And Improvement Of Licensing Systems" (translated), 2/5/2016, http://health.chosun.com/healthcarenews/mp216/2016/02/05/ mp21620160205112121702.html&usg=ALkJrhhADTOdD9q3hgyZjZFpd9 weih2Uw
- ¹²⁸ Ibid. http://health.chosun.com/healthcarenews/mp216/2016/02/05/ mp21620160205112121702.html
- www.yonhapnews.co.kr/bulletin/2016/02/05/020000000A KR20160205049000017.HTML
- Orphan drugs in development were defined as those treating diseases that affect fewer than 20,000 people and diseases for which an appropriate treatment has yet to be developed or, if it has, drugs that can provide a significant improvement in terms of safety and efficiency compared to previous treatments. A yearly revenue/value of import ceiling of 5 billion won (USD5 million) applied for approved drugs to be defined as orphan, in addition to the recurrence and lack of treatment requisites. See Korean Ministry of Food and Drug Safety (2015), "Regulation on Designation of Orphan Drugs", www.mfds.go.kr/eng/ eng/index.do;jsessionid=fxSrAGSxxwwJwYWA3cYr31qvfDTNB0kSEkJ WOhq0VWidlqWGq0aaJ5q7PDBijFNv?nMenuCode=128&page=2&mo de=view&boardSeq=70115
- ¹³¹ Pacific Bridge Medical (2014).
- Text available at www.tfrd.org.tw/english/laws/ upload/20080328098114_01.html 132
- 133 Aarti Sharma et al (2010).
- 134 Panion Biotech (2011), "Orhpan Business in Taiwan", 9/15/2011, www. slideshare.net/122843386/orphan-business-in-taiwan; Peipei Song et al (2011), "Rare Diseases, Orphan Drugs, And Their Regulation In Asia: Current Status And Future Perspectives", Intractable & Rare Diseases Research. 2012; 1(1):3-9, www.irdrjournal.com/action/downloaddoc. php?docid=511
- 135 New chemical entities benefit from 3 years of data exclusivity and 2 additional years of market exclusivity as per Art. 40-2 of the Pharmaceutical Affairs Act. In 2015 the TFDA proposed (Art 40-3) to extend he 5 years exclusivity period also to new indications. See eng-Yuan Liu, Kate Shu-Yin Chu, Katherine Juang/Lexology (2016), "Patents Taiwan Seeks to Join TPP with Draft Pharma Law Amendments",1'4'2016, www.lexology.com/library/detail. aspx?g=e64e5361-6624-45d1-afcd-98a6238e533b
- 136 art 14.1 of the Therapeutic Products Act (text available at www.admin. ch/opc/en/classified-compilation/20002716/index.html) and Ordinance of 22 June 2006 of the Swiss Agency for Therapeutic Products On The Simplified Authorization Of Medicinal Products And The Authorization Of Medicinal Products With Notification Procedure At Art. 24-27 (text available at www.loisuisse.ch/fra/sr/812.212.23/index.htm)
- ¹³⁷ SwissMedic, "AW Information Sheet Explanations regarding Orphan Drugs'
- ¹³⁸ Office of Legislative and Regulatory Modernization, Policy, Planning and International Affairs Directorate, Health Products and Food Branch. Initial draft discussion document for a Canadian orphan drug regulatory framework [Internet]. Ottawa: Government of Canada; 2012 Dec 13. [cited 2016 Jan 18]. Available at www.orpha.net/national/ data/CA-EN/www/uploads/Initial-Draft-Discussion-Document-for-A-Canadian-Orphan-Drug--Regulatory-Framework.doc ¹³⁹ Ibid.

- ¹⁴⁰ Carly Weeks/The Globe and Mail (2014), "Canada Lags Behind on Rare Disease Drugs", 2/27/2014, www.theglobeandmail.com/life/ health-and-fitness/health/canada-lags-behind-on-rare-disease-drugs/ article17137268/
- ¹⁴¹ The analysis was performed on the Aggregate Analysis of ClinicalTrials. gov (AACT) database as of March 27, 2016, provided by the Clinical Trials Transformation Initiative (CCTI). 133,889 trials were registered for the examined countries during the period between 2005 and 2015 (inclusive), based on 'first received' dates. Identification of clinical trials on rare diseases within the sample was performed by comparing the trials' official titles with the list of 1825 conditions defined as 'rare diseases' by clinicaltrials.gov (https://clinicaltrials.gov/ct2/search/ browse?brwse=ord_alpha_all&brwse-force=true). A total of 3,950 clinical trials on rare diseases conducted in the sampled countries between 2005 and 2015 were identified. One potential consequence of the above describe methodology is that a number of false positive results (i.e. clinical trials on non-rare conditions) may be included in the total figure analyzed, due to external issues such as incorrect categorization as well as issues relating to application of text matching. Nevertheless similar studies that have used different methods have reached fairly similar figures with regards to clinical trials on rare diseases, further corroborating the above described analysis (see for example: Bell, S. A. and Tudur Smith, C. (2014). "A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov", Orphanet Journal of Rare Diseases, Vol. 9, No. 170, p.4.).
- ¹⁴² EvaluPharma (2017); EMA (2017), "Orphan Medicines Figures 2000-2016", www.ema.europa.eu/docs/en_GB/document_library/ Other/2015/04/WC500185766.pdf
- 143 Ibid.
- ¹⁴⁴ Thomas Morel et al. (2016), "Regulatory Watch: The Orphan Drug Pipeline In Europe", June 2016, www.researchgate.net/ publication/303717564_Regulatory_watch_The_orphan_drug_ pipeline_in_Europe
- ¹⁴⁵ Manabu Murakami & Mamoru Narukawa (2016), "Matched Analysis On Orphan Drug Designations And Approvals: Cross Regional Analysis In The United States, The European Union, And Japan", Drug Discovery Today, Volume 21, Issue 4, April 2016, Pages 544–549
- ¹⁴⁶ PharmaTimes (2013), "EU Pharma Smes Seeing Growing Success: Report", 2/28/2013, www.pharmatimes.com/news/eu_pharma_smes_ seeing growing success report 1004541
- seeing_growing_success_report_1004541
 ¹⁴⁷ Article 77-2 of the Pharmaceutical Affairs Law available at www.mhlw. go.jp/english/policy/health-medical/pharmaceuticals/dl/05.pdf
- ¹⁴⁸ Manabu Murakami & Mamoru Narukawa (2016).
 ¹⁴⁹ Calculated on data of designations and approvals from 2001 until 2013
- for Japan, and from 2001 to 2016 for US and EU. ¹⁵⁰ US FDA website, "Developing Products for Rare Diseases & Conditions" (accessed March 2017), www.fda.gov/forindustry/ developingproductsforrarediseasesconditions/ucm2005525.htm
- ¹⁵¹ Office of the Assistant Secretary for Planning and Evaluation (ASPE)/ US Ministry of Health (2016), "Report to Congress: Prescription Drugs: Innovation, Spending, and Patient Access", http://delauro.house. gov/sites/delauro.house.gov/files/Prescription-Drugs-Innovation-Spending-and-Patient-Access-12-07-16.pdf
- ¹⁵² Manabu Murakami & Mamoru Narukawa (2016).
- ¹⁵³ EMA (2017).
- ¹⁵⁴ Ibid.
- ¹⁵⁵ FDA (2016) "FDA approves first drug for spinal muscular atrophy", FDA News Release, December 23 2016
- ¹⁵⁶ Manabu Murakami & Mamoru Narukawa (2016).
- ¹⁵⁷ M Pugatch, If it ain't broke, Don't Fix it, A discussion paper on the Benefits of the Volnutary Market-driven approach to Innovation, Stockholm Network 2008, pp. 9-10.
- ¹⁵⁸ Although it should be noted that characterising innovation as being either incremental or radical is perhaps slightly misleading as most innovations are not as easily pigeonholed. For example, incremental improvements to existing radical innovations can lead to wider dissemination and use of such innovations. Thereby leading to a degree of social or economic disruption normally associated only with radical innovation.
- ¹⁵⁹ See CM Christensen, The Innovator's Dilemma: When new technologies cause great firms to fail, Harvard Business School Press, Harvard 1997
- ¹⁶⁰ S Kauffman, At Home in the Universe, Oxford University Press, New York 1995
- ¹⁶¹ A full discussion of these different types of innovation and how they work within their biomedical context will be provided below in Section 1: Understanding Biomedical Innovation.
- ¹⁶² Financial Times, July 11 2000, from Wertheimer, Levy and O'Connor, 'Too many Drugs? The Clinical and Economic Value of Incremental Innovations', Investing in Health: The Social and Economic Benefits of Health Care Innovation, Volume 14, pp. 77-118, p. 78.
- ¹⁶³ CBO, Research and Development in the Pharmaceutical Industry, CBO 2006, p. 2.
 ¹⁶⁴ EDA, "DMEa approved by CDEP", www.fda.app/
- ⁶⁴ FDA, "NMEs approved by CDER", www.fda.gov/ downloads/Drugs/DevelopmentApprovalProcess/
- HowDrugsareDevelopedandApproved/
- DrugandBiologicApprovalReports/UCM242695.pdf (Accessed October 30 2011)

- ¹⁶⁵ See, for example, the above cited CBO report which argued that while the drop in NME approvals from 1996 "could simply mark a return to their long-term average...the pace of new-drug approvals has not matched the rise in real R&D spending.", CBO, pp. 10-11.
- ¹⁶⁶ JB Graham, Trends in US Regulatory Approvals of Biopharmaceutical Therpaeutic Entities, Harvard MIT 2005, Msc thesis, p. 18.
- ¹⁶⁷ Ibid.
- ¹⁶⁸ IM Cockburn, "Is the Pharmaceutical Industry in a Productivity Crisis?", in J Lerner and S Stern (eds), Innovation Policy and the Economy, MIT Press 2006, p. 6.
- ¹⁶⁹ JA DiMasi, RW Hansen and HG Grabowski, "The Cost of Innovation in the Pharmaceutical Industry", Journal of Health Economics, Vol 10, 2003, pp. 107-142.
- ¹⁷⁰ A.I. Wertheimer and A. Morrison, "Combination Drugs: Innovation in Pharmacotherapy", Pharmacy and Therapeutics, Vol. 27, No 1, January 2002, pp. 44-49, p. 44.
- ¹⁷¹ Wertheimer, A. and Santella, T.M. (2005) Pharmacoevolution: the advantages of incremental innovation, International Policy Network, London, p. 15.
- ¹⁷² M Tratjenberg, Economic Analysis of Product Innovation: The Case of CT Scanners, Harvard Economic Studies, Volume 160, Harvard 1990, p. 161.

- 174 Ibid.
- ¹⁷⁵ Aronson, J.K. (2007), "Old Drugs New Uses", British Journal of Clinical Pharmacology, Vol.64, No.5, pp.563-565 www.ncbi.nlm.nih gov/pmc/articles/PMC2203255/
- ¹⁷⁶ Berndt, E., Cockburn, I. & Grepin, K. (2006), "The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilisation in Original and Supplemental Indications", Pharmacoeconomics, Vol.24, pp.69-86
- ¹⁷⁷ Interestingly, NovoNordisk's success as an insulin manufacturer and innovator has been attributed to its success in incremental innovation. See for example: Euro Pharma Today, "Novo Nordisk: Riding High on Diabetes", June 1 2007, www.europharmatoday.com/2007/06/novonordisk-riding-high-on-diabetes.html (Accessed November 2 2011)
- ¹⁷⁸ Ralph Landau, Basil Achilladelis, Alexander Scriabine (eds), Pharmaceutical innovation: revolutionizing human health, 1999 Chemical Heritage Foundation, p. 54.
- ¹⁷⁹ S Leichter, "The Business of Insulin: A relationship between Innovation and Economics", Clinical Diabetes, Vol 21, Number 1, 2003, pp. 40-1.
- ⁸⁰ For Biocon's biosimilar insulin see: Biocon, About Us, www.biocon. com/biocon_aboutus.asp For details of analog insulin see Leichter, "The Business of Insulin...", p. 40.
- ¹⁸¹ Leichter, "The Business of Insulin...", p. 40.
- ¹⁸² Fierce Biotech, "FDA Approves Apidra(R) SoloSTAR(R) a Prefilled Disposable Insulin Pen", February 26 2009, www.fiercebiotech.com/ press-releases/fda-approves-apidra-r-solostar-r-prefilled-disposableinsulin-pen#ixzz1ceXgPM5B (Accessed November 2 2011)
- ¹⁸³ MayoClinic, "Beta blockers", www.mayoclinic.com/health/betablockers/HI00059 (Accessed November 7 2011)
- ¹⁸⁴ RE Klabunde, "Cardiovascular Pharmacology Conpcets, Beta-Adrenoceptor Antagonists (Beta-Blockers)", www.cvpharmacology. com/cardioinhibitory/beta-blockers.htm (Accessed November 9 2011)
 ¹⁸⁵ Ibid.
- ¹⁸⁶ Wertheimer, A., Levy, R., O'Connor, T. (2001), "Too Many Drugs? The Clinical and Economic Value of Incremental Innovations", in Investing in Health: The Social and Economic Benefits of Health Care Innovation (Research in Human Capital and Development, Volume 14), Emerald Group Publishing Limited, pp. 77-118, pp. 88. Re-arranged to correspond to first, second and third generation development.
- ¹⁸⁷ Ibid.
- ¹⁸⁸ Mayo Clinic, "Angiotensin-converting enzyme (ACE) inhibitors", www. mayoclinic.com/health/ace-inhibitors/HI00060/NSECTIONGROUP=2 (Accessed November 11 2011)
- ¹⁸⁹ SG Molhoek, "Past, Presnt and Future of ACE Inhibitors", Netherlands Heart Journal (2007), Vol. 15, pp. 12-3, p. 12.
 ¹⁹⁰ R Wennberg and C Zimmermann, "The PROGRESS trial three
- 170 K Wennberg and C Zimmermann, "The PROGRESS trial three years later: time for a balanced report of effectiveness", BMJ, 2004 October 23; 329(7472): 968–970, www.ncbi.nlm.nih.gov/pmc/articles/ PMC524114/ (Accessed November 11 2011)
- ¹⁹¹ SG Molhoek, p. 12.
- ¹⁹² Ibid.
- ¹⁹³ Wertheimer et al, "Too many Drugs?..." p. 101
 ¹⁹⁴ Wertheimer et al, "Too many Drugs?..." p. 92.
- ¹⁹⁵ Ibid.
- ¹⁹⁶ SL Cerel-Suhl and BF Yeager, "Update on Oral Contraceptive Pills", American Family Physician, November 1 1999, www.aafp.org/ afo/991101ao/2073.html (Accessed November 11 2011)
- ¹⁹⁷ WHO, Reproductive Health Librray, "Monophasic versus multiphasic oral contraceptives", http://apps.who.int/rhl/fertility/contraception/ dscom/en/index.html (Accessed November 11 2011)
- ¹⁹⁸ Wertheimer et al, "Too many Drugs?..." pp. 92-3.
- ¹⁹⁹ Ibid. ²⁰⁰ TP Stos
- TP Stossel, "The discovery of statins", Cell, 134, September 19 2008, pp. 903-5.
- ²⁰¹ Ibid.
- ²⁰² University of Michigan Business School, "Lipitor: At the Heart of Warner Lambert", December 1999, www-personal.umich.edu/~afuah/ cases/case26.pdf (Accessed November 14 2011)

¹⁷³ Ibid.

- 203 Ibid
- 204 Ibid.
- ²⁰⁵ Patent family CA 543290
- Patent family US052287B2.
 S.R. Hosein, 'The Evolution of HIV Treatment' (2016) www.catie.ca/en/ positiveside/winter-2016/evolution-hiv-treatment.
- S. Broder, 'The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic' (2009) Antiviral Research 85(1).
- ²⁰⁹ TRIPS Agreements, art. 27(1). ²¹⁰ Idem art. 27(3)(a).
- ²¹ M Bhagwat et al, 'Second Medical Use Patenting: A Review of Practises Accross Different Jurisdictions' (2016) Journal of Intellectual Property Rights 21 pp 260-264.
- ²¹² M Burdon & K Sloper, "The Art of Using Secondary Patents to Improve Protection" (2003) Olswang p4.
- ²¹³ T Calame et al "Second medical use and other second indication claims" (2008) AIPPI p5.
- G 0002/08 (Dosage regime/ABBOTT RESPIRATORY) of 19.2.2010.
- ²¹⁵ G 0005/83 (Second medical indication) of 5.12.1984 ²¹⁶ Administrative Judgment (2008) GaoXingZhongZi No.378, Beijing High Court
- 217 4.5.2 Chapter 10 Part II Guidelines for examination 2006
- ²¹⁸ Article 25(3) Patent Law of the People's Republic of China.
- ²¹⁹ 35 U.S.C. § 101. Under this provision method claims are considered as new processes, since there is no novelty in the "composition of matter
- ²²⁰ Article 18 Patents Act 1990
- 221 Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd & Others [2013] HCA 50
- ²²² Art. 21 Decision 486 of the Andean Pact.
- $^{\rm 223}\,$ Art. 16 Decision 486 of the Andean Pact describes the novelty requirement of patents under the Andean patent regime. ²²⁴ Article 16 Decision 344 of the Andean Pact.
- ²²⁵ ATJ Case 89-AI-2000 at 40.
- 226 Código Orgánico de Economía Social del Conocimiento, la Creatividad y la Innovación. ²²⁷ Art. 4(f) Law of the Republic of Indonesia No. 13 of July 28, 2016, on
- Patents.
- ²²⁸ Section 3 Indian Patents Act 1970, from a 2007 amendment
- ²²⁹ Joint Regulations 118/2012, 546/2012 and 107/2012, May 2, 2012.
- ²³⁰ Art. 6(e) Law No. 24.481 of March 30, 1995. 231
- Article 2(2) Law No. 82 of 2002 on the Protection of Intellectual Property Rights. ²³² Article 2(3) supra
- ²³³ Art. 10(VIII) Law No. 9,279, of May 14, 1996.
- ²²⁴ 3.75 & S.76 Resolution 124/2013.
 ²³⁵ D Kappos (2010) Under Secretary of Commerce & Director of the USPTO David Kappos June 29, 2011 Biological Industry Organization Celebrating 30 years of Biotech "From Chakrabarty to Today
- ²³⁶ Triadic patenting is generally considered to be the best indicator of the perceived overall value and quality of a patent. The patent application is filed in three separate locations and filing costs are quite high. The three major patenting offices in which protection is sought are: the European Patent Office, the US Patent Office and the Japanese Patent Office.
- ²³⁷ S White Junod (2007) "Celebrating a Milestone: FDA's Approval of First Genetically Engineered Product", FDA, About FDA (Accessed May 2017)
- ²³⁸ M Kinch (2015) "An overview of FDA-approved biologics medicines", Drug Discovery Today. 2015 Apr;20(4):393-8
- 239 Ibid
- ²⁴⁰ M Serebrov (2016) "Biologics' share of medicine chest grows, and so do the pricing concerns", BIOWORLD, Jan 4 2016, Thomson Reuters. 241
- Association for Molecular Pathology v. Myriad Genetics, No. 12-398 (569 US, 2013); Mayo Collaborative Services v. Prometheus Laboratories, Inc. (566 US, 2012); See also, for instance: National Law Review, "USPTO Provides Meaningful Direction on Patentable Subject Matter Eligibility", 7/30/2015
- AIPLA (2017) "Comments of the AIPLA on Notice of Roundtables and Request for Comments Related to Patent Subject Matter Eligibility...", 1/18/2017
- MedCity News (2017), "What SCOTUS's refusal to review cases on patent-eligible subject means", 1/5/2017
 The Economist (2002), "Innovation's Golden Goose", Technology
- Quarterly Section, p. 3. December 14, 2002 ²⁴⁵ V. Loise & A.J. Stevens (2010). "The Bayh-Dole Act Turns 30",
- Les Nouvelles, December 2010, pp. 185-186, www.bu.edu/otd/
- files/2011/02/The_Bayh-Dole_Act_Turns_30.pdf.
 Shane, S, (2004), "Encouraging university entrepreneurship? The effect of the Bayh-Dole Act on university patenting in the United States", Journal of Business Venturing, 19, pp. 127-151. See introduction to this article for a full discussion of the academic debate over the effects of Bavh-Dole.
- 247 L Pressman et al (2015), The Economic Contribution of University/ Nonprofit Inventions in the United States: 1996-2013, BIO 2015, p. 3.
- 248 Ibid

- ²⁴⁹ USPTO, (2006), Technology Profile Report: Patenting Examining Technology Center Groups 1630-1660, Biotechnology, Washington 2006 250
- B Huggett (2014) "Top US universities and institutes for life sciences in 2013", Nature Biotechnology, Volume 32 No 11 November 2014.
- ²⁵¹ Ministry of Economy (2015) PR NewsWire (2014)
- 253 Protalix Biotherapeutics, "Elelyso", www.protalix.com/products/ elelyso-taliglucerase-alfa.asp
- ²⁵⁴ Pugatch, M., Teubal, M. and Zlotnick, O. (2010). "Israel's High Tech Catch-Up Process: The Role of IPR and Other Policies" in Intellectual Property Rights, Development, and Catch Up, Odagiri, H. et al. (Eds), Oxford University Press, 2010.
- 255 Ibid.
- ²⁵⁶ United States Trade Representative, (1998). "Special 301 Annual Review", Washington DC, 1 May 1998. For an overview of why the amendment is referred to as the "Teva exemption" see: Knesset Protocols, Meeting. No. 140 of the 14th Knesset (17 February 1998).
- 257 Patent Law (Amendment No. 7) 2005.
- Pharmacists Ordinance (Amendment No. 12) 2005. 258
- 259 See: Luzzatto & Luzzatto, Intellectual Property in Israel: Legislation, Work Environment, Results, IP Blog; 2008 Submission of the Government of Israel to the United States Trade Representative with Respect to the 2008 "Special 301 Review", February 2008, p. 11. 260
- See: PhRMA Special 301 Submission 2007.
- ²⁶¹ Pharmacist Ordinance, 1981 (Amendment No. 21, 2011). 262 Ibid.
- ²⁶³ Under the Pharmacists Regulations (Pharmaceutical Products) of 1986 (2005 version) the 21 'recognized countries' are the US, Japan, Australia and New Zealand, Iceland, Norway and the following EU member states: Austria, Italy, Ireland, Belgium, UK, Germany, Denmark, the Netherlands, Greece, Luxembourg, Spain, Portugal, Finland, France and Sweden
- 264 Patent Law (Amendment No. 7) 2005.
- Patent Law (Amendment No. 7) 2003.
 Patent Law (Amendment No. 7) 2014.
 RC Attorneys (2012), "Israeli Patent Act Amendment Early Publication of Patent Applications and Other Changes", 10/01/2012 Government of Israel, Decision No.183 "Optimization of the new
- medicines registration process" of 12.5.2009.
- ²⁶⁸ Government Decision N. 2118 of 22.10.2014. Text available (in Hebrew) at www.pmo.gov.il/policyplanning/Regulation/Documents/dec2118. pdf
- ²⁶⁹ Ibid.
- ²⁷⁰ RC Attorneys (2014). "Israeli Patent Office to Function as International Searching & Examining Authority for US-PCT Applications as international October 2014", 20.10.2014; RC Attorneys (2012), "Israeli and US Patent Offices Extend and Expand Mutual PPH Pilot Program: Now Applies also to PCT Applications Examined by Both Offices", 1.10.2012.
- 271 Teva Pharmaceuticals Ltd., About Teva (in Hebrew), www.teva.co.il/ About/CompanyProfile/Pages/WhoAreWe.aspx.
- Fortuna, G., Niv, Y. and Freeman, D. (2014). "Estimating Teva's Contribution to the Israeli Economy", Samuel Ne'eman Institute, August 2014, p.4, (Published in Hebrew).
- See for example: Ha'aretz, Will Israel Sacrifice Teva in order to Join the OECD?, 11.11.2009.
- Calcalist, Interview with Israel Makov, 6.6.2011. Haaretz, Teva's Copaxone Sales Jump 30% in 2004 to \$936 Million, 27.1.2005, www.haaretz.com/print-edition/business/teva-s-copaxone-salesjump-30-in-2004-to-936-million-1.148404. Teva Pharmaceuticals Ltd., , About Teva (in Hebrew), Fortuna, G., Niv, Y. and Freeman, D. (2014). "Estimating Teva's Contribution to the Israeli Economy", Samuel
- Ne'eman Institute, August 2014, p.4, (Published in Hebrew). World Bank, data bank, GDP per capita (current US\$), 2015, World Development Indicators
- 276 Ibid. 1990 data
- 277 PharmaForum (2014)
- 278 EDB (2013), Singapore Biotech Guide 2012/2013, p.15
- 279 Ibid. 280
- A*STAR (2013) 281
- OECD (2014), "Education at a Glance", p.2
- 282 EDB (2014) ²⁸³ Ibid
- ²⁸⁴ NIH/Clinicaltrials.gov
- 285 Ibid.
- ²⁸⁶ EDB website (accessed October 2015), "Pharmaceutical and Biotechnology", https://www.edb.gov.sg/content/edb/en/industries/ industries/pharma-biotech.html
- UNITED STATES SINGAPORE FREE TRADE AGREEMENT, Article 16.7 and 16.8
- ²⁸⁸ Pugatch & Chu (2011) "The strength of pharmaceutical IPRs vis- à -vis foreign direct investment in clinical research: Preliminary findings", Journal of Commercial Biotechnology, 1-11, 2011
- ²⁹⁰ Pugatch Consilium (2016) Biopharmaceutical Competitiveness & Investment (BCI) Survey,Third Edition, 2016, 2016
- ²⁸⁹ Ibid.





CONTACT US

Israel Office 10 Hanechoshet St, Tel Aviv 6971072 Tel: +972 3 6299294 Fax: +972 3 6204395

UK Office 88 Sheep Street, Bicester, Oxon OX26 6LP Tel: +44 1869 244414 Fax: +44 1869 320173

U.S. Office 1101 Pennsylvania Avenue, Suite 6635, Washington, DC 20004 Tel: +1 202-756-7720

E: info@pugatch-consilium.com

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