

**WITHOUT REGULATORY DATA
PROTECTION, THERE WILL
BE LESS INVESTMENT IN
DEVELOPING THE GROUND-
BREAKING BIOMEDICAL
TREATMENTS OF TOMORROW**

WHY REGULATORY DATA PROTECTION MATTERS FOR MEDICINES

■ By Jack Ellis, Geneva Network

- The world's most innovative countries in medical biotechnology all have in common rules for the protection of valuable data generated during clinical trials
- This data is very expensive to generate, and biotech companies are required to submit it to regulators for drug approval. Regulatory data protection (RDP) prevents competitors from free-riding off that data to launch their own similar products for a limited period
- Biologic drugs are far more complicated than their small-molecule counterparts, and are much more difficult to protect using patents
- RDP therefore provides a vital complementary form of intellectual property protection vital to mobilise investment into the high-risk biotech sector
- Countries that have introduced RDP for biologic medicines have not seen any significant rise in overall levels of pharmaceutical spending

In medicine, the dominance of small-molecule drugs is coming to an end. Increasingly, current and future treatments will be biologic - complex drugs with molecular structures many times larger, manufactured inside living structures such as animal cells or bacteria.

The new era of biotechnology promises a revolution in how doctors treat and prevent disease, in many cases offering hope to patients where there is no current treatment. Advances in gene therapy, the development of safer vaccines, precision medicine and superior diagnostics stand to benefit millions around the world.

Despite its transformative potential for humanity,

“For innovation in biologic medicines the key intellectual property right is not patents but regulatory data protection”

biotechnology medicine research and development remains geographically concentrated. The world leader in biotechnological output by some margin is the United States, followed by a handful of high-income countries – the United Kingdom, Switzerland, Germany, France and Japan.

While emerging markets such as China have nascent biotech industries, there is a long way to go before medical biotech R&D goes global, harnessing the scientific potential that is found in most countries.

So why is it that medical biotech companies and their lifeblood – the small start-ups with promising technology to develop – are clustered in a handful of countries?

Human capital, a good regulatory environment and adequate R&D infrastructure are obviously key¹. Also crucial are strong and readily enforceable intellectual property (IP) rights that are necessary to mobilise the large investments required to fund risky biotech R&D.

For innovation in biologic medicines the key IP right is not patents but regulatory data protection (RDP), which prevents competitors from exploiting the data generated during clinical

trials for a certain period of time. The most innovative countries in the biotechnology sphere all have one thing in common – they all have clear rules on their statute books for the protection of this data.

So what precisely is RDP, and why is it so important?

■ REGULATORY DATA PROTECTION EXPLAINED

Broadly defined, the ‘data’ element of RDP refers to the information that is required by regulatory authorities in order to approve a technology for consumer use. Therefore, RDP is relevant to technologies for which safety and effectiveness are paramount, and which need regulatory approval before entering the market; in particular, pharmaceutical products – both ‘small molecule’, chemically-synthesised formulations, and more complicated biologics – and various products used in agriculture. In the context of the former, the data will typically be generated and collected from conducting the preclinical and clinical trials that are required to demonstrate a medicine is safe and efficacious for humans.

This painstaking clinical trials process comes at great expense, in

terms of both time and money, to the innovator company which has developed the technology. Some estimates of the cost of developing a new medicine range between \$1.2bn to \$2.6 billion^{2,3}.

Susan Finston, co-founder and director at Indian biomedicine start-up Amrita Therapeutics and a strategic consultant, points out that this situation fundamentally puts biologic innovators and other biotech companies at a competitive disadvantage, since the test data, vital for gaining regulatory approval, would likely be protected as a trade secret in any other context.

“Every company has recourse to similar protection under trade secrecy laws,” she says. “But biopharma companies actually face an additional requirement to disclose trade secrets, in the form of regulatory data. A typical food and beverage company can hold trade secrets on their recipes and so forth, and they can do that in perpetuity. But if you are a biopharma innovator, you have to disclose to regulators what your cookbook is.”

As such, she argues that there is an imperative to incentivise these innovators. This ensures that competition cannot enter the market by gaining approval on the back of the innovator’s regulatory

data before the innovator itself has had a fair opportunity to recoup its hefty investment in compiling it.

And that’s where the ‘exclusivity’ part of the equation comes in. “In highly regulated industries like biopharma or agritech, there is a compelling public interest in regulators having access to the innovator’s test data,” says Finston. “Regulatory data protection allows for regulators to gain that access on the basis that they will not disclose it.”

In return for access to test data, governments commit to refraining from public disclosure of the data – ensuring that competitors are not able to rely on it to seek approval for their own drugs for a limited period of time. The scope and term of that exclusivity can vary according to jurisdiction and subject matter. Furthermore, the full extent of what is broadly categorised as RDP may include periods of exclusivity concerning the test data itself, as well as additional spells of market exclusivity where prospective competitors may have their follow-on drugs approved but are still restricted from selling them until the term of the protection expires.

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), of which World Trade Organisation

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¹ “Building the Bioeconomy 2016: Examining national biotechnology industry development strategies globally”, Pugatch Consilium

² Mestre-Ferrandiz et al (2012), “The R&D cost of a new medicine”, Office of Health Economics (United Kingdom)

³ DiMasi J, Grabowski H, Hansen R (2014), “Innovation in the pharmaceutical industry: new estimates of R&D costs”, Boston: Tufts Center for the Study of Drug Development, November 18, 2014

(WTO) members are signatories, includes obligations for the protection of proprietary data submitted by innovators to governments for regulatory purposes.

Article 39.3 of the TRIPS Agreement requires governments of WTO member states to protect test data submitted to regulatory authorities against unfair commercial use and disclosure, except when necessary to protect the public, or unless the data is otherwise protected against unfair commercial use. Since 1st January 2000, all WTO members, with the exception of those which are classified as least developed countries, have been required to have TRIPS-compliant protection for proprietary registration data.

Many, though, have failed to implement it.

CLINICAL TEST DATA AND BIOSIMILARS

Among other things, regulators want access to an innovator's test data in order to vet and approve follow-on versions of its drug that are produced by competitors. Just as originators of small-molecule pharmaceuticals face follow-on competition from generics, biologic innovators must contend with competition from 'biosimilars'.

But there is a marked difference. Compared to 'traditional' chemically synthesised pharmaceuticals, biologics,

as noted above, are far more structurally complex. As such, it is not currently possible for a competitor to precisely replicate the original biologic. Rather, the competitor can only produce a biosimilar – a product that may be structurally similar to the original biologic it follows on from but likewise may only be similar, rather than identical, in terms of its effectiveness.

As a result, regulatory authorisation of a biosimilar is conditional on it demonstrating comparable efficacy, quality and safety to the innovator's original product. This means that the innovator's original test data is instrumental for approval – and explains why regulatory authorities require access to it.

Moreover, these nuances make the protection of biologics using patent law a complicated affair. In many jurisdictions the question of whether biotechnological inventions are eligible for patent protection remains unsettled.

WHY PATENTS AREN'T ENOUGH

According to Dr Kristina Lybecker, an associate professor at Colorado College whose research focuses on IP rights in the pharmaceutical space, RDP grants biologics innovators some much-needed additional security.

"Patent protection and data exclusivity are complementary forms of IP protection that both serve to incentivise the tremendous investments required for the development of biologic medicines," she says.

Despite this, critics often argue that RDP is an overreach, gifting additional quasi-monopolistic power on top of that already obtained through patent ownership. From this perspective, RDP only serves to further delay cheaper biosimilars, keeping prices higher for healthcare providers and patients.

Jack Lasersohn is a general partner with the Vertical Group, a healthcare-focused venture capital firm based in New Jersey. In July 2009, while he was on the board

of directors at the US National Venture Capital Association (NVCA), Lasersohn testified at a US Congressional hearing in support of legislative proposals to secure a significant, 12-year RDP period for biologics in the United States. The following year, the Biologics Price Competition and Innovation Act was signed into law, ushering in 12-year regulatory exclusivity for new biologics starting from the date of first approval by the US regulator.

Venture capital investment is absolutely critical to the biotechnology industry; US VC firms pumped a record \$8.95 billion into biotech start-ups during 2015. That's around 50% more than the previous year. Nonetheless, these figures give an indication of the scale of venture capital's contribution. Without the promise of returns, VCs would have little reason to invest in such a high-cost, high-risk sector – and billions of dollars in funding for cutting-edge medicines would be lost.

Based on his experience investing in and managing biotechnology companies, Lasersohn thinks that RDP is vital if there is to be continued, sustained investment. "The patent laws give you that protection up to a point, but not completely," he says. "Put simply, the main reason is that it is more difficult to protect a biologic from a biosimilar than it is to protect a small molecule from a generic that

is chemically identical. The patent laws simply do not afford the same level of protection if you are going to allow similar drugs to be approved using the same data."

In addition to the high costs of producing the relevant data, uncertainty over the eligibility of biotech inventions for patent protection – as well as the ability to effectively enforce these rights – further underlines the need for RDP. "The trend has gotten worse," says Lasersohn, speaking specifically about the US market. "Patent laws offer even less protection today, as a result of *eBay* and a whole bunch of other Supreme Court decisions. So in that sense, regulatory data protection has become even more important."

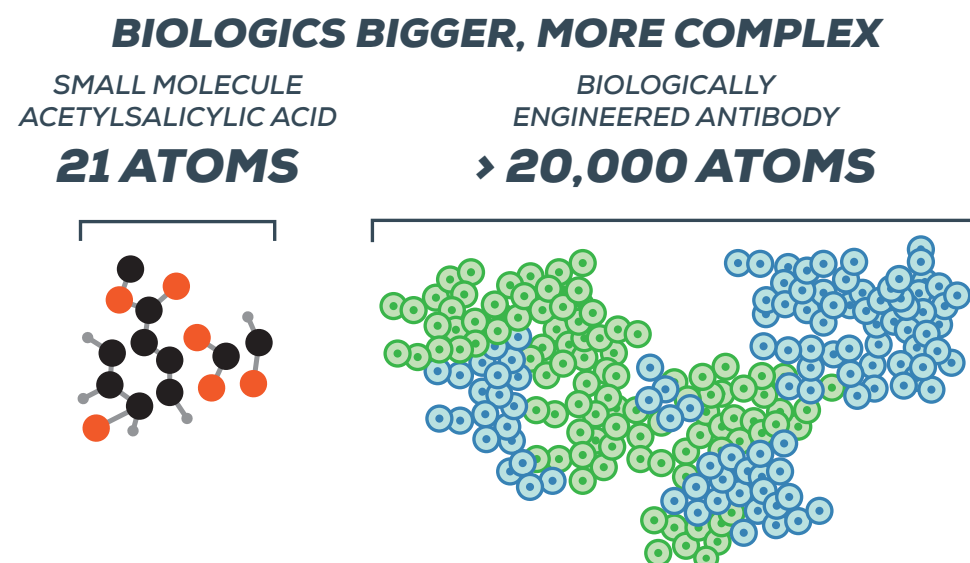
The US Supreme Court's *eBay v MercExchange* decision in 2006 significantly raised the bar for obtaining injunctive relief for patent infringement, while its rulings in *Mayo v Prometheus* in 2012 and *Association for Molecular Pathology v Myriad* in 2014 placed restrictions on the patentability of inventions relating to diagnostic methods and isolated genetic material.

Throw in the astronomical costs of US litigation, and it is clear to see that it is probably tougher than ever to be a biotech start-up today than at any point in the past.

"For a small company like Amrita,

Figure 1

Adapted from: Amgen Inc. *Biologics and Biosimilars: An Overview* March 2014



“Property rights, including patents and RDP, are the foundation of investment. No-one wants to invest in something that they don’t own a part of”

RDP is very much of practical importance because you can’t count on being able to make it through a lengthy patent litigation,” says Finston. “But if you have RDP and marketing exclusivity, then you essentially have some administrative protection from the state. That provides more assurance that you are not relying merely on patent protection.”

■ RETURN ON INVESTMENT

For Lasersohn and other VCs like him, the bottom line is simple: They are more likely to invest in a biotech company if its test data is protected for a reasonable period of time. “When a VC looks to make an investment, they need to justify it on the rate of return over time,” he says. “The return you get is directly a function of the durability of the investment - in other words, how long it will produce cash flows and profit. The shorter the period of durability, the less profit that could be made; and therefore, the smaller the investment that could be justified.”

He gives the same analogy that he used when arguing the case for a 12-year RDP period before Congress in 2009: “Say you’ve invested in a \$100-million-dollar apartment building for rental. If it lasts for 10 years and then crumbles, it is only worth what it earned during those 10 years. But if it stands for

a hundred years, it is potentially going to earn much, much more, which means you can sell it before the 100 years is up based on how much cash flow a prospective buyer can anticipate.”

In the VC business - where the aim is often to achieve exit by selling a start-up on to a larger company - this represents the durability in the investment. “For biotech, that durability is associated with data exclusivity,” he adds. “Once you lose that, the apartment building crumbles to dust - and it just doesn’t generate profits any more.”

Lasersohn argues that strong IP protections have been the cornerstone of the United States’ longstanding leadership in the development of new, game-changing technologies. “Property rights, including patents and RDP, are the foundation of investment,” he says. “No-one wants to invest in something that they don’t own a part of. Patents and RDP give you a form of ownership, and therefore make it possible to invest.”

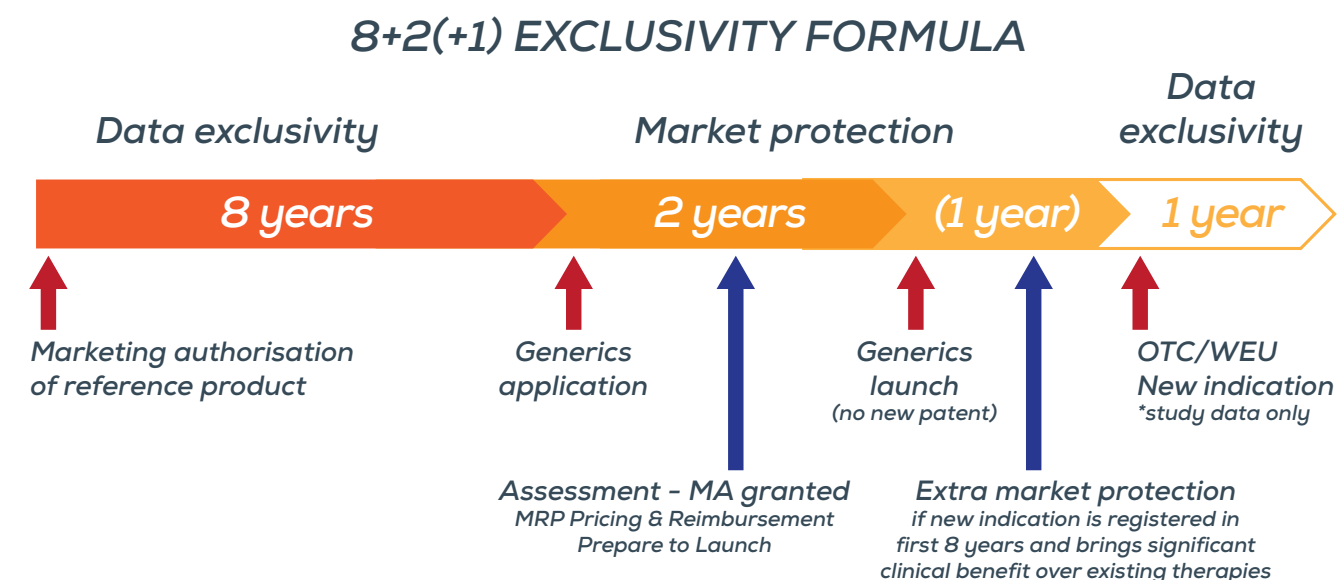
■ EMERGING MARKETS

Despite the important role played by RDP in making the US a biotech innovation world leader, the availability, strength and scope of RDP for biologics differ from country to country, with many not providing any.

The United States stands alone in

■ **Figure 2**

How regulatory data protection works in the European Union



Source: Zaide Frias, Head of Regulatory Affairs, European Medicines Agency (EMA), presented at SME Workshop, EMA, April 2013

offering a 12-year term (in a 2011 paper, Duke University economist Henry Grabowski reasoned that a representative biologic could not recoup its R&D costs with a data protection period of less than 12 years). The European Union provides for up to 11 years of regulatory exclusivity protection in certain circumstances (see Fig 2 - European Union 8+2(+1) formula) - and this particular regime is generally applicable to both biologics and small-molecule drugs.

Canada and Japan each offer eight years of RDP for biologics, while a significant number of jurisdictions make provision for five to six years.

At the other end of the scale, it is typically developing economies that fail to provide any form of RDP for biologics.

Anil Joshi is managing partner at Unicorn Ventures, a Mumbai-based venture capital firm. He notes that India has some way to go to catch up with the likes of the United

States and Japan in terms of the IP protections on offer for biotech innovators.

“These are early days for India’s IP system, but we can say that positive steps have been initiated,” he says, pointing to the Indian government’s recently launched ‘Startup India’ initiative. “From an investor’s perspective, it would be risky if there is not a strong IP regime, especially with regard to biotech, as a lot of investment goes into research and if the IP is not there to protect the innovation

then the entire investment could be at risk.”

There are a number of reasons why Amrita Therapeutics is looking to move many of its operations out of Ahmedabad, India, to the United States. One of the major factors in the decision is the perceived weakness of the country’s IP protections for biotech businesses.

“Amrita is transitioning towards becoming a US company,” says Finston. “There are many challenges for biotech start-ups in India - corporate governance issues, special burdens under the tax code and weaknesses in IP. So RDP is just one of a plethora of issues. When we set up Amrita we did it partly as a demonstration, to show, from soup to nuts, you could set up a business like this in India, to bring something important to market. But we didn’t claim we could spearhead a biotech angel and VC culture in the country. To actually get to the clinic, we need to be a US company.”

From the VC perspective, Joshi agrees that the introduction of RDP would have a positive impact on biotech investment in India. “With regards to biotech, investors would prefer exclusivity as it is important to protect the investment,” he says. “I would like to see more refined and clear guidelines in protecting IP not only for biotech but for all innovation. I think the government needs to promote

the importance of IP rights more heavily and encourage innovators to file for IP rights.”

Last year, Finston was commissioned by the development-focused Wadhvani Foundation to compile a report on India’s high-tech start-up environment. Among the policy recommendations made in the final report are a call to address the difficulty faced by biotech start-ups in “gaining regulatory exclusivity for commercially valuable clinical dossiers (data exclusivity periods)”, as well as the “less than effective patent protection for new chemical entities and biotechnology inventions”.

It was hoped that the Biotechnology Regulation Bill - first introduced into the Indian parliament in April 2013 - would aim to address some of these issues. But at the end of 2015, the bill was returned to the drawing board after objections from some lawmakers, activists and NGOs.

“You need incentives for primary research,” says Finston. “It needs to be a holistic environment. In that context RDP is very important - particularly for small companies that don’t have deep pockets for litigation. But the bill was defeated mainly due to the objections of academics and NGOs that didn’t really know what they were objecting against.”

■ DOES REGULATORY DATA PROTECTION UNDERMINE ACCESS TO MEDICINES?

Critics of India’s biotech regulation bill, and of IP protections more generally, have characterised RDP as another avenue for large pharmaceutical corporations to maintain a monopoly over the drugs they have invented, even after their patents expire. This, they argue, increases the price of medicines, restricting access to healthcare for the world’s poorer patients and creating insurmountable public welfare costs for developing nations.

The main fear of critics is that RDP will drive up healthcare costs to unsustainable levels by prolonging the period of market exclusivity enjoyed by biologic drugs. However, research from Geneva Network suggests that such fears are ungrounded. Analysing the examples of Canada and Japan, which have both lengthened their respective terms of RDP in recent years, shows that state expenditure on pharmaceuticals as a percentage of GDP remained pretty much flat in the years preceding and following the change.

Moreover, any consideration of the costs associated with longer RDP periods should also take into account the value they add in regards to long-term investment in, and availability of, treatments. The implementation of an RDP

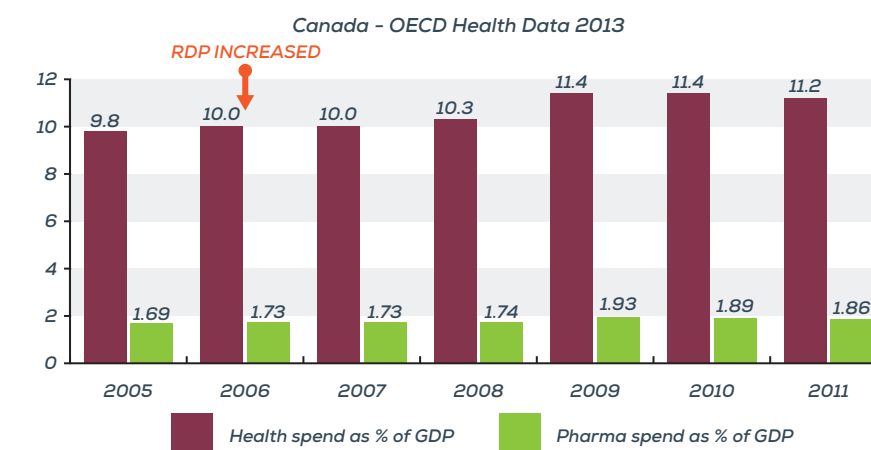
framework may even encourage more innovation, suggests Lybecker: “Regulatory data protection provides an additional form of IP protection and will delay biosimilar firms from bringing their product to market unless they generate their own preclinical and clinical safety and efficacy data.”

While RDP may extend the period of time in which biologic drugs do not face biosimilar competition, several additional elements must be weighed against this effect, she adds. “First, data exclusivity incentivises innovation which results in the development of biologic treatments and cures

that might not otherwise come into existence. Second, these medicines provide significant benefits to patients, both improving and extending their lives. This results in healthier individuals and cost savings to healthcare systems.”

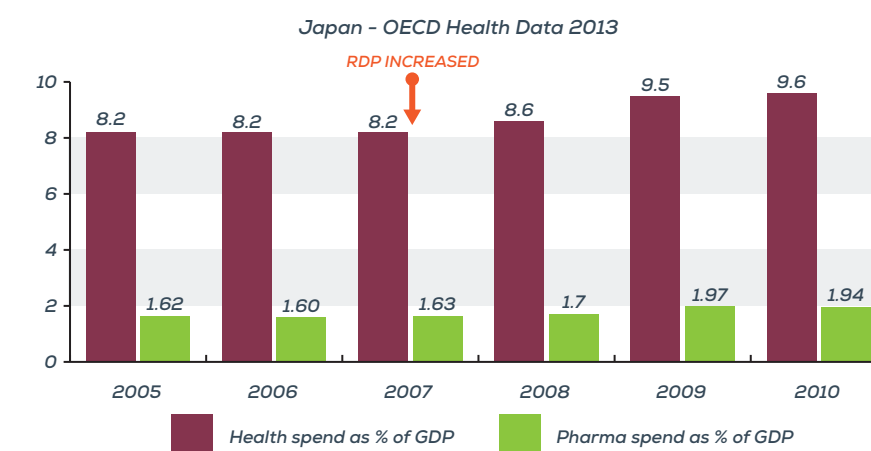
■ **Figure 3**

Health and pharmaceutical expenditure as a percentage of Canada’s GDP (2005-2011)



■ **Figure 4**

Health and pharmaceutical expenditure as a percentage of Japan’s GDP (2005-2011)



Source: ‘Will increasing the term of data exclusivity for biologic drugs in the TPP reduce access to medicines?’ Philip Stevens, Geneva Network, July 2015

Refraining from granting an innovator an RDP period may lead to much cheaper versions of the same drug arriving on the market more quickly. But this would only be a short-term benefit - and would be short-sighted too, Lasersohn suggests. “Data exclusivity may raise the cost of a particular drug,” he says. “But I think ‘supports the

price’ is the better way to put it. It doesn’t raise prices above a natural level, but rather supports the price that the market should pay for the investment of time and money that has gone into the development of the drug.” Without the availability of IP rights like RDP in the biotech space, there wouldn’t be

any drugs to begin with, he concludes. “The reality is that VCs are not required by law to invest in biotech. We could invest in social media and smartphone apps instead. But as a society, it is probably more important that we are able to fund the next Herceptin, rather than the next WhatsApp.”



ABOUT THE AUTHOR

Jack Ellis is an associate researcher at Geneva Network and a freelance journalist. Previously, Jack was the Asia-Pacific editor of *Intellectual Asset Management* magazine. He has also worked in a number of editorial and research roles covering intellectual property, the legal services market and the non-profit civic sector.

Case Study – Israel: Start-up Nation to Biotech Nation

Israel has long been lauded as the ‘Start-up Nation’. But for many years, the country was curiously conspicuous by its lack of a significant R&D base in pharmaceuticals and biotechnology. Back in 2010, Israel’s Chief Scientist, Dr Eli Oppen, had pinpointed biotech as a key area for future growth. His office had pushed through the establishment on several life sciences-focused incubators and was working to set up a biotech investment fund in an effort to attract investment in the nascent sector. But Oppen was frustrated by the low level of interest in these incentives. When he attended the BIO2010 US-Israel Dialogue later that year, one theme became apparent in all of his conversations with the companies and investors

that he wanted to bring to Israel: the country’s IP protection system was proving a turn-off. Israel had failed to implement long-promised IP reforms; but even while Oppen came face-to-face with the indictments of the country’s IP policy, it was already working towards significant improvements. Over the following five years, Israel undertook a deep and wide-ranging reform of its IP system, including the institution of RDP for chemical drugs of up to six years. Since then, there has been a boom in investment in the life science sector: in 2010, foreign capital accounted for around \$56 million, or 17%, of all investment in Israeli life sciences companies. Fast forward to 2014, and foreign investment made up the majority (59%), at \$469 million of a total \$801 million.

Figure 5: Capital invested by Israeli VC funds vs. other investors in life sciences, 2005-2014 (\$m)

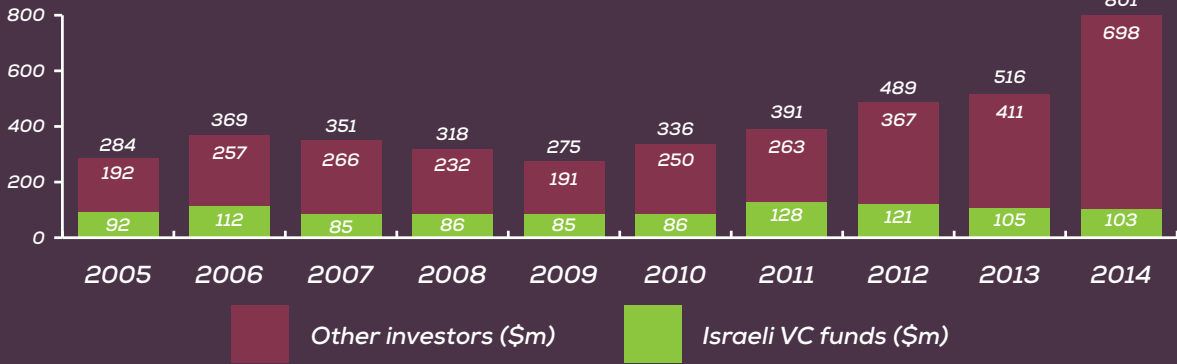


Figure 6: Capital invested in Israeli life sciences companies by investor: Israeli vs. foreign investors, 2010-2014 (\$m)

