

# INSULIN PATENT PROFILE

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April 2016



**acciss**   
Addressing the Challenge and Constraints  
of Insulin Sources and Supply

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April 2016

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## Acronyms

ACCISS	Addressing the Challenge and Constraints of Insulin Sources and Supply
BPCIA	Biosimilars Price Competition and Innovation
EPO	European Patent Office
FTA	Free Trade Agreement
HC	Health Canada
INPADOC	INternational PATent DOCumentation
INN	International Nonproprietary Name
IP	Intellectual Property
IPR	Intellectual Property Rights
NAFTA	North America Free Trade Agreement
OB	Orange Book
PCT	Patent Cooperation Treaty
TRIPS	Trade Related Aspects of Intellectual Property Rights
US	United States
USD	United States Dollar
US FDA	United States Food and Drug Administration
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

# Executive Summary

This study on insulin patents was undertaken as part of Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) Study. Insulin is an essential medicine that is needed for all people with type 1 diabetes, and a growing number of people with type 2 diabetes. It is crucially important that people in need can access this life-saving medicine.

Patents confer a 20 year period in which the patented product has market exclusivity, therefore third parties need permission from the patent owner to manufacture the product. Whether or not patents on insulins are a barrier to access is an important issue. This research looked at which insulins are not patented, or no longer patented.

Publicly-accessible databases from the United States (US), European, Chinese and Indian patent offices, as well as the US Food and Drug Administration (US FDA) and Health Canada, were reviewed to determine the patent status of human and analogue insulins.

Patents on analogue insulins in the market in the US and Canada have already expired or will soon expire in these countries and elsewhere. Only four companies own these key patents: Novo Nordisk, Sanofi, Eli Lilly and Pfizer. Patents on these insulins are geographically restricted roughly to North America, Europe, Australia, and China. In general, where US or Canadian patents were detected, about half were found in high-income countries, a quarter in middle-income countries, and the remainder in lower-middle-income countries. Patents in low-income settings were rare.

Patents and patent applications on insulins that are being developed have a wider geographic scope than insulins marketed in the US and Canada. Across the four companies, the patent expiration dates are delayed so any insulin patents that might eventually be granted will expire as late as 2030.

Patent applications or issued patents filed by other companies (i.e. excluding Novo Nordisk, Sanofi, Eli Lilly and Pfizer), such as those in India and China, appear to be surprisingly limited in number and scope. The ACCISS Study has identified about 40 insulin manufacturers, however, less than 10 percent have filed for any sort of intellectual property (IP) protection with respect to insulin. Based on this, it is expected that the major companies will continue to dominate the global market.

The public health implications of these findings include:

- In principle, third parties in the US and Canada may be free to exploit the technology claimed by expiring patents. Whether or not this will happen is unknown, as is whether or not existing (i.e. non-expired) IP portfolios of Eli Lilly, Novo Nordisk, Sanofi and Pfizer in the US and Canada will prevent such exploitation.
- The patent estates of these four companies that are directed to new insulins and methods, i.e. that lie outside of the presently marketed insulins and analogues, are extensive. The significance of this finding, for markets outside North America, is that it offers some empirical evidence that patent portfolios on insulins could, in principle, still effectively block generic competition. In other words, in areas of the world where IP protection is strong, even for products that do not yet have market approval, patent-holding manufacturers may be sole suppliers. This dynamic could contribute significantly to high insulin prices, and thereby affect access.

A practical way forward would be to engage with biosimilar insulin manufacturers and in order to expand their markets. Stimulating markets for acceptable yet older products is critical for changing

market dynamics; otherwise the major companies will continue to introduce new patented products, deeming their older offerings as obsolete and pulling them from the market.

IP ownership can increase the price of the patented product due to the exclusive market conferred by the patent. Further, third parties who want to make the patent product need to absorb the cost of patent licenses, plus other transactional costs, which can increase the cost of the product. Indeed, intellectual property is just one part of the larger system of trade, trade agreements, supply, distribution, taxes, tariffs, corruption and the like and impact access to medicines..

To understand how insulin IP acts as a barrier in both upstream (research) and downstream (development and commercialisation) domains, we need to quantify the term “barrier” as well as the strategies that companies have in dealing with insulin-related IP, such as how much time, how much effort (e.g. human resources) and how much money the license negotiations took; how much time, effort and money it took to ‘invent around’ a third party patent; and how much time, effort and money the patent challenge costs. Interviews with insulin manufacturers and insulin researchers will be required for this.

## **1. Introduction**

### **1.1 ACCISS Study**

Today, approximately 100 million people around the world need insulin, including all people living with type 1 diabetes and between 10-25 percent of people with type 2 diabetes. Although insulin has been used in the treatment of diabetes for over 90 years, globally more than half of those who need insulin today still cannot afford and/or access it. Without insulin, people living with type 1 diabetes will die. Many more will suffer from diabetes-related complications, like blindness, amputation and kidney failure, and, ultimately, premature death.

There are many complex issues that affect access to this life-saving medicine, creating inequity and inefficiency in the global insulin market. These issues include the global insulin market domination by three multinational manufacturers, import duties affecting the price insulin entering different countries, and mark-ups, taxes and other charges in the public and private sector supply chains that affect the final patient price.

The innovative global study, Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS), sets out to identify the causes of poor availability and high insulin prices and develop policies and interventions to improve access to this essential medicine, particularly in the world’s most under-served regions. The three-year study involves a unique group of leading international experts as members of the study’s advisory and technical groups. ACCISS is co-led by Margaret Ewen at Health Action International, David Beran from Geneva University Hospitals and the University of Geneva, and Richard Laing from Boston University School of Public Health.

The study will be carried out in three phases. The first phase was mapping the global insulin market from various angles including trade issues, patents on insulin, market issues (including which pharmaceutical companies manufacture and distribute insulin) prices, trade issues, tariffs and taxes on insulin, and current initiatives to improve access to insulin.

This profile on insulin patents is a result of the mapping work in phase one, and is one of several profiles on the global insulin market to be published. All profiles can be accessed on the ACCISS Study section of HAI's website: <http://haiweb.org/what-we-do/acciss/>

## 1.2 Terminology

This profile discusses the role that IP, specifically patents, play in access to insulin, including a general overview of role that patents play in innovation.

IP is a legal term that refers to creations of the mind. Examples of IP include music, literature, and other artistic works, discoveries and inventions, and words, phrases, symbols, and designs. Under IP laws, owners of IP are granted certain exclusive rights. Some common types of intellectual property rights (IPR) relevant to medicines are patents and trademarks. The latter provides exclusionary rights to the name of a good or a service. In this profile, we are focusing on patent rights.

A patent is a legally binding contract by a government authority conferring a set of rights to the inventor for a set period. These are exclusionary rights, especially the sole right to exclude third parties from making, using, selling, advertising, or importing the invention.

Every country that is a member of the World Trade Organization (WTO) has agreed to a multi-lateral agreement called the Trade Related Aspects of Intellectual Property Rights (TRIPS). The TRIPS Agreement provides a minimum level of patent protection. Patents are granted for “new, useful and non-obvious inventions” for a period of 20 years from the filing date of a patent application.

In exchange for these exclusionary rights for 20 years, the inventor agrees that the invention must be sufficiently described when the patent is granted and will be given over to the public when the patent term expires. Patents are territorial, meaning that one must apply for patent protection in each country or region where protection is sought. US patent grants are effective only within the US, territories, and possessions.

## 1.3 A Brief History of Patents on Insulin

Insulin was first extracted from whole animal pancreas in 1921, by Frederick Banting and Charles Best, both of the University of Toronto. The first patient was treated in 1922. The history of insulins, recently reviewed, is linked with patents in a very clear demonstration of the power of patents to exclude third parties from developing the product.(1)

A patent application on the insulin isolated by Banting and Best was delayed until 1923 (and later sold to the University for \$1 USD) because “academic medicine viewed the patenting of biomedical research products with some distaste”. (1) The two inventors naively believed that their primary purpose of patenting insulin was to allow anyone the freedom to prepare the extract.(1) They received Canadian Patent (CA 234336) on 19 September 1923, and US Patent (1,469,994) on 9 October 1923, for a “substance prepared from fresh pancreas....causing a reduction in blood sugar....”.

Banting and Best could not manufacture insulin to scale using the University facilities so they allowed (i.e., “licensed”) their US patent rights to Eli Lilly, allowing Lilly to apply for its own US patents on improvements to their process. Eli Lilly only filed for patents in the US and Canada on process improvements, and Banting and Best retained rights to their technology for the rest of the world.(2)

As a result, the Toronto team was free to allow third parties outside the US and Canada to produce insulin using Toronto's original technology. Such third parties included Denmark's Nordisk Insulinlaboratorium (which later merged with Novo Terapeutisk Laboratorium to form Novo Nordisk). Novo improved the original technology adding protamine to insulin and prolonged its action, as well as making further innovations, such as adding zinc to form the crystalline protamine isophane insulin, now known as neutral protamine Hagedorn (NPH), which was patented in 1946.(3) This made it possible to combine longer-acting and short-acting insulin. Many of these improvements resulted in patents being granted.

Soon afterward, Novo Nordisk was able to extend the duration of insulin's action without protamine.(4) Insulin patents were now expiring well into the 1970s. A series of innovations in the insulin manufacturing process in the early 1970s helped to improve purity and reduce side effects, which further extended insulin exclusionary patents into the late 1980s.

The first recombinant DNA insulin was made in 1978 and Eli Lilly brought the first recombinant human insulins - Humulin R (regular) and Humulin N (NPH) - to the US market in 1982. Novo Nordisk eventually marketed its first recombinant insulin in 1988. Patents on human insulin were now extended into the early part of the 21<sup>st</sup> century. (1)

Around this time, recombinant DNA technology allowed the substitution and/or alteration of the amino acid sequence of human insulin, resulting in 'analogues' such as lispro (1996), aspart (2000), glargine (2000), glulisine (2004) and detemir (2005).(1) The first patents on these analogues began expiring in 2014-2015.

Unlike small molecule chemical entities, it is difficult to produce an exact copy of a biological product (called a "biosimilar") that is produced using recombinant DNA technology. Because of the complexity of biosimilar products, patent holders tend to file many patents to protect methods of making, methods of using, as well as the biological product itself.

## **2. Intellectual Property Laws and Policies Impacting Access to Insulins**

### **2.1 The Doha Declaration**

The Doha Declaration (2001) confirms "the right of World Trade Organization (WTO) Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility" to protect public health.(5)

TRIPS flexibilities are options so that national interests are accommodated and TRIPS provisions and principles are also complied with. For example, WTO members have "the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted". The Doha Declaration also confirms the freedom of each WTO member state "to establish its own regime for ...[patent] exhaustion without challenge". Patent exhaustion governs the extent to which a patent holder can prevent the resale and importation of a patented product that they placed on the market in the same country or in another country. Countries are thus free to determine whether or not they want to allow parallel importation of patented goods, including insulin.

## 2.2 Laws and Policies Related to Patents

There is an enormous amount of literature on the role that IPRs have in either retarding or accelerating access to medicines.(6-8) Annex 1 summarises some important TRIPs flexibilities, as well as IP rules that inhibit access to medicines.

While the role of TRIPS in improving access to generic medicines is widely known, there are few examples of the use of TRIPS flexibilities for biologicals. However, there should be nothing in principle to prevent TRIPS flexibilities from being applied to biosimilar products.

Nevertheless, international trade agreements have incorporated ever-stronger protections for intellectual property. The WTO's 1995 Agreement on TRIPS sets the minimum standards for IP protection in the international system. Heightened protections since then have been termed "TRIPS-plus" and protection data submitted for the registration of pharmaceuticals is one of the most prominent.

Data refers to the safety- and efficacy-related data generated during a product's pre-clinical tests, clinical trials, and other studies. TRIPS instructs countries to take measures to protect this data from unfair commercial use, granting broad discretion to determine what constitutes unfair commercial use and what measures are appropriate. Under TRIPS-plus provisions, data owners have exclusive rights for prescribed durations. Data protection has become especially important for biologics like insulin, as they are more complex structurally, and produced using living host organisms. The industry's position is that because of the greater difficulties involved in developing a biological, generating the requisite data for drug approval entails more investments of time, money and other resources than does organically synthesised 'small molecules'.

Data exclusivity provides the innovator of a biological drug with a period of exclusive rights to the data, during which a national regulatory authority cannot approve a biosimilar drug that relies on the original data.

The recently signed (February 2016) Trans-Pacific Partnership Agreement (TPP) between the US and 12 Pacific Rim countries (Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, and Vietnam) provides a minimum period of data protection for five years, with options for an additional three years of data protection. The hope is that this range will be long enough to encourage development of new medicines, while still making existing ones accessible for the less-developed countries in the TPP. These provisions could reduce access to medicines in the countries that previously had no minimum exclusivity period. For example, Peru, Vietnam, Malaysia and Mexico had no protection at all for biologics, and now will have to enact five-year waits for more affordable biosimilars.

## 2.3 The US "Patent Dance"

In early 2015, an advisory committee to the US FDA recommended approval of the first biosimilar application submitted to the agency. Sandoz, the generics division of Novartis, was seeking approval for a biosimilar version of Neupogen® (filgrastim), a medicine produced by the California-based Amgen that helps cancer patients produce more white blood cells. (9)

But even as the agency reviews the application, Amgen and Sandoz are in litigation over the patents pertaining to Neupogen®. The medicine's key patents expired in 2013, but Amgen wants assurance that Sandoz's product does not infringe any of its remaining patents. So in October 2014, Amgen filed a

lawsuit against Sandoz. “This lawsuit is necessary because Defendants refuse to follow the rules,” states the complaint. (10)

The rules in question can be found in the Biosimilars Price Competition and Innovation Act (BPCIA). The law, part of the 2010 US Patient Protection and Affordable Care Act, lays out an expedited approval pathway for biosimilars. It also includes a procedure for resolving patent disputes that contains so many carefully timed and choreographed steps it has become known as the “patent dance”. (11)

The patent dance is supposed to help resolve disputes by forcing the parties to share information and resolve their differences. Once the original developer of the medicine reviews the biosimilar manufacturer's FDA application, the originator company has 60 days to compile a list of all the active patents it believes could be infringed by the applicant for the biosimilar. The two parties then embark on an exchange of patent lists and explanations of infringement and validity, all according to a set schedule. The goal of this back and forth is for the two parties to reach an agreement over which patents will be the subjects of the first round of patent infringement litigation. (11)

However, Sandoz unilaterally chose to not supply Amgen with a copy of its biosimilar application. This, of course, thwarted Amgen's ability to avail itself of the statutorily mandated patent exchanges. Sandoz chose not to do so because it did not want to share its licence application or manufacturing process with a future competitor, notwithstanding the statute's confidentiality provisions and the limitations on disclosure placed on recipients as found in the statute. Remarkably, Sandoz argues that the BPCIA does not compel biosimilar applicants to provide their applications to the companies that make the medicines they plan to mimic. Sandoz has made a prior attempt to bypass this patent dance. In 2013 the company filed a lawsuit against Amgen and Hoffman-LaRoche over a generic version of Amgen's Enbrel® (etanercept). (12) Although there have only been a handful of disputes involving this U.S. biosimilars statute, BPCIA of 2009, Amgen and Sandoz have been the protagonists in four of them.

A follow-on insulin has yet to be approved under the BPCIA. After 2020, all follow-on biological drugs will be required to use the BPCIA pathway, not the 505 (b) (2) pathway as was used for Basaglar®. At that point, whether any ‘patent dances’ over biologics, including insulin, will delay market entry is an open question. That said, it would appear that no application for any follow-on biologic (including insulin) is going to be approved under the rather simpler 505 (b) (2) pathway after 2020. (13)

In December 2015, Eli Lilly and Company and Boehringer Ingelheim Pharmaceuticals, Inc. announced that the US FDA granted approval for Basaglar® (insulin glargine injection) 100 units/mL. It has an identical amino acid sequence to Lantus®, another U-100 insulin glargine. It is not supposed to be launched in the US until December 2016. Basaglar® was approved by the US FDA via a different regulatory pathway than the BPCIA, the 505(b)(2) pathway. A 505(b)(2) marketing application contains full safety and effectiveness reports but allows at least some of the information required for approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by Eli Lilly and Boehringer. Indeed, the regulatory pathway for Basaglar® relied, in part, on the FDA's finding of safety and effectiveness for Lantus® to support approval. Eli Lilly and Boehringer demonstrated that Basaglar® was sufficiently similar to Lantus to scientifically justify reliance, and also provided Basaglar-specific data to establish the drug's safety and efficacy for its approved uses. The Basaglar-specific data included two clinical trials enrolling just 534 and 744 patients with type 1 and 2 diabetes mellitus, respectively.

### 3. Definitions

To help understand the methodology and findings, the following definitions are given:

**Priority document:** When the very first patent application is filed on a particular subject, the inventor can file one or more subsequent patent applications in another country for the same invention and the filing date of the subsequent invention will be the same as of the date of filing the first application. The very first application is the “priority document”. All subsequent applications must be filed within a certain time period (usually 12 months from the first) or else the priority is lost.

**Patent claim:** This is one of the numbered paragraphs found at the end of every published patent application and issued patent. The claims define, in technical terms, the boundaries of the subject-matter protected by the patent (or sought to be protected by the patent application). This is termed the notice function of a patent claim and warns others of what they must not do if they are to avoid patent infringement liability.

**WO starting documents:** “WO” is a suffix to a patent number that indicates that the original patent application was filed under the Patent Cooperation Treaty, an international treaty that harmonizes the patent application process among member nations. Although the World Intellectual Property Organization (WIPO) oversees this process, it does not issue international patents. Applicants must complete the last phase of the patent application process with the patent office of each nation where they desire patent protection.

**Patent Cooperation Treaty (PCT):** This assists applicants when seeking patent protection internationally for their inventions, helps patent offices with their patent granting decisions, and facilitates public access to a wealth of technical information relating to those inventions. By filing one international patent application under the PCT, applicants can simultaneously seek protection for an invention in 148 different countries. See Annex 2 for a map of the PCT countries.

**Orange Book:** Published by the US FDA, the Orange Book lists all medicines approved by them on the basis of safety and effectiveness under the Federal Food, Drug, and Cosmetic Act. In addition, the Orange Book lists therapeutic equivalents for approved medicines. It also lists patents that are purported to protect each medicine. Patent listings are provided by the applicant seeking marketing approval; the FDA is obliged to list them.

**Health Canada:** HC is the Canadian Medicines Regulatory Authority. They maintain a Patent Register which is a listing of medicinal ingredients and their associated patents, the patent expiry dates and other related information established in accordance with Canadian law. The Patent Register lists patents on medicines that have received marketing authorization. The database contains patent-related information on human and veterinary medicines from 12 March 1993 to date.

**WIPO Patentscope:** This is a database that provides access to international PCT applications in full text format on the day of publication, as well as to patent documents of participating national and regional patent offices.

**INPADOC:** This stands for INternational PATent DOCumentation, a database of international patents, which is maintained by the European Patent Office (EPO). It contains patent families and legal status information, and is updated weekly. Due to the nature of the patent system worldwide, patents must be applied for in individual countries. This creates a situation where a single idea might have many individual patents associated with it depending on the number of countries the applicant sought protection in. In some cases, protection is sought in dozens of countries, and thus there will be many

equivalent documents associated with their invention. INPADOC is freely accessible via the EPO's Espacenet website.

**Patent family:** This is a set of either patent applications or publications taken in multiple countries to protect a single invention by a common inventor(s) and then patented in more than one country. A first application is made in one country - the priority - and is then extended to other offices. Thus, it comprises all documents having exactly the same priority or combination of priorities and this means that sometimes the subject matter may vary among the different members of the family. An INPADOC patent family is referred to as an extended family since it includes all family members that share at least one priority number. It is not unusual to see a well-developed INPADOC patent family cover several hundred individual documents when you take into account all of the priority documents, applications vs. granted patents, and the different countries where the assignee is seeking patent coverage. All the documents directly or indirectly linked via a priority document belong to one patent family.

## **4. Intellectual Property as a Barrier to Access and Company Strategies**

Patents have multiple purposes with strategic motives, such as blocking competitors and preventing lawsuits. These are usually among the main motivations to patent, after the traditional motives of protecting inventions from imitations. In some extreme cases, patent applications are filed with the sole purpose of withdrawing the application before it gets granted a patent. Companies consider such a strategy when they want to prevent a third party from filing a patent on their invention but are not ready to incur the costs of maintaining and enforcing a patent. Some companies file applications with the intention of polluting a technological field by creating uncertainty.

A variety of problems can emerge if companies need to access knowledge that has been patented by other companies. For example, multiple patent holders for commercial products can, in principle, block each other from using their inventions. (14) In order to manage this risk, companies use pragmatic solutions such as licensing, inventing around, abandoning R&D, and simply using the technology without a license (i.e., infringement) to get around blocking patents.

Blocking can occur when a marketed product (i.e., an insulin product) needs several, complementary inventions (e.g., a key DNA sequence, specific purification chemistry, an important device, method of administering insulin), such that the holder of a patent on one particular invention (e.g., methods of purifying insulin) can block others from commercialising a product.

Patent barriers inevitably impose delays with research and development, cost in terms of human resources, and potentially delay introduction of the company's insulin product to market. Therefore, the presence of blocking patents has important legal, business and policy implications with regard to access to medicines. Our research did not include investigating the cost to a company of attempting to avoid a blocking patent.

## 5. Innovation Regarding Insulin Patents

It is widely agreed that if patents are to promote innovation, they should only be given for the physical manifestation of an idea that is novel, i.e., not known previously. Imagine an original patent on insulin being overly broad, and therefore encompasses all variants of the insulin protein. In this case, a truly novel variation may not be granted a patent or its inventor may have to pay the owner of the original patent so much as to attenuate incentives for further innovation.

Pharmaceutical companies try to extend the effective life of their patents by making incremental improvements on existing medicines. Insulin has seen almost continuous patenting since the early part of the 20th century. The question as to whether IP is a barrier to access raises the question as to how a merely descriptive patent landscape is really useful in terms of trying to understand whether an individual patent is really an innovation. To attempt to answer this question involves a tremendous amount of time, effort and technical expertise, may involve developing legal opinions, and is well beyond the scope of this profile.

Nonetheless, we attempt to further investigate the strategy of what the patent owner is attempting to protect in terms of insulin innovation. “Inventing” with regard to patenting of products and methods is not the same as innovation with regard to clinical and/or cost effectiveness.

Invention is about creating something new, while innovation introduces the concept of actual use of this new invention. This is a subtle but important difference. In the context of biomedicine, IP in the form of patents is evidence of inventiveness, i.e., creating something new and providing to the respective patent offices that the invention legally deserves to be patented. Put another way, innovation occurs when there is an improvement on existing product, process or service. Many patents on medicines, although legally capable of being granted, are not innovative in the sense that they do not have much clinical or cost-effective value when they are actually used on patients. It can be said that medicines (e.g., insulin) patents without such a “use” are not innovative.

## 6. Methodology

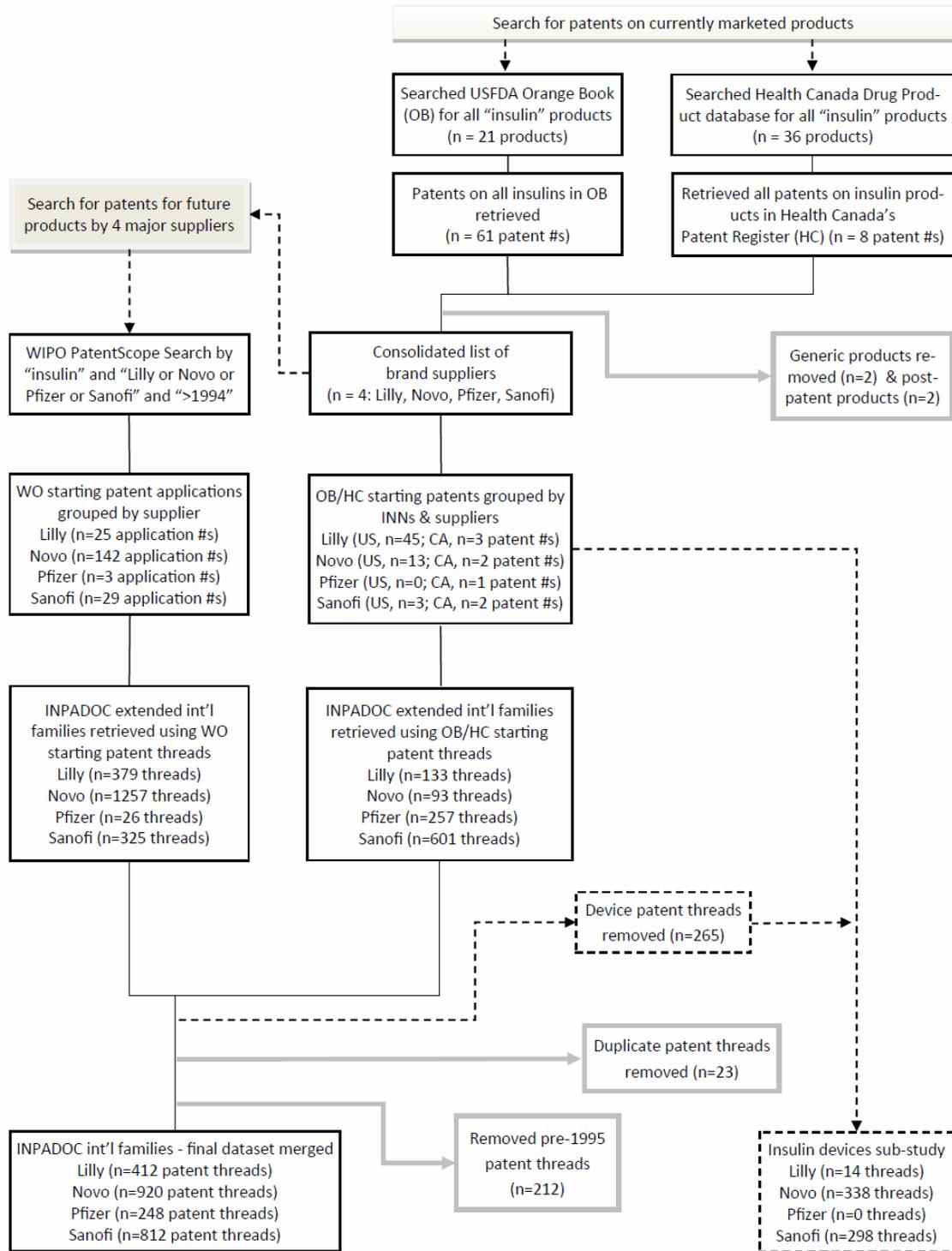
While collecting insulin patent estates directly from brand name companies was not feasible, we used patent information companies are required to provide to the US FDA and HC as part of the medicine approval processes. While other countries practice this form of patent linkage between the patent system and medicine regulatory bodies, only these two countries publish this information online in English in a format that is searchable by product’s proprietary or International Nonproprietary Name (INN). (15)

The ideal design for medicine patent landscape studies would be to survey all suppliers of the medicine in question, requesting the disclosure their global patent estates. While this approach has been used in the past, it is generally not feasible as companies rarely release this information. (16,17) A variety of other methods, of varying complexity, have been used by commercial and public entities to gather patent data. (18)

We wanted a method that could be replicated using publicly-accessible data available on the Internet and that could be performed by experts and non-experts alike. We built our methodology upon protocols outlined by previous published studies by scholars and international organisations. (19-25) A visual depiction of our approach is illustrated in Figure 1.

The primary analyses were a patent search of the Orange Book, HC, WIPO and INPADOC databases. Several supplementary analyses were undertaken as described in Section 7.2.

Figure 1. Flowchart of the methodology to collect data (with numerical results).



## 6.1 Primary Analyses

### 6.1.1 Orange Book and HC Searches

Using the term “insulin”, we searched the US FDA Orange Book (26) and Purple Book (27), and HC’s Online Drug Product Database Online Query (28) and its Patent Register (29). We also checked the DrugBank website (30), which contains a historical log of patents that have been previously disclosed in the US or Canada.

For each product found, we recorded the available patent data i.e. patent numbers, expiration dates, specific product (e.g., Lantus 10ml vial solution 100 units/ml), and the supplier. The data was then sorted by company and then by the type of insulin (i.e., human or analogue). The patent numbers that were retrieved through this process are labeled “OB/HC starting patents” in Figure 1.

The term “insulin” provided a better retrieval of relevant patents than “analogue” or any combination of these two terms. We tested this using two different search engines, WIPO Patentscope and the US Patent Office.

We searched the abstracts in both databases of all patent documents filed by the companies of interest with the word “insulin” between January 1994 to 1 January 2015.

#### WIPO Patentscope

Abstract search term	Assignee: “Lilly”	Assignee: “Novo”	Assignee: “Pfizer”	Assignee: “Sanofi”
insulin*	254	839	179	444
analog*	334	485	126	142
analog* OR insulin*	472	1090	279	516
analog* AND insulin*	126	234	8	70

*“\*” is the wildcard search term in WIPO Patentscope.*

#### US Patent Office

Abstract search term	Assignee: “Lilly”	Assignee: “Novo”	Assignee: “Pfizer”	Assignee: “Sanofi”
insulin\$	54	135	27	59
analog\$	54	22	20	13
analog\$ OR insulin\$	82	167	47	64
analog\$ AND insulin\$	26	40	0	8

*“\$” is the truncation wildcard in the USPTO*

When we used “insulin” alone, it resulted in more relevant results and was therefore a more robust search term. We noted during screening that the term “insulin” always used in relevant applications, but the term “analog” often did not appear in the abstract. Therefore, adding the term “analog” to the search terms was not value add. The lack of these two terms used in combination is illustrated in the results above by the increase in results by adding the “OR” operator and the sharp decrease when using the “AND” operator.

## 6.1.2 WIPO Patentscope Searches

As the Orange Book and HC databases do not contain process patents nor patents for insulins under development, supplementary searches of the WIPO PatentScope database were undertaken.<sup>(31)</sup> While there are no global patent grants, there is a nearly global patent application system. The PCT enables applicants to apply to WIPO and indicate in which of the 148 contracting states they intend to gain patent protection. WIPO reviews the application and produces a report, which applicants may use when pursuing actual patent grants in each state or region. PatentScope, therefore, is a vital resource for any global patent landscape report.

The WIPO PatentScope database was searched for patent publications containing the word “insulin” on the front page, with a filing date more recent than 1 January 1994, and that were submitted by the four insulin suppliers identified during the primary search (Eli Lilly, Pfizer, Novo Nordisk, and Sanofi Aventis).

We documented all results found in WIPO PatentScope, noting the product, supplier, patent numbers and expiration dates as in the primary analysis. The patent application numbers that were retrieved through this process are labeled “WO starting patents” in Figure 1.

## 6.1.3 INPADOC Searching for Patent Families

With a list of Orange Book/HC starting patent numbers and WO starting patent applications numbers, we turned to the E PO’s INPADOC database. INPADOC has bibliographic information from over 95 countries.<sup>(32)</sup> It allows users to enter a patent or patent application number and retrieve information on group equivalent patent documents (called a simple patent family) and on related ones (called an extended patent family) from other jurisdictions.<sup>(33)</sup> An advantage of the extended family feature is that all equivalent and related patent documents published around the world are included which expands the reach of the search and compensates for unforeseen gaps in our methodology, including those in North America. INPADOC helps capture domestic patents in the US and Canada as well as those around the world.

Based on Orange Book/HC and WO starting patent publication numbers, a list of related patent publications from around the world were retrieved. The data was grouped by the initial patent publication, to enable traces of each patent publication to a marketed product by each of the four suppliers in the North American market, or to a publication found in WIPO PatentScope.

An important point for understanding the statistics reported here is that INPADOC gives you so-called patent publication threads. A thread may include multiple legal events or publications that may eventually culminate in a patent grant. The type of event is indicated by “kind codes” For example, European patent EP2107069 is a for a novel insulin derivative and was filed by Novo Nordisk. INPADOC lists the following three entries in the publication number field: EP2107069 (A2); EP2107069 (A3); EP2107069 (B1). “A2”, “A3”, and “B1” are kind codes; EP indicates the European patent office. An “A2” publication has no search report (which is a report performed by a third party that confirms that the proposed invention is truly novel and is not duplicative of prior art). “A3” indicates the publication of a European search report for EP2107069. “B1” signifies the publication of a patent grant by the European patent office. Therefore, while there are three publications in this thread, they are within the same file of a single patent application.

When reporting on INPADOC output data, it is important to consider whether one is counting the number of threads (e.g., one thread, namely, EP2107069) or the number of publication documents (e.g., three publications EP2107069 (A2); EP2107069 (A3); EP2107069 (B1)). Unless otherwise noted, we report the number of threads in our findings (tables and figures). We have taken this approach because not all threads in INPADOC are complete, especially for developing countries, nor do they necessarily end with the granting of a patent. Despite this limitation, our data provide a sound perspective on where patent rights are being pursued by insulin suppliers from the vantage point of the world's largest international patent database that is freely available to the public. To address the limitation, we provide several figures that are based only on granted patents. Note that this data does not indicate the legal status of the patent in a particular jurisdiction. While INPADOC is kept as up-to-date and complete as possible, it is not real time and documents from some jurisdictions are more complete than others.

## **6.2 Supplementary Searches**

Upon inspecting the primary search results, some gaps in the data were clear which warranted further investigation. Specifically, in the WIPO and INDAPOC searches, surprisingly few documents were found by research universities, from China or India, and from some manufacturers known to be, or suspected of, producing insulin. Therefore, supplementary investigations into each one of these three areas were undertaken. The results from each are listed below. Note: these are not depicted in Figure 1.

### **6.2.1 University-based Patent Applications and Issued Patents**

We performed a preliminary search for the word “insulin” in the abstract of any WO starting document and the term “University” as the entity submitting the original WO starting document. We got 1,846 documents and reviewed just the first 800.

### **6.2.2 Specific Other Manufacturers**

Rather than using Orange Book/HC in order to define our list of manufacturers, we reviewed a list of 42 potentially independent insulin producers (see Annex 3) and searched WIPO PatentScope using the company name and the search term “insulin” found anywhere in either the front page of the WO-patent application or in the abstract of the WO-patent application, with a filing date more recent than 1 January 1994.

### **6.2.3 Searching National Patent Offices: India and China**

Given the importance of India and China in the manufacturing of active pharmaceutical ingredients and finished products, we searched online using the Indian Patent Office (34) and the Chinese Patent Office (35) for any patent applications and/or issued patents with the word “insulin” in the title of the invention.

## 6.3 Data Analysis

As shown in Figure 1, a database of threads was developed based on the various searches. Duplicates were removed, as well as any documents related to applications filed more than 20 years ago since most jurisdictions do not grant patents for longer periods. We also set aside filings describing devices related to insulin administration.

In order to report on the amount of granted patents contained in the INPADOC data, we referenced INPADOC's kind code key for each respective jurisdiction. Further, we scored each patent thread by which categories its claims covered, i.e., those relating to the product/compound; the method by which it is made; the way it which it is used for the treatment of patents; or other categories such as new formulations.

## 7. Results

### 7.1 Insulin Products Marketed in the US and Canada

#### 7.1.1 Patents of Sanofi, Novo Nordisk, Eli Lilly and Pfizer

Figure 1 gives overall results for each stage of our main analysis. For example, in the first stage, 21 products were found when searched using “insulin” in the Orange Book and 36 products in Health Canada, many of these being identical between the two lists (Annex 7). A product includes any formulation or strength by any manufacturer listed. Eight different insulins were found (Table 1).

Table 1. Insulin types with unexpired patents listed in the Orange Book or HC's Patent Register (as of April 2015).

All insulins found, North America market	Country	Supplier
INSULIN ASPART RECOMBINANT	US/Canada	Novo Nordisk
INSULIN DETEMIR RECOMBINANT	US only	Novo Nordisk
INSULIN GLARGINE RECOMBINANT	US/Canada	Sanofi US
INSULIN GLULISINE RECOMBINANT	US/Canada	Sanofi US
INSULIN LISPRO PROTAMINE RECOMBINANT; INSULIN LISPRO RECOMBINANT	US/Canada	Eli Lilly
INSULIN LISPRO RECOMBINANT	US/Canada	Eli Lilly
INSULIN RECOMBINANT HUMAN (Inhaled)	US/Canada	Pfizer (Canada). Sanofi US, but no unexpired patents listed
INSULIN ASPART PROTAMINE RECOMBINANT; INSULIN ASPART RECOMBINANT	US only	Novo Nordisk

Annex 4 lists thirty nine different patented insulin products (combined OB and HC) stratified by company, insulin type and product.

The Orange Book listed 61 patents on any insulin and HC listed 8 (Figure 1, second row of boxes). The fourth row shows the number of patents by company in the US and Canada. For example, OB had 45 US patents listed for products supplied by Eli Lilly. When we searched INPADOC for the extended

family using these 45 patent numbers, the database returned 133 patent document threads for Eli Lilly, 93 for Novo Nordisk and so on (Figure 1, fifth row of boxes).

After searching WIPO PatentScope for patents owned by the four major suppliers, using the results to search INPADOC, and removing duplicates, documents related to devices, and patents likely to be expired, we were left with 412 patent threads for Eli Lilly, 920 for Novo Nordisk, 248 for Pfizer and 812 for Sanofi (Figure 1, bottom row).

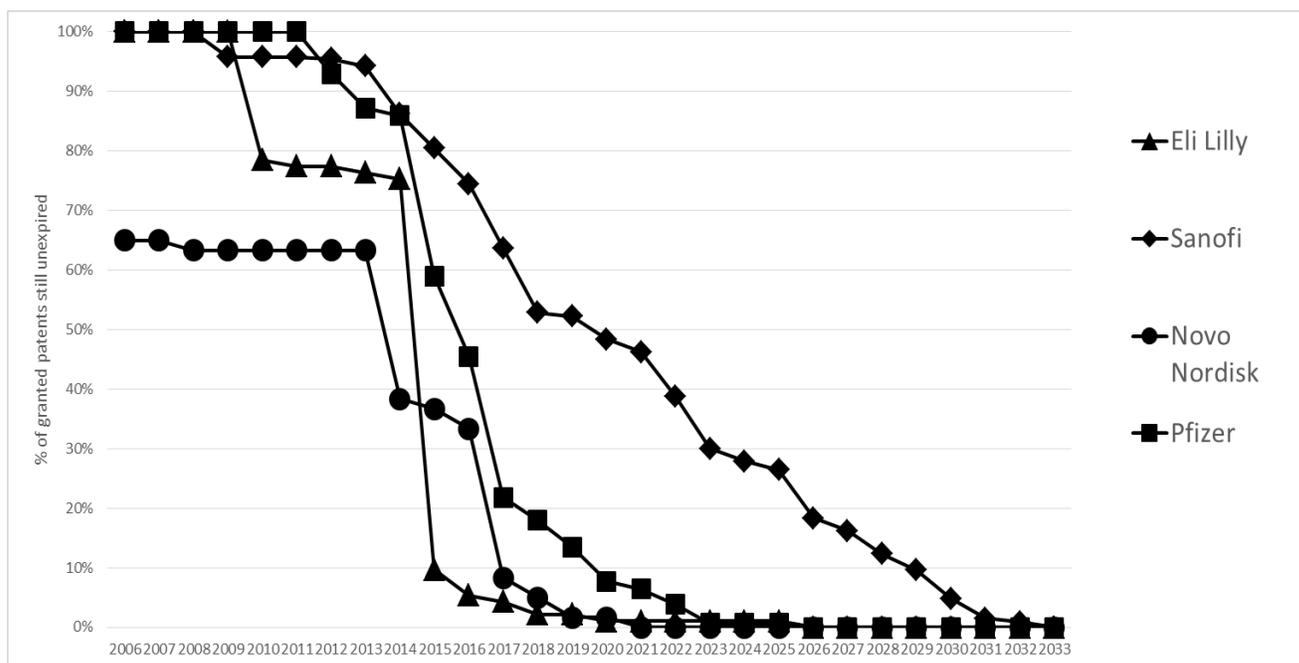
### 7.1.2 Worldwide Expiration Dates

Figure 2 shows the cumulative percentage of all worldwide patent expirations by company, assuming the expiration dates of all granted patents (i.e., a kind code indicating a patent grant) within the extended INPADOC family listed on the Orange Book/HC, as being 20 years after the application date listed in the Orange Book. As can be seen, patents on insulins in the US and Canada are set to expire within the next few years.

The sharp decline in cumulative expiration dates for Eli Lilly, and to a lesser extent Pfizer, represents their US and Canadian patents listed in the Orange Book and Health Canada whose patent applications were filed in 1995.

After 2015, few Orange Book/HC patents remain, except those of Sanofi who appear to have Orange Book/HC patents whose expirations extend well into 2030 and beyond (filed in 2010). About 35 percent of the Novo Nordisk Orange Book /HC portfolio had expired by 2006. Figure 2, thus shows how relatively quickly the Eli Lilly, Novo Nordisk and Pfizer insulin Orange Book/HC patents are expiring (the so-called patent cliff), compared to Sanofi.

Figure 2. Cumulative percent worldwide patent expiries of insulins marketed in the US and Canada by company.



### 7.1.3 Country of Patent Expiration

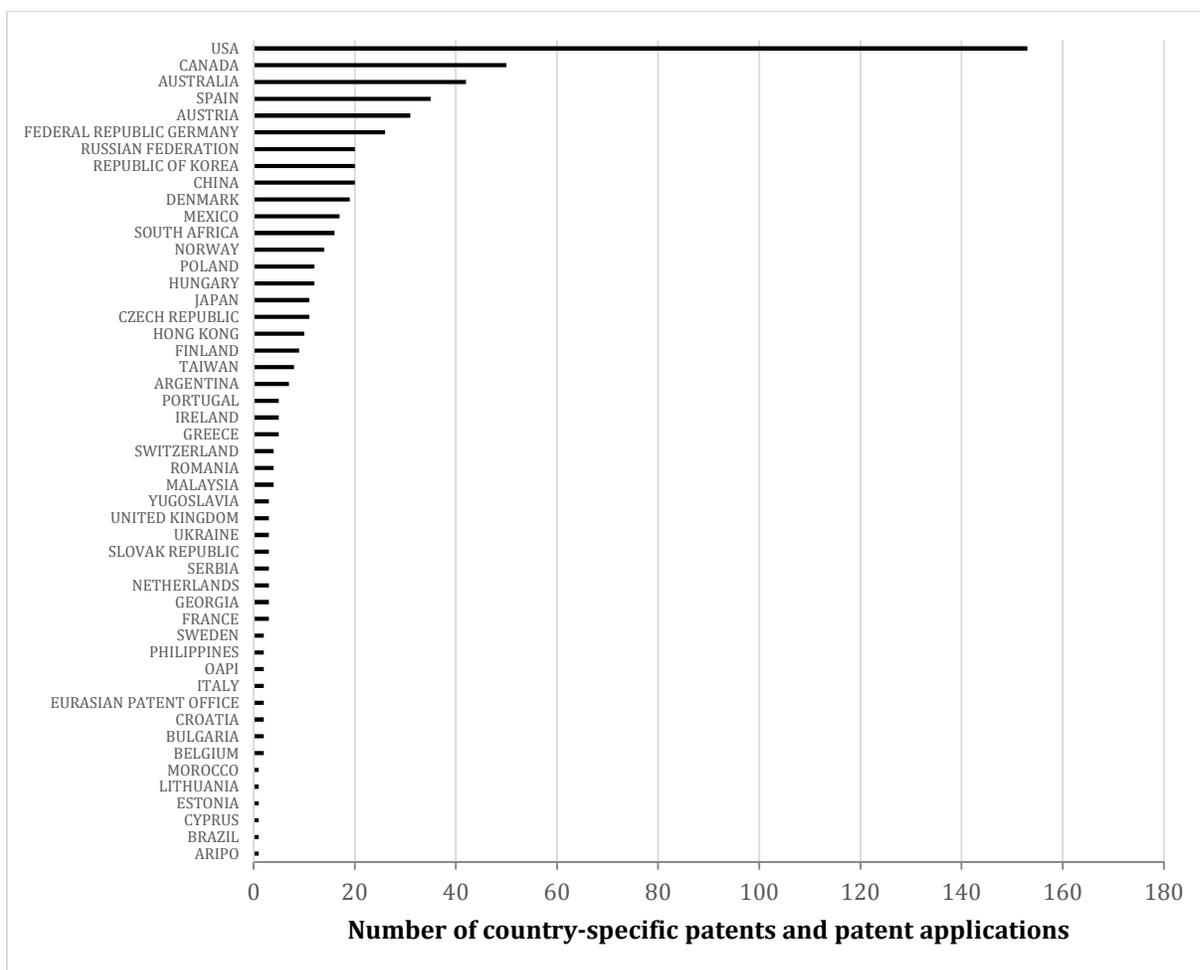
Figure 3 lists the number of patent threads that have already expired on marketed insulins (all companies combined) by country. The ranking should not be surprising. Most of the filings are in the North America FTA countries (Mexico, US and Canada), the European Union countries (although not all), China and Japan. Few filing were seen in the OAPI and ARIPO groupings of African countries (West Africa and East Africa respectively).<sup>1</sup>

Note: it is not known whether all the patent applications filed in the WIPO PatentScope will mature into actual patents. In this analysis we have assumed all applications filed do result in patents.

Figure 3. Countries where patents are set to expire (Orange Book/HC)

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<sup>1</sup> OAPI countries: Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Gabon, Guinea, Equatorial Guinea, Mali, Mauritania, Niger, Guinea Bissau, Senegal and Togo.  
ARIPO countries: Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, São Tomé and Príncipe, Sierra Leone, Somalia, Sudan, Swaziland, Tanzania, Uganda, Zambia, Zimbabwe



## 7.2 Products Under Development or not yet Marketed

### 7.2.1 Patents for Products Under Development or not yet Marketed in the US and Canada

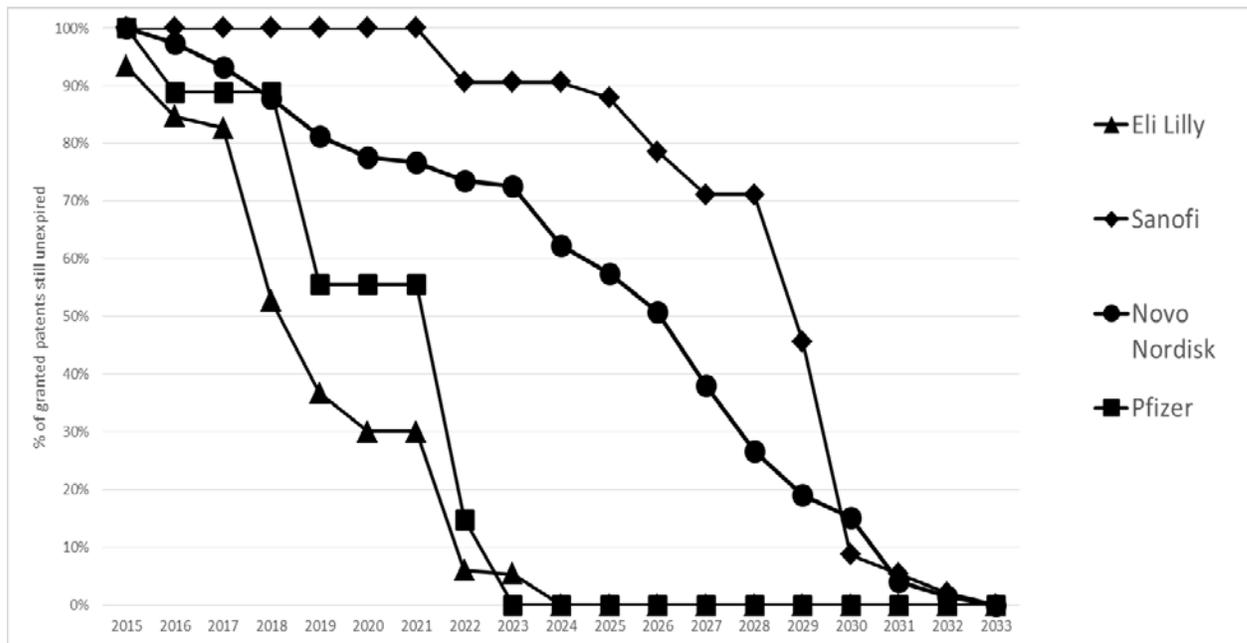
For each of the four companies, there was little overlap between the patents listed in the Orange Book or HC databases, and in the WIPO PatentScope. For Eli Lilly, there was no overlap hence many of their patent families were not identified in the Orange Book/HC databases. In practical terms, this means there is an extensive patent estate of Eli Lilly directed to insulin products in development (not yet marketed in the US and Canada) and/or methods. Similarly, there was no overlap for Sanofi or Pfizer patent families. For Novo Nordisk, only two patent families were common to Orange Book/HC and WIPO PatentScope.

This shows that the results of a patent search are highly depended upon the methods used and that finding the actual patents related to actual marketed products can be exceedingly difficult when relying on sources such as the Orange Book or HC.

## 7.2.2 Worldwide Expiration Dates

Figure 4 shows cumulative patent expirations (20 years from filing) based on the WIPO PatentScope. Novo Nordisk has filed non-OB/HC insulin documents in a manner similar to Sanofi i.e. expirations tend to be spread out over many years. A different picture is seen for the Eli Lilly or Pfizer portfolios. Eli Lilly's insulin patent portfolio is likely to expire at least a decade before that of Novo and Sanofi.

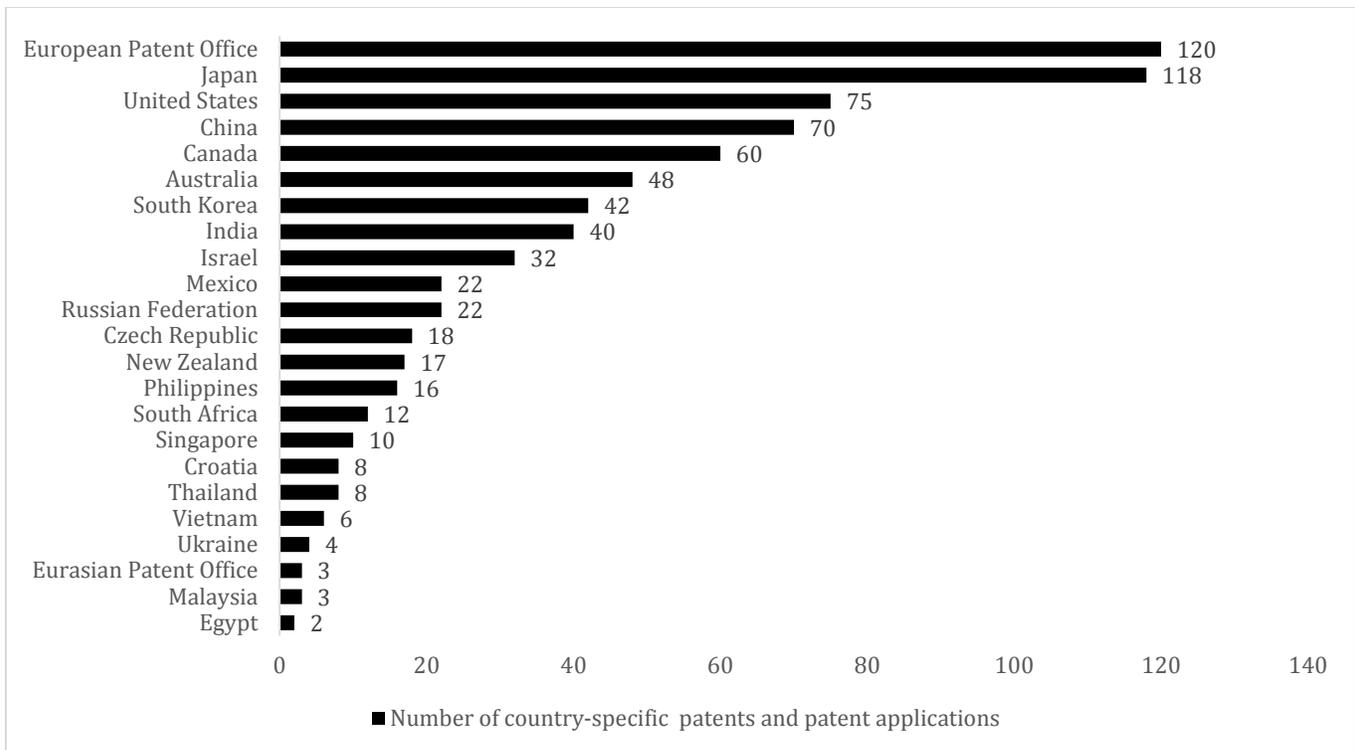
Figure 4. Cumulative percent worldwide patent expiries of insulin products under developments and/or not marketed in the US and Canada



The country-designations for these documents list both the EPO and also individual European members. The latter were removed from this analysis. Figure 5 lists the countries and the number of patents and patent applications that are yet to expire.

A number of countries, such as India, Israel, South Africa, Singapore, appear in Figure 5 (patents on products in development but not in Figure 3 (patents on marketed products). There are apparently no filings in Africa, except for South Africa.

Figure 5. Countries where non-OB/HC documents are yet to expire (WIPO PatentScope).

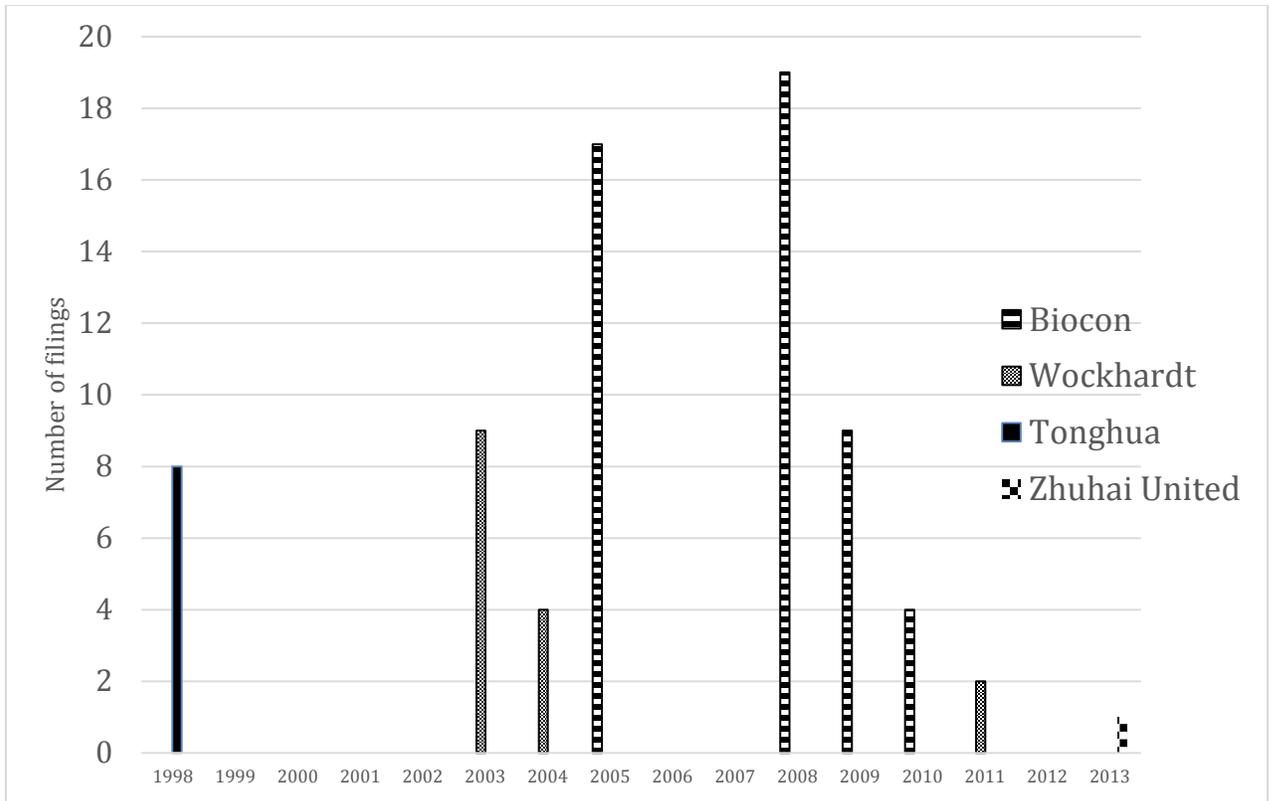


The WIPO PatentScope search (Figure 5) has what appears to be a different collection of national filings than those of marketed products (Figure 3). This confirmed that our dual search strategy, capturing patent documents related to currently marketed insulin products and products under development, is useful for gaining a prospective on the current situation as well as what the future holds. Perhaps the results illustrate that much of the research and development is taking place outside of the North America. It may also reflect that Novo Nordisk and Sanofi, both European-based companies, are more active in research and development than Eli Lilly (our results show that Pfizer is not active in insulin R&D).

### 7.3 Other Insulin Manufacturers

Of the insulin manufacturers identified in the ACCISS Insulin Market Profile (Annex 4) and excluding Eli Lilly, Sanofi and Novo Nordisk, only four had any publicly-available patent applications related to insulin. The four companies were Biocon and Wockhardt from India, and Tonghua Dongbao and Zhuhai United Laboratories from China. This indicates that their focus is on manufacturing existing insulins, rather than developing new insulins.

Figure 6. Number of patent applications filed by Biocon, Wockhardt, Tonghua Dongbao, and Zhuhai United Laboratories.



Each of the patent applications of these companies were filed in a number of countries. Figure 7 lists the countries where these manufacturers have had patent applications filed or are in the review process. These manufacturers have designated many other countries as potential filings but the available data does not show if they are being reviewed.

Figure 7. Countries where patent applications are in process for Biocon, Wockhardt, Tonghua Dongbao and Zhuhai United Laboratories.

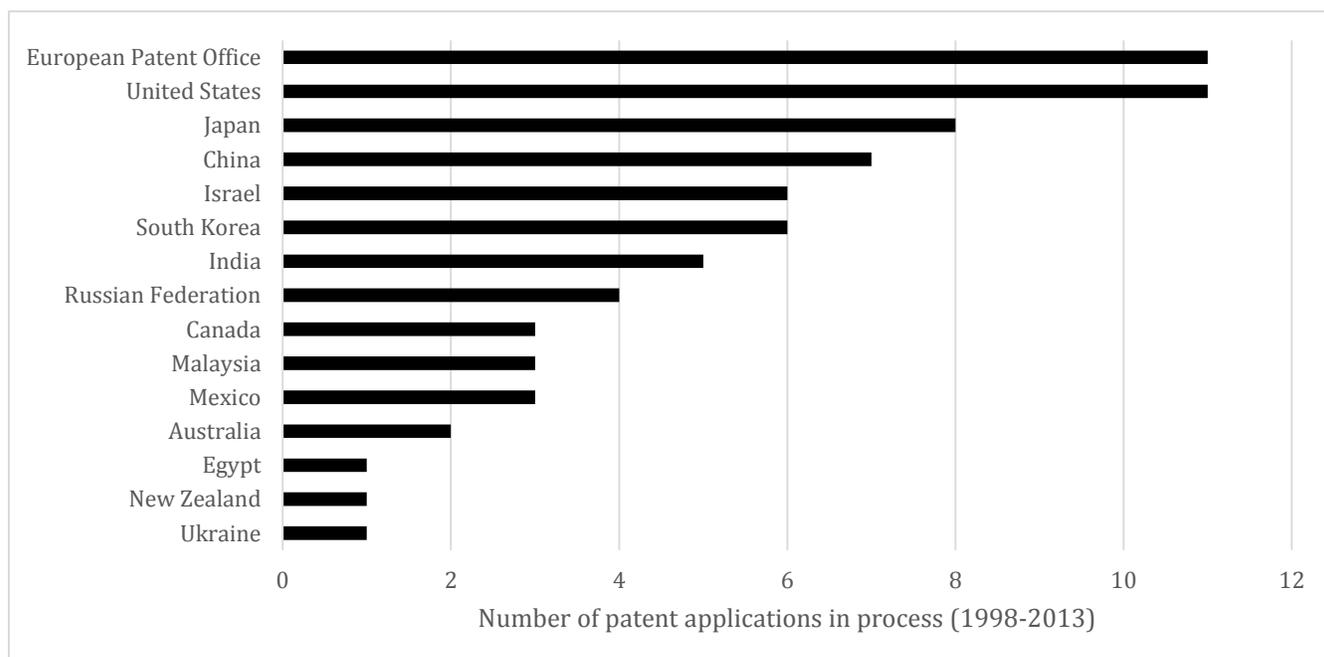


Table 2 lists the few countries in which insulin patents have already been granted for three of the four companies (no data was found for Zhuhai United Laboratories). The numbers of issued patents are in parentheses.

Table 2. Countries where granted patents exist for Biocon, Wockhardt, Tonghua Dongbao.

Country	Patents granted
Australia	Tonghua Dongbao (1)
European Patent Office	Biocon (1), Wockhardt (1), Tonghua Dongbao (1)
India	Biocon (1), Wockhardt (1)
Republic of Korea	Biocon (4), Tonghua Dongbao (1)
United States of America	Biocon (5), Wockhardt (1)

WO-documented patent applications outnumber granted patents for all four companies. These are listed in Annex 6.

## 7.4 Indian Patent Office Filings

There are a series of patents issued in India that have been filed by Eli Lilly, Novo Nordisk and Sanofi (see Annex 7). We did not identify any documents filed by Pfizer. We were able to find related PCT filings to these in INPADOC, but there were no specific records for India. Less than half of these related PCT records had data available for India at the national level in WIPO Patentscope. Most documents filed by the major manufacturers are directed to insulin products (No. 1-4, 8, 10, 12, 13 in Annex 7), production processes (No. 5-7, 9, 11, 14 in Annex 7) and therapeutic uses (No. 1-4,8). We also located patent filings that were filed by entities other than the major manufacturers (Annex 8). These

include filings by Biocon (as expected) plus organisations not found in the list of 42 manufacturers such as Itoham Foods, Reliance LifeSciences, and Savient Pharmaceuticals.

## 7.5 Chinese Patent Office Findings

There were 62 Chinese patent applications for Novo Nordisk with “insulin” in the title. The application dates were 2005-2012 and these would expire, if granted, between 2024-2031.

There were 17 Chinese patent applications for Eli Lilly with application dates between 1995-2002. These would expire between 2014 and 2021. There were 15 Chinese patent applications for Sanofi with filing dates between 2006-2014. These would expire between 2025 and 2033.

We identified other documents in which the entity filing the patent application were a group of individuals, a university /research institute (see Annex 9). Our sense is that this “insulin” IP is at an early research stage and shows some interest in producing insulin in plants (No. 1-3). Further technology is directed to diagnostic methods (No. 4-7), a vaccine against type 1 diabetes (No. 8), modified insulin (No. 9) and a computer-assisted database containing information about diabetes (No. 10).

## 7.6 University Filings Related to Insulin

The majority of filings by universities are from the US, specifically from the laboratory of Dr. Michael Weiss at the Case Western Reserve University and from the laboratory of Richard Di Marchi who developed lispro at Indiana University (see Annex 5).

## 7.7 INPADOC Extended Patent Families

Generally, the largest extended patent families are those for insulin products already on the market. We took an arbitrary number of 35 family members as a threshold and that yielded 10 families to look at in-depth from Eli Lilly, Novo Nordisk, Pfizer and Sanofi. Our assumption is that the larger the family, the more the company has invested in that particular intellectual property and is, therefore, more likely to bring the product to market and enforce patent rights. In this section, we briefly summarise the technology described in the largest patent families for each of the four companies.

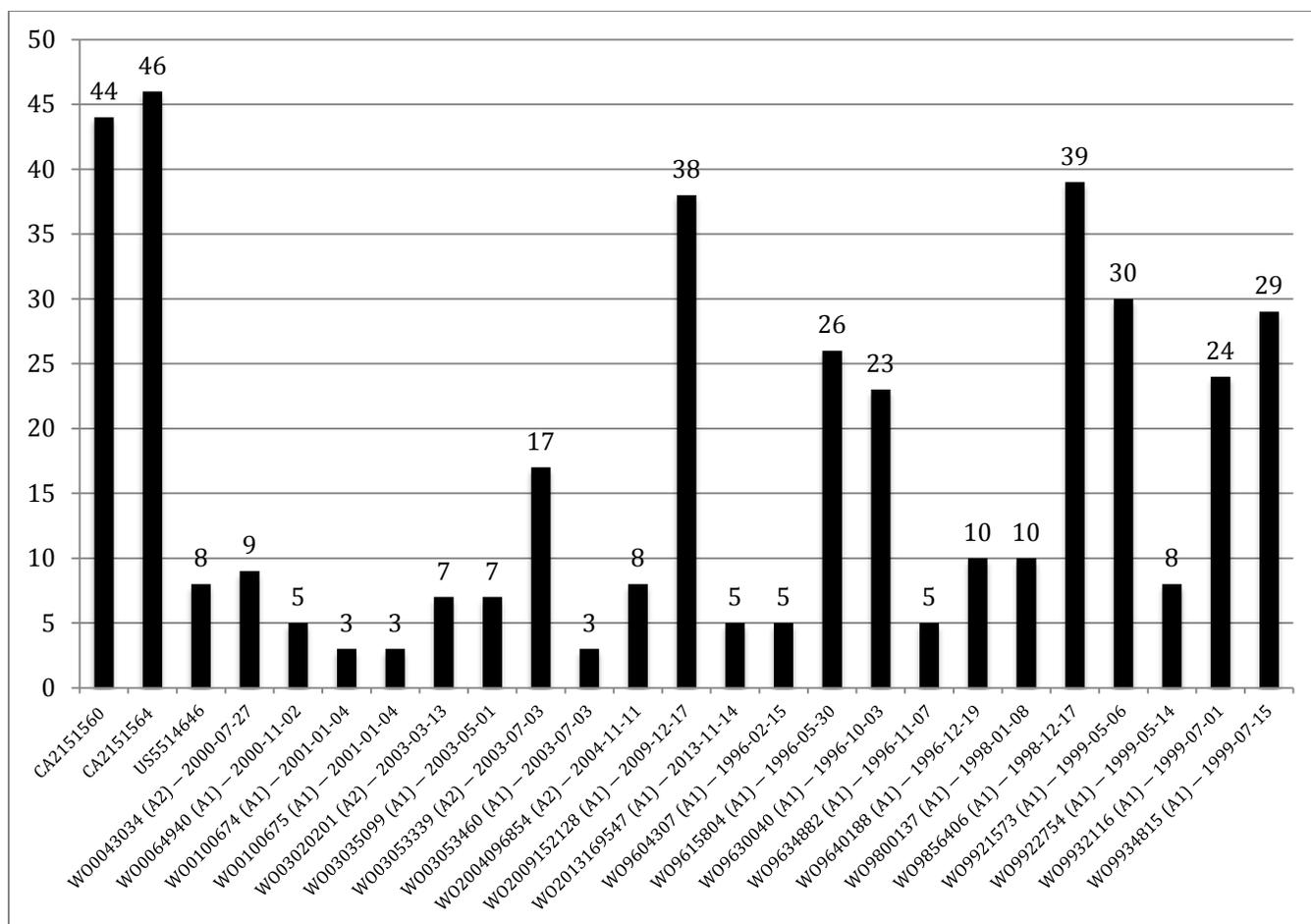
### 7.7.1 Eli Lilly

Figure 8 lists the first “parent” patent application filed for each one of the 25 different Eli Lilly insulin patent families. The original patent application number in the patent family is on the x axis and the numbers above the vertical columns show the number of patent threads in the particular patent family. Not all of these family members are issued patents as some are applications but all will expire 20 years from initial filing. We briefly describe the four largest Eli Lilly patent families:

- Lilly 44: This technology is directed to certain insulin analogues, principally lispro, that contain zinc and certain organic compounds. Thirty-nine of these family members expired mid-2015.
- Lilly 46: This technology is primarily directed to insulin lispro, although it encompasses other analogue variations. Thirty-two of these family members expired mid-2015.

- Lilly 38: This technology is directed to insulin lispro and variants, that are conjugated with poly-ethylene glycol to increase stability and provide a longer duration of activity. All of these members will expire between 2029 and 2031.
- Lilly 39: This technology is based on the idea that when certain ‘buffers other than phosphate...’ are used the physical stability of the insulin is “.... unexpectedly and considerably greater than when phosphate buffer is used.” All of these members will expire between 2018 and 2021.

Figure 8. Relative size of patent family of Eli Lilly’s insulin patent holdings

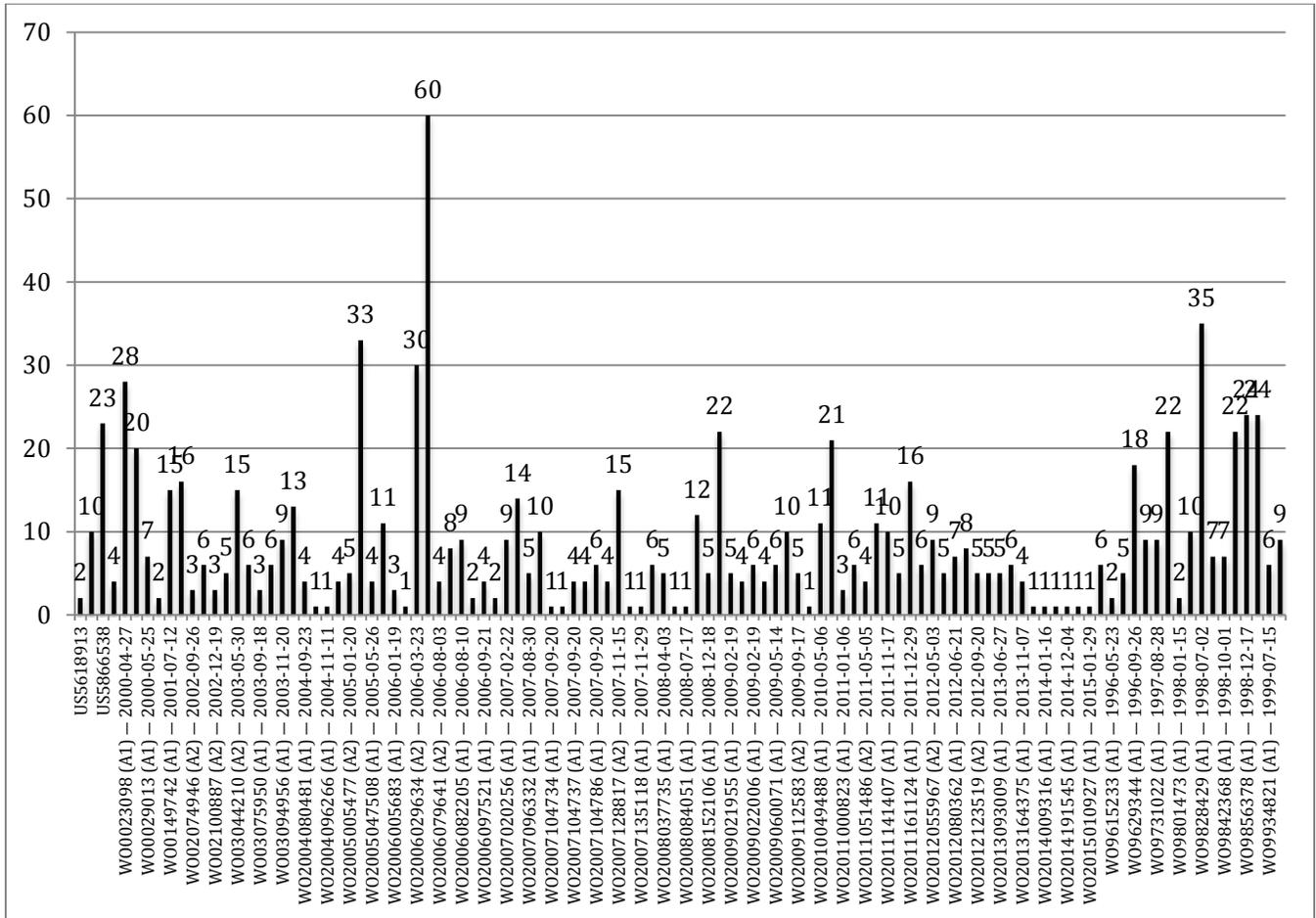


## 7.7.2 Novo Nordisk

Figure 9 shows (on the x axis) the first parent patent application filed for each one of the different Novo Nordisk insulin patent families and (on the Y axis) the numbers of patent threads in the particular patent family. The subject of the two largest Novo patent families (labelled 60 and 35) are described below. Not all of these family members are issued patents as some are patent applications, but all will expire 20 years from initial filing.

- Novo 60: This is an example of an extended patent family where most of the technology is not directed to insulin or diabetes. This is a function of how extended patent family is defined, as members of an extended family only need to be related to a patent that itself is related to an equivalent patent of the first filed patent application. Of the 60 members, 12 are directed to “novel formulations...” of crystalline insulin and dissolved insulin. Patents arising from these 12 members will expire between 2024 and 2029.
- Novo 35: This technology is directed to a general method of using yeast to secrete proteins more efficiently, so it is not restricted to insulin production. Twenty-seven members of this family will expire within the next year.

Figure 9. Relative size of patent family of Novo Nordisk’s insulin patent holdings.

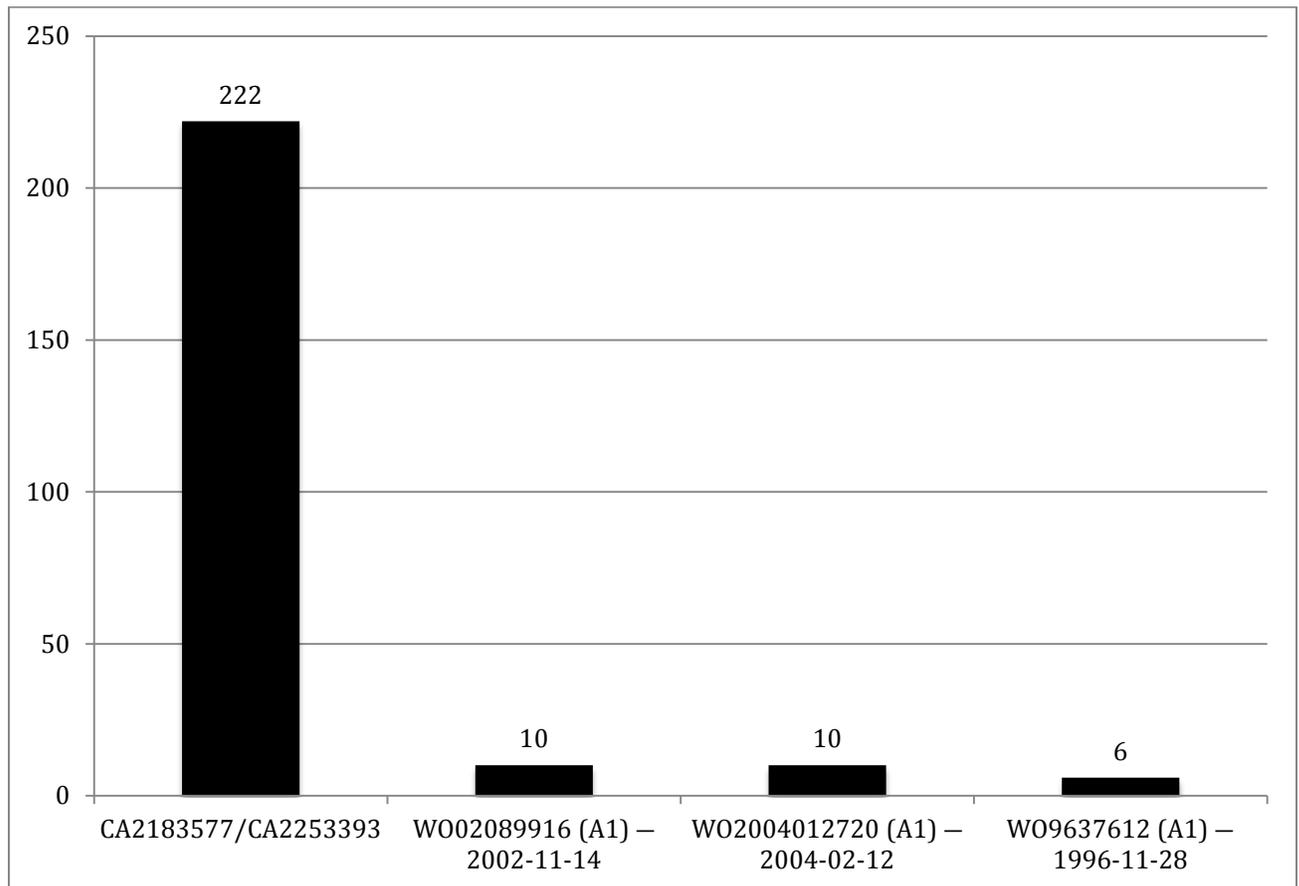


### 7.7.3 Pfizer

Figure 10 shows the first parent patent application filed for each one of the four Pfizer insulin patent families. The largest (Pfizer 222 is described). Given the few Pfizer filings in PatentScope, we are confident that the company is not active in research and development in this area. Their main presence in the insulin market is for the product Exubera®, but we do not anticipate Pfizer introducing new products in the future.

**Pfizer 222:** This large patent family covers Pfizer’s hoped-for pulmonary insulin product and delivery system. It is certainly worth noting that in 2007, after 11 years of development and barely one full year of sales, Pfizer stopped production of Exuberra. The product had sales of just \$12 million for the first nine months of 2007. Seventy members of this family expired in 2015, the remainders are set to expire between 2016 and 2029.

Figure 10. Relative size of patent family of Pfizer’s insulin patent holdings.



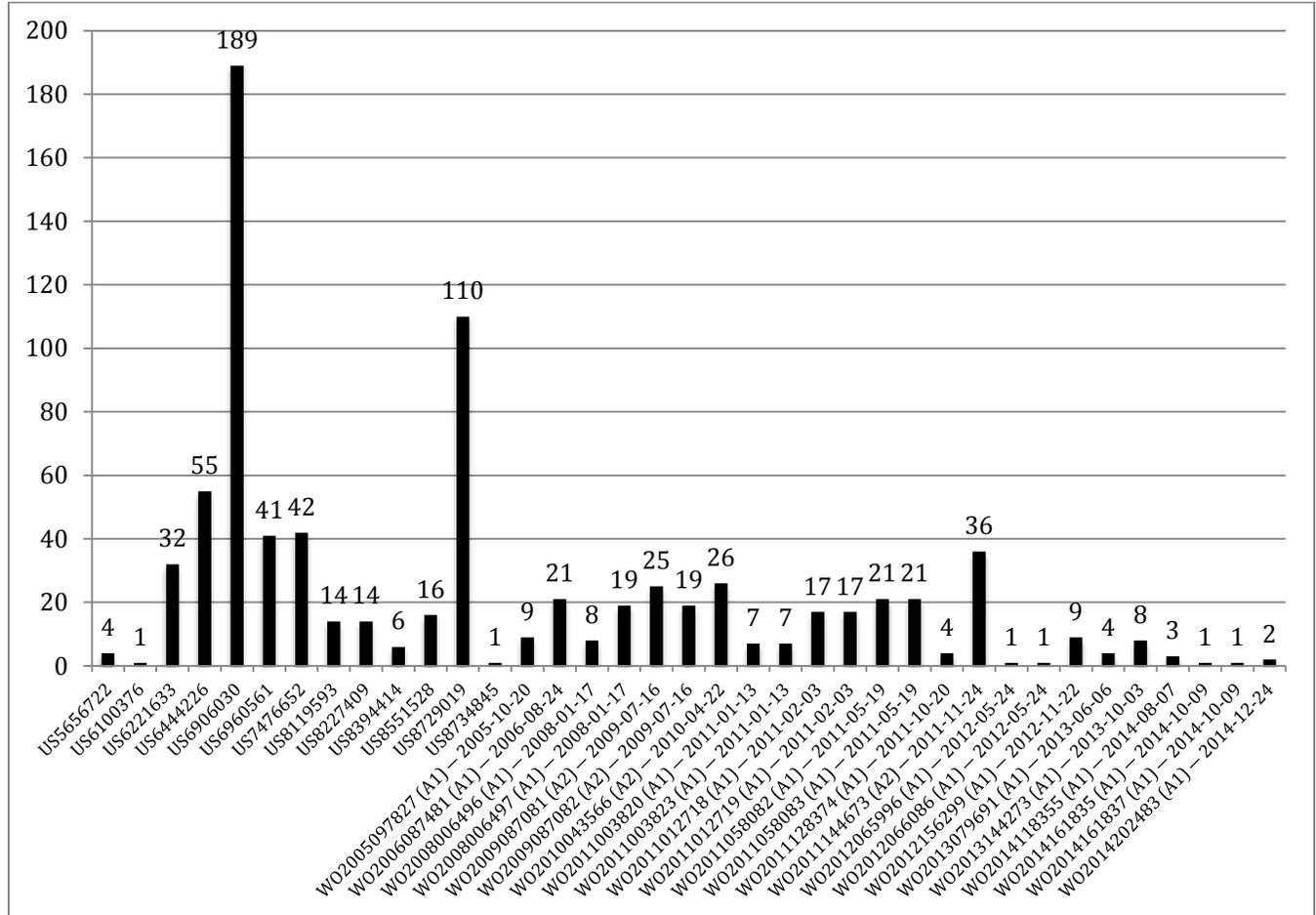
### 7.7.4 Sanofi

Figure 10 shows the 34 different Sanofi insulin patent families. We note three large patent families:

- **Sanofi 189:** This large patent family is directed to a variety of methods for delivery of antigens, which can include insulin. Much of the documents deal with oral delivery systems. Most documents in this family were filed by Emisphere, a company promoting new uses for Eligen® for oral delivery. All members of this patent family will expire between 2020 and 2034.
- **Sanofi 110:** This is another key technology for Sanofi and is directed to binding of an active agent (insulin) to a “... crystalline microparticle in suspension”. Similar to the 189 family, this technology is related to methods and products for oral administration of insulin. All members of this patent family will expire between 2023 and 2031. Most documents in this family were filed by MannKind Corporation who has partnered with Sanofi to produce Afrezza®, currently the only available oral insulin product on the US market.

- **Sanofi 36:** This is a recently filed patent family that appears to be directed to very specific long-acting formulations of insulin glargine. All members of this family will expire between 2031 and 2033.

Figure 11. Relative size of patent family of Sanofi’s insulin patent holdings.



## 8. Patents and Innovation

In Section 7, we inferred some key insulin-related technology from the number of total patent threads. Here we provide some examples of the patent claims and, in several cases, the patent application history in a preliminary attempt to understand the innovative aspect of these patent filings. This is clearly a different, but related, question to whether insulin patents inhibit access.

A patent innovation in the insulin patent space is merely one that is legally distinguishable from what is already known about the particular subject, such that the patent claim describes something that meets the patentability standards set forth in the particular Patent Office. These standards are rather similar, but not identical, in all countries that are contributors to the global insulin market. Clinical trials are not an absolute requirement as supporting evidence to obtain a patent on methods of using insulin to treat diabetes, although many insulin patent applications would already have clinical data

available as support. A public health innovation with regard to insulin would be quite different as it entails a consideration of clinical effectiveness, cost, cost-effectiveness and the like.

We provide several examples below to illustrate that innovation with regard to obtaining a patent is not the same as biomedical innovation.

## **8.1 Case Study - Novo Nordisk: Publication WO/2007/128815**

*Insulin derivative: Filed 2007; Granted: European Patent Office; Pending: Japan, US*

The technical aspect of this invention is based on the recognition that having a specific organic molecule attached to an insulin derivative molecule is important for prolonging in-vivo duration of action of insulin. For proof, the patent application described several chemical syntheses plus in-vivo pharmacokinetic experiments in rats and pigs.

This European patent is directed to a method of treating diabetes and the patentable aspect of the invention lies in the insulin compound itself. The broadest patent claim is: A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of an insulin derivative according to claims 1-10 optionally together with a pharmaceutically acceptable carrier.

This is a standard way of presenting a method of treatment patent claim as it offers as few technical details as possible, aside from the essential inventive element. Claims 1-10 provide protection for the particular compound in which one part of its inventive nature is, according to Novo Nordisk, the fact that it will “self associate into large soluble complexes...” and will form a “subcutaneous depot” upon injection so that it can be released more slowly than prior insulin. The prior insulin against which this long-acting insulin was compared is found in a very old U.S. patent 3,528,960 (expired 1983), filed by Eli Lilly.

COMMENT: No clinical data were presented and none is required. Patentability rested on the structure of the insulin, and not on its effectiveness nor on the presence of a subcutaneous depot. According to the law, this is not an essential aspect of the patent claim. Clinical trial data is not needed to get a patent.

## **8.2 Case Study - Case Western Reserve University (USA): Publication WO2010014946**

*Halogen-stabilised insulin: Filed 2009; Granted: European Patent Office; Pending: Australia, China, India, Korea, New Zealand*

Dr. Michael Weiss' laboratory is working on thermally stable insulin analogues in which the stability is created, in part, by adding a halogen atom (e.g., fluorine, bromine etc.) to one particular protein of the insulin chain.

Initially, the EPO said the patent claims were not patentable in light of what was known about this subject but suggested making claims more specific and restrictive to introduce technical material into the patent claim so that it would describe something that was not found previously. Weiss further presented evidence on thermal stability of insulin using chemical methods and in-vivo activity in lowering blood sugar levels in rats.

COMMENT: If this insulin is thermally stable and a commercial product has this property, it may well be a major public health innovation. In order to make this product, multiple licenses will likely be needed which could increase the final patent.

### **8.3 Case Study - Biocon: Publication WO/2007/007345**

*Preparation of insulin conjugates: Filed 2005; Granted: European Patent Office, South Korea, United States, India; Pending: China, Israel, Japan, Mexico*

This invention is a method for making an insulin-oligomer conjugate in a reaction vessel, rather than multiple vessels. Biocon asserted in this patent that "...the instant invention is a more simplified and economical in the making of an insulin conjugate wherein several steps of purification to obtain pure insulin in biologically active form are circumvented".

The EPO initially said the invention was not patentable because, although the chemical steps were not previously disclosed, it would have been obvious to develop the invention given what was known previously. The inventor simply restricted the patent claims in the application and added very specific reaction conditions to avoid what was known before. The patent was then granted.

COMMENT: In this patent application for a method of making insulin, it is fairly easy to obtain a novel and non-obvious invention by reciting steps not found in the literature. Whether or not this is a real commercial innovation is unclear although Biocon asserted that they made a simplified and economical chemical reaction that would lower the overall cost of production. No evidence was presented to show an improvement in the speed of the reaction and/or in reductions in the cost of production, although the patent was granted.

### **8.4 Case Study - Sanofi: Publication WO/2011/144673**

*Treatment of diabetes mellitus by long-acting formulations of insulins; Filed 2010; Pending: Canada, European Patent Office, Thailand, Philippines, Israel*

This patent application is directed to a liquid formulation for type 1 or type 2 diabetes "wherein the treatment reduces the risk of nocturnal hypoglycemia...". The formulation comprises 200 - 1000 U/mL [equimolar to 200 - 1000 IU human insulin] of glargine. The most preferred formulation was 300 U/ml glargine. This dosage showed a "flatter ... exposure and ... activity profile than insulin glargine U100" and this was "surprising and unexpected...".

The EPO acknowledged that differences in bioavailability in the Sanofi clinical trial among U100 and U300 dosages were significant. They considered the claims were novel because none of the documents cited described glargine in the dosage range specified by Sanofi in their patent claims. However, the broadest claims were considered obvious because, in effect, anyone who knows about insulin could easily figure out what an optimal dosage was.

COMMENT: This application is of interest as Sanofi will have to convince the EPO that their dosage range is non-obvious. The "surprising and unexpected" language is a hint that Sanofi will argue exactly that. In many countries, a patent application directed to a specific dosage regimen may be simply thought of as protecting a doctor's choice, within the frame of a medical use (e.g., insulin to treat diabetes). A specific dosage regime may be considered by some patent jurisdictions as a therapeutic method, and excluded from patentability by TRIPS. In other words, the determination of the ideal

dose of active ingredient for treating an illness is determined by the practitioner. Courts mostly in Europe, US, Japan and Canada have considered whether such “dosage” patent claims constitute a limitation of a doctor’s professional skill or judgment. They have decided that dosage inventions are otherwise capable of being patented. This may not be the case in other jurisdictions.

## **9. Limitations**

Starting with searching patents in the Orange Book and HC databases is a reasonable first step. Nevertheless, this approach risks overlooking patents associated with products marketed outside of North America and those that are key for future insulin development. Further, neither the Orange Book nor HC list patents on manufacturing processes, intermediate compounds, or metabolites. HC also does not list patents covering chemical forms (e.g. salts, esters, isomers/enantiomers, hydrates or solvates). Additionally, publically disclosing patent information with HC is optional. In contrast to the US FDA, HC has the patents screened and reviewed before listing them, meaning that one or more patents disclosed may not (yet) be visible in the HC Patent Register.

Using the word “insulin” as a search term in the title of a patent application is a reasonable first step, but will miss documents in which “peptide”, “hormone” or “polypeptide” is used instead of “insulin”, although we suspect such terms would not have added anything new. The search term “analog” resulted in a subset of patents when “insulin” was searched.

The documents contained in INPADOC are not exhaustive. Therefore, it is often not possible to determine the definitive, current legal status of each patent using INPADOC. A thorough check of the legal status requires investigation in each country or region. In this study, investigating the legal status for each patent was not feasible given the large number of documents identified.

As insulin is a biologic, it is likely that patents exist on host cells, DNA sequences, recombinant DNA technology, purification methods and the like, that a potential manufacturer would need to access in order to produce insulin. The patent literature for these sorts of technologies was not searched.

# 10. Conclusions

## 10.1 Patent Cliff

The patent cliff is real and the expiration of key Orange Book/HC patents on most marketed analogues have already taken place or will soon take place. Most of Orange Book /HC patents related to insulins on the US and Canadian markets have expired. It appears that Sanofi has filed patent applications which have matured into Orange Book/HC patents with later expiration dates than their competitors.

Notwithstanding the patent cliff, key Orange Book /HC patents of the major suppliers of marketed analogues are geographically restricted. These patents were not filed in Africa, and appear to be roughly restricted to North America, Europe, Australia and China. However, outside the Orange Book /HC insulin patent portfolio, there is no obvious patent cliff or the major suppliers and their filings have a wider geographic scope than their Orange Book /HC counterparts. For patent application filings outside of the Orange Book /HC portfolio, expiries for Novo Nordisk and Sanofi products are somewhat delayed so that issued patents expire later than those of Pfizer and Eli Lilly.

There are large patent families outside the Orange Book/HC filings of the four companies, some with over one hundred different filings that appear restricted to oral, inhaled insulin. We have identified two patent families owned by Sanofi, filed between 2011-2013, that each contain over 100 individual worldwide filings and are directed to products and methods pertaining to oral, inhaled insulin.

Similarly, a Pfizer extended family with 222 members is also directed to oral, inhaled insulin technology. The subject matter of insulin IP is directed to both products and processes but there are no apparent biases towards any one technology. Our preliminary assessment is that the claims of the insulin patents are divided approximately equally between product, method of use, and method of manufacture.

Patent applications/issued patents filed by other companies appear to be surprisingly limited in number and scope. A few companies thought to be making insulin outside of the major multinational companies are filing patent applications related to insulins but the numbers are small. The geographic scope is similar to that of the major companies, as might be expected.

## 10.2 Does IP on Insulin Inhibit Access?

This question is difficult to answer, in so far as IP is just one of a set of interactions in the healthcare system that impacts access. One would need to investigate both 'upstream' and 'downstream' components of the insulin value chain. By upstream we mean primarily pre-clinical research in which third party IP might inhibit, or even eliminate, insulin research programmes based in patent applications (and patents) to research tools like modified DNA sequences, cell lines, vectors, plasmids, laboratory diagnostic devices and so on. Needing to access multiple licenses for such research tools may be a potential disincentive to further research. To the extent such IP is actually a barrier to research remains an open question. (36,37) By downstream, we mean primarily late stage clinical research, development and commercialisation, based on patent applications/patents critical to process development such as purification methods, dosages, formulations, active ingredients, point-of-care diagnostics, and devices. Similarly, if there are multiple license negotiations with a number of parties, the risk of negotiation breakdown is increased. Projects might be either not started or abandoned at some stage. As the number of relevant intellectual property rights increases, the task of "inventing around" becomes more onerous (38).

To understand how insulin IP acts as a barrier in both upstream and downstream domains, we also need to quantify the barrier in terms how much time, effort, and money did license negotiations take, invent around a third party patent or challenge a patent. Interviews with insulin manufacturers and researchers will be required for this.

## **10.3 Public Health Implications of the Insulin Patent Landscape**

### **North American Market**

The North American insulin market is dominated by just four companies who are the sole suppliers of one or more of the various insulin analogues, which are available exclusively as brand name products. Almost without exception, all brand name products had one or more unexpired patents and/or data exclusivity in these two respective jurisdictions.

A state of affairs in which an entire pharmaceutical market has virtually no generic alternative is rare but this appears to be the case for the insulin market in North America.<sup>(1)</sup> When we consider the number of expirations within each patent estate, it is clear that the patent cliff for many of the marketed insulins in North America is not far away (Eli Lilly has stated it will market biosimilar glargine in December 2016) , as the overwhelming majority of the patent estates have already expired or will soon expire.

In principle, third parties may be free to exploit the technology claimed by these expiring Orange Book/HC patents. Whether or not this will happen is unknown. Whether or not existing (i.e., non-expired) IP portfolios of Eli Lilly, Novo Nordisk, Sanofi and Pfizer in the US and Canada will prevent such exploitation is also unknown, and beyond the scope of this study.

### **Markets outside North America**

#### *Orange Book/HC Portfolio*

As would be expected, the major players in the Canadian, US and European markets have filed patent applications, and have received issued patents, on technology claimed by these rapidly expiring Orange Book/HC patents in PCT countries. Interestingly, IP filings are rather sparse geographically, particularly in Africa.

Generally speaking (and excluding regional patents), where our study detected an Orange Book/HC patent filing, about 65 percent were in high-income countries, a quarter (28 percent) were in upper-middle-income countries, and the remaining were in lower-middle-income countries. Most patent filings are restricted to North America, Europe, Australia and China. Patents in low-income settings were rare. In principle, third parties may be free to exploit the technology claimed by these expiring Orange Book/HC patents in Africa. Many off-patent insulins can effectively manage diabetes and in principle off-patent analogues may be available in markets outside of North America. Other scholars have observed the need for older human insulins to be manufactured, and our findings support and underscore this need. (1)

A possible way forward would be engage with biosimilar insulin manufacturers and encourage them to expand their markets to increase competition. Stimulating markets for acceptable, yet older products is critical for changing market dynamics; otherwise the major companies will continue to introduce new

patented products, possibly deeming their older offerings as obsolete and pulling them from the market.

*Non-Orange Book/H C Portfolios: Sanofi, Novo Nordisk, Eli Lilly and Pfizer*

The patent estates of Sanofi, Novo Nordisk, Eli Lilly and Pfizer that are directed to new insulins and methods, which lie outside of the presently marketed insulin products, are extensive. The significance of this finding for markets outside North America is that it offers some empirical evidence that patent portfolios on insulins could, in principle, effectively block competition. In countries where IP protection is strong, even for products that do not yet have marketing approval, patent-holding companies may be the sole suppliers and this dynamic could contribute significantly to high medicine prices, thereby impacting access.

*Other Manufacturers of Insulin*

Over 40 potential insulin manufacturers have been identified, but less than 10 percent of these have filed for any sort of IP protection with respect to insulin. Therefore it is expected that the major companies will continue to dominate the global insulin market.

## **10.4 Biosimilar Insulin and Global IP Rules**

In our view, it makes no difference whether or not a product is a biologic or a small molecule, as TRIPS flexibilities (such as compulsory licensing) are applicable for either technology. It also follows that provisions inhibiting access to small molecules such as patent linkage, onerous data exclusivity provisions and so on, also apply to biosimilars.

With all the uncertainty about the rules of the patent dance, it is not clear how this impacts the development of biosimilars in the US. It may be that foreign biosimilar companies interested in marketing in the US would be deterred by the patent dance as this is, in effect, a forced negotiation and might be unappealing to developers of biologics. However, if the courts rule that biosimilar companies can avoid the patent dance and instead resolve patent disputes through some simpler process, such as alternate dispute resolution without litigation, that might be an incentive to develop biosimilars.

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## **Annex 1. Summary of important TRIPs flexibilities and IP rules that impact access to medicines**

### **Research exception to patent infringement**

As patent protection allows the patent owner to exclude others from making, using, selling, importing etc the invention, it can inhibit forms of competition (such as market entry for generic medicines) and also hinder further innovation. A research exception or experimental use exception is one of the most commonly used types of “limited exceptions” to national patent laws pursuant to TRIPS Agreement. The research exception is “the exception under which use of the patented product for scientific experimentation, during the term of the patent and without consent, is not an infringement”. (1)

Some countries limit the exception to acts carried out without commercial or gainful intent. This exemption enables researchers to examine patented inventions and to research on improvements without having to fear that they are infringing the patent. For example, Brazilian patent legislation very broadly exempts acts carried out by third parties without the consent of the patent owner for experimental purposes in connection with scientific or technological studies or research. (1)

Where the general research exception is not wide enough in a particular jurisdiction to allow particular follow-on research, such as use of a patented research tool, the researcher needs to obtain a licence on terms to be mutually agreed.

### **Regulatory exception to patent infringement**

During the process of obtaining marketing authorization for a product, the applicant has to produce a first batch of the product, which may be considered an infringement of a related patent. Because regulatory approval may take several years, the inability to use the patented invention during the approval process, prior to patent expiration, would delay market entry of generic versions.

The regulatory review exception (or so-called “Bolar” exception) alleviates this by, in general, entitling anyone to use a patented invention during the patent term without the consent of the patent holder for the purposes of developing information to obtain marketing approval.(2) This exception thus favours market entry by competitors immediately after the end of the patent term, and is, therefore, an instrument that is specifically designed to ensure early access to generic medicines.

### **Making patents more difficult to obtain: Indian Section 3(d)**

When revising its patent law to comply with the TRIPS requirement that pharmaceutical products be patentable, India adopted specific patentability criteria for chemical products by introducing Section 3(d) to its Patent Act (Patents Amendment Act of 2005). According to this section (paraphrased here), “the ... discovery of a new form of a known substance ... or new use for a known substance...” must result in “enhancement of the known efficacy of that substance...” or else it will not be patentable. In effect, Section 3(d) disallows patenting of new forms of already known molecules, also known as evergreening, unless the patent applicant shows significant enhancement in efficacy for its product.

The decision was expected to have major implications for the future supply of generics manufactured in India and indeed in 2007, the Indian Patent Office denied Novartis a patent for the cancer medicine imatinib mesylate (Gleevec) based on Section 3(d). The patent office considered the beta crystalline form of imatinib mesylate to be a new form of a known substance without the enhancement in efficacy required under Section 3(d). Novartis filed several lawsuits in response. In April 2013, the Supreme Court of India dismissed Novartis’ appeal for a patent to this form of Gleevec. The Indian Supreme

Court has recognised the impact of patents on access to medicines and called for a strict interpretation of section 3(d). (3)

In January 2015, Gilead Science was not granted a patent for its blockbuster Hepatitis C drug Sovaldi® (sofosbuvir) in India. India's patent office asked for evidence that more than "minor changes in the molecule" substantially improved the drug. Gilead has not said if it will appeal the decision to reject its patent; however, the door is now open to generic companies in India to produce the drug without licensing. (4)

### **Maintaining quality of patents: opposing patent applications and issued patents**

Depending on national rules, third parties often have the option of filing oppositions against a patent either before or after the grant, or of filing observations during the patent examination process. India, for example, provides both a pre-grant and a post-grant opposition system. (5)

Since patent examination and opposition procedures have an impact on what types of inventions are ultimately patented, they can be decisive in relation to short-term market entry by generic producers. Opposition proceedings are designed to ensure that patents are not granted on claimed inventions that do not satisfy the patentability requirements. For example, an opponent might submit documents showing that the key features of the claimed invention had already been publicly disclosed. Opposition procedures are thus a tool that can contribute to higher quality of patents and legal certainty.

Most, if not all, countries publish a patent application before a patent grant, hence third parties can analyse the claimed invention before the patent office makes a decision. In some countries, third parties may submit information relevant to the patentability of the claimed invention without participating in the subsequent procedure.

Similarly, many patent laws allow decisions of a patent office to grant a patent to be challenged by a third party, within a certain period of time, before an administrative review body such as an appeal board in a patent office. Erroneously granted patents can lead to delayed entry of generic versions, thus negatively impacting access to medicines. They can also become problematic with regard to patent linkage, for instance, when the granting of marketing approval is linked with patent status. The regulatory agency may refuse to register generic products based on the existence of patents that should not have been granted in the first place.

### **Compulsory licensing**

Compulsory licensing allows the exploitation of a patent during the patent term without the consent of the patent holder. This authorization may be given to a third party (e.g., a privately owned local manufacturer), or, in the case of government use, to a government agency (e.g., a Thai or Brazilian federal manufacturer) or to a third party authorized to act on the government's behalf. The Doha Declaration confirmed that WTO members have the freedom to determine the grounds upon which compulsory licences are granted. They are thus not limited to emergencies or other urgent situations. A range of grounds have been set out in national laws that are relevant for insulins:

*Non-working or insufficient working:* Many countries provide that where a patentee fails to exploit (i.e., make, use, sell, import) a patented invention in its jurisdiction, or where such exploitation by the patent owner is insufficient, a compulsory licence may be granted.

*Anti-competitive practices:* Some countries provide specific provisions under the patent law that allow the granting of a compulsory licence in order to remedy an anti-competitive practice (e.g., prices too high, illegal dumping of product) by the patent owner.

*Public interest:* Many countries allow the granting of compulsory licences on grounds of public interest, without further defining the term. Others mention specific grounds, in particular, national emergencies and circumstances of extreme urgency, national security and public health in general. However, a national emergency or extreme urgency is not a prerequisite requirement for a compulsory licence under the TRIPS Agreement. There is nothing in principle from preventing a country declaring diabetes to be a national emergency.

Health-specific grounds for granting a compulsory license, for example, can be found in France and Morocco. Under provisions on the license, the health minister can seek the grant of a compulsory licence if the product or method is made available by the right holder in insufficient quantity or unsatisfactory quality, or if the prices charged are “abnormally high”.(6)

*Government use:* A number of national laws explicitly entitles the government, or a third party authorized by the government, to use a patented invention without authorization of the patent holder. The grounds may vary but typically relate to public policy objectives such as national security or health. The problematic limitation of compulsory licences to “predominantly supply the domestic market”, found in Article 31(f) of the TRIPS Agreement, was revised following the Doha Declaration to allow production under a compulsory licence exclusively for export under certain terms and conditions. (7,8,9)

### **The WTO Paragraph 6 System**

Paragraph 6 of the Doha Declaration mandated the TRIPS Council to find a solution to the difficulties faced by countries with insufficient or no pharmaceutical manufacturing capacities in making effective use of compulsory licensing (which is often the case with insulin). The System applies where an importing country need a medicine to deal with a public health problem, but a potential exporting country faces a legal impediment because Article 31(f) of the TRIPS Agreement which limits supply under a compulsory licence predominantly to the domestic market. The term “predominantly” has never been defined. By 2015, only one special export licence under the Paragraph 6 System has been exercised. In that instance, the licence was used by a Canadian company to export medicines to Rwanda.(10)

### *Parallel importation*

Parallel imports refer to patented products first sold on the market in another country by the patent owner (or someone with legal authorization) and imported through a channel parallel to the one authorized by the patent holder. They are sometimes referred to as grey market goods. They are not black market goods, but neither have they been imported through a channel authorized by the right holder. The reason why the patent owner cannot prevent the the product from being subsequently imported is because of patent exhaustion. This is a legal doctrine according to which the patent owner of the product cannot prevent the further distribution or resale of the shipment after consenting to the first sale. In such a situation, the patent holder is considered to have exhausted its rights over these goods (the exhaustion doctrine is also known as the “first sale doctrine”).

Patent exhaustion plays a role in enabling access to medicines, as the decision by a country to adopt different forms of patent exhaustion is an important factor in determining whether products can be imported (or re-imported) from other countries where prices are lower. Another important factor that determines whether parallel imports can take place is the set of health regulations for market approval of medicines. Any country may prohibit parallel imports of different versions of the same pharmaceutical product if those versions lack marketing approval in the country of importation.

## **IP policies that can inhibit access to medicines**

Below are summaries of major laws and policies related to IP that can inhibit access to medicines.

### *Data exclusivity*

In some developed countries and bi-lateral free trade agreements (FTAs), it is specified that a period of exclusivity is required for the protection of clinical trial data. This is usually set at five years, but sometimes extends to eight years.(11) During the data exclusivity period, the regulatory authorities are not allowed to permit generic competitors to market the same or similar product on the basis of the approval granted to the originator company, unless the latter authorizes it. Thus data exclusivity acts like a patent, even when no patent exists.

In certain FTAs, data exclusivity also covers cases involving the granting of a marketing approval of a product in one country based on an earlier marketing approval of the same or similar product in another country. This has the effect of preventing generic companies in a third country from relying on the test data supplied by the originator company to another country's government.

Provisions affecting the pharmaceutical sector are an integral part of most FTAs concluded by the US and the European Union, and reflect the fact that these nations are among the world's largest producers and exporters of pharmaceutical products.(12) Provisions on patents or data protection are comparatively rare in, or absent from, FTAs concluded without the involvement of the US, the European Union and European Free Trade Association, and especially in cases where such agreements are concluded among developing countries only (such as the MECOSUR FTA).

### **Patent linkage**

Although government authorities may grant patents on pharmaceutical inventions and approve the marketing of patented pharmaceutical products, the two functions are not related. Most countries have separate agencies that grant patents (patent offices) and approve pharmaceutical products (medicine regulatory authority) and do not link these functions.

Nevertheless, regulatory approval (ordinarily based on safety, quality and efficacy of the product), is often linked to the patent status of the product. This so-called patent linkage can take several forms. In its simplest form, linkage may involve a requirement that the applicant disclose all patent information on the product for transparency purposes. Such transparency gives others looking to enter the same market the opportunity to review that patent portfolio and make decisions as to whether or not entering the market is feasible (which may involve a patent challenge or known infringement). The patent information submitted may or may not be used later to inform a patent owner of the identity of any manufacturer seeking regulatory approval for a generic version of the originator's product. In the US and Canada, patent numbers of all medicines with for marketing approval by the medicine regulatory authority must be listed online. A stronger version of patent linkage prohibits the granting of marketing approval for a product by a third party before the patent on the originator product has expired (or was invalidated). An even stronger form of linkage prohibits not only the granting of marketing approval, but also even the consideration of a generic marketing application during the patent period.

A number of FTAs include patent linkage provisions, such as the Colombia–Mexico FTA, the Japan–Thailand FTA, the Dominican Republic–Central America–United States FTA (CAFTA-DR), and several other FTAs to which the United States is a party.

Some stakeholders argue that patent linkage places regulatory authorities in the role of patent enforcers, that some patent linkage provisions make no exception for generic medicines produced under compulsory license, and they can unjustifiably extend exclusivity if the medicines regulatory authority is unable to begin a review of a generic product application during the patent period. Conversely, proponents of patent linkage argue that it increases transparency and predictability through the identification of patents relevant to each product as part of the marketing approval process, which can also lead to more challenges of questionable patents.(13)

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## **Annex 2. Map showing countries belonging to the Patent Cooperation Treaty**



Countries belonging to the Patent Cooperation Treaty are in blue

Reference: [http://www.wipo.int/pct/en/pct\\_contracting\\_states.html](http://www.wipo.int/pct/en/pct_contracting_states.html)

### Annex 3. List of potentially independent insulin manufacturers

Company Name	Headquarters Country	Number of Countries with Products Registered and/or Sold	Percent of Countries with Products Registered and/or Sold	Website (if available)
<b>Novo Nordisk</b>	Denmark	111	91.74%	<a href="http://www.novonordisk.com/default.asp">http://www.novonordisk.com/default.asp</a>
<b>Sanofi</b>	France	101	83.47%	<a href="http://www.sanofi.us/1/us/en/index.jsp">http://www.sanofi.us/1/us/en/index.jsp</a>
<b>Eli Lilly</b>	United States	94	77.69%	<a href="http://www.lilly.com/Pages/Home.aspx">http://www.lilly.com/Pages/Home.aspx</a>
<b>Bioton</b>	Poland	26	21.49%	<a href="http://www.bioton.pl/en">http://www.bioton.pl/en</a>
<b>Wockhardt</b>	India	17	14.05%	<a href="http://www.wockhardt.com/">http://www.wockhardt.com/</a>
<b>Biocon</b>	India	17	14.05%	<a href="http://www.biocon.com/">http://www.biocon.com/</a>
<b>Julphar</b>	United Arab Emirates	13	10.74%	<a href="http://www.julphar.net/">http://www.julphar.net/</a>
<b>Tonghua Dongbao</b>	China	7	5.79%	<a href="http://www.dongbao.com/index.htm">http://www.dongbao.com/index.htm</a>
<b>Pisa</b>	Mexico	5	4.13%	<a href="http://en.pisa.com.mx/">http://en.pisa.com.mx/</a>
<b>Berlin Chemie*</b>	Germany	3	2.48%	<a href="http://www.berlin-chemie.com/">http://www.berlin-chemie.com/</a>
<b>Polfa Tarchomin</b>	Poland	3	2.48%	<a href="http://www.polfa-tarchomin.com.pl/">http://www.polfa-tarchomin.com.pl/</a>
<b>Popular</b>	Bangladesh	2	1.65%	<a href="http://www.popular-pharma.com/">http://www.popular-pharma.com/</a>
<b>Soperquimia</b>	El Salvador	2	1.65%	<a href="http://www.soperquimia.com/">http://www.soperquimia.com/</a>
<b>SEDICO</b>	Egypt	2	1.65%	<a href="http://www.sedico.net/English/Default_e.htm">http://www.sedico.net/English/Default_e.htm</a>
<b>CJSC Brinsalov</b>	Russia	2	1.65%	<a href="http://ferain.com/company/about/">http://ferain.com/company/about/</a>
<b>Probiomed</b>	Mexico	2	1.65%	<a href="http://www.probiomed.com.mx/">http://www.probiomed.com.mx/</a>
<b>Aspen</b>	South Africa	2	1.65%	<a href="http://www.aspenpharma.com/">http://www.aspenpharma.com/</a>
<b>Shanghai Fosun</b>	China	2	1.65%	<a href="http://www.fosunpharma.com/">http://www.fosunpharma.com/</a>
<b>ACI Limited</b>	Bangladesh	1	0.83%	<a href="http://www.aci-bd.com/pharmaceuticals.php">http://www.aci-bd.com/pharmaceuticals.php</a>
<b>Aristopharma</b>	Bangladesh	1	0.83%	<a href="http://www.aristopharma.com/index.php">http://www.aristopharma.com/index.php</a>
<b>Hongye Biochem</b>	China	1	0.83%	<a href="http://www.hongyechem.com/en/">http://www.hongyechem.com/en/</a>
<b>Beier</b>	China	1	0.83%	
<b>Shanghai Biochem and Pharma</b>	China	1	0.83%	
<b>BCN Medical</b>	Colombia	1	0.83%	<a href="http://bcnmedical.com">http://bcnmedical.com</a>
<b>Nanjing Xinbai</b>	China	1	0.83%	<a href="http://www.njxbyy.com/english/about/gsjj.asp">http://www.njxbyy.com/english/about/gsjj.asp</a>
<b>Vacsera</b>	Egypt	1	0.83%	<a href="http://www.vacsera.com/">http://www.vacsera.com/</a>
<b>USV</b>	India	1	0.83%	<a href="http://www.usvindia.com/">http://www.usvindia.com/</a>
<b>Laboratorios Antibioticos</b>	Mexico	1	0.83%	<a href="http://www.amsamexico.com.mx/">http://www.amsamexico.com.mx/</a>
<b>Denver</b>	Argentina	1	0.83%	<a href="http://www.denverfarma.com.ar/productos.asp?buscar=c0">http://www.denverfarma.com.ar/productos.asp?buscar=c0</a>
<b>Institute Bioorganic Chemical*</b>	Russia	1	0.83%	<a href="http://www.ibch.ru/en/about">http://www.ibch.ru/en/about</a>
<b>MedsynteZ</b>	Russia	1	0.83%	<a href="http://www.medsintez.com/en/">http://www.medsintez.com/en/</a>
<b>National Biotechnology*</b>	Russia	1	0.83%	<a href="http://nbiotech.ru/history2.html">http://nbiotech.ru/history2.html</a>
<b>Pharmstandard</b>	Russia	1	0.83%	<a href="http://pharmstd.com/">http://pharmstd.com/</a>
<b>Sanbe</b>	Indonesia	1	0.83%	<a href="http://www.sanbe-farma.com/">http://www.sanbe-farma.com/</a>
<b>Exir</b>	Iran	1	0.83%	<a href="http://www.exir.co.ir/">http://www.exir.co.ir/</a>
<b>Laboratorios</b>	Mexico	1	0.83%	<a href="http://www.grupoifaco.com/laboratorios-cryopharma.php">http://www.grupoifaco.com/laboratorios-cryopharma.php</a>

<b>Cryopharma</b>				
<b>Amoun Pharmaceuticals</b>	Egypt	1	0.83%	<a href="http://www.amoun.com/">http://www.amoun.com/</a>
<b>United Laboratories</b>	China	1	0.83%	<a href="http://www.tul.com.cn/en/">http://www.tul.com.cn/en/</a>
<b>Union Pharmaceuticals</b>	China	1	0.83%	
<b>Shanghai Biochemical Research</b>	China	1	0.83%	
<b>Jinhua</b>	China	1	0.83%	
<b>Asia Pharma*</b>	Syria	0	0.00%	<a href="http://www.asiapharma-syria.com/">http://www.asiapharma-syria.com/</a>

\*Since compiling this list, we have received information from industry representatives and other sources indicating that Berlin Chemie is associated with Eli Lilly; the Institute of Bioorganic Chemistry is not an insulin manufacturer; National Biotechnology is an independent insulin manufacturer operating under the name Geropharm; and Asia Pharma is unlikely to be now manufacturing insulin.

## Annex 4. Patented insulin products, North America, by company and insulin type

<b>Eli Lilly</b>		
<b>INN and proprietary name</b>	<b>Route</b>	<b>Strength</b>
INSULIN LISPRO PROTAMINE RECOMBINANT; INSULIN LISPRO RECOMBINANT		
HUMALOG MIX 50/50	injection	50 U/ml; 50 U/ml
HUMALOG MIX 50/50 KWIKPEN	injection	50 U/ml; 50 U/ml
HUMALOG MIX 75/25	injection	75 U/ml; 25 U/ml
HUMALOG MIX 75/25 KWIKPEN	injection	75 U/ml; 25 U/ml
HUMALOG MIX25	suspension for injection	75 U/ml; 25 U/ml
HUMALOG MIX50	suspension for injection	50 U/ml; 50 U/ml
HUMALOG MIX50 PEN	suspension for injection	50 U/ml; 50 U/ml
INSULIN LISPRO RECOMBINANT		
HUMAJECT HUMALOG (injection)	solution for injection	100 U/ml
HUMAJECT HUMALOG MIX25/HUMALOG MIX25 PEN (injection)	suspension for injection	75 U/ml; 25 U/ml
HUMAJECT HUMALOG MIX50/HUMALOG MIX50 (injection)	suspension for injection	50 U/ml; 50 U/ml
HUMALOG	injection	100 U/ml
HUMALOG KWIKPEN	injection	100 U/ml
INSULIN RECOMBINANT HUMAN		
HUMULIN R	injection	500 U/ml

<b>Novo Nordisk</b>		
<b>INN and proprietary name</b>	<b>Route</b>	<b>Strength</b>
INSULIN ASPART PROTAMINE RECOMBINANT; INSULIN ASPART RECOMBINANT		
NOVOLOG MIX 70/30	subcutaneous injection	700 U/10ml; 300 U/10ml (70 U/ml; 30 U/ml)
NOVOLOG MIX 70/30 FLEXPEN	subcutaneous injection	210 UNITS/3ML; 90 UNITS/3ML (70 U/ml; 30 U/ml)
INSULIN ASPART RECOMBINANT		
NOVOLOG	subcutaneous injection	1000 U/10ML (100 U/ml)
NOVOLOG FLEXPEN	subcutaneous injection	300 U/3ML (100 U/ml)
NOVOLOG FLEXTOUCH	subcutaneous injection	300 U/3ML (100 U/ml)
NOVOLOG PENFILL	subcutaneous injection	300 U/3ML (100 U/ml)

NOVOMIX 30	subcutaneous injection	100 U/ml
NOVOMIX 50	subcutaneous injection	100 U/ml
NOVOMIX 70	subcutaneous injection	100 U/ml
NOVORAPID	subcutaneous injection	100 U/ml
INSULIN DETEMIR RECOMBINANT		
LEVEMIR	subcutaneous injection	1000 U/10ml (100 U/ml)
LEVEMIR FLEXPEN	subcutaneous injection	300 U/3ml (100 U/ML)
LEVEMIR FLEXTOUCH	subcutaneous injection	300 U/3ml (100 U/ml)

<b>Pfizer</b>		
<b>INN and proprietary name</b>	<b>Route</b>	<b>Strength</b>
INSULIN RECOMBINANT HUMAN (inhaled)		
EXUBERA	powder	1mg
EXUBERA	powder	3mg

<b>Sanofi</b>		
<b>INN and proprietary name</b>	<b>Route</b>	<b>Strength</b>
INSULIN GLARGINE RECOMBINANT		
LANTUS	injection (10 ml vial solution)	100 U/ml
LANTUS SOLOSTAR	injection	300 U/3ML (100 U/ml)
APIDRA	injection IV (infusion), subcutaneous	1000 US/10ml (100 U/ml)
APIDRA	injection IV (infusion), subcutaneous	300 U/3ml (100 U/ml)
APIDRA (10 ML VIAL)	solution	100 U/ml
APIDRA (3ML CARTRIDGE)	solution	100 U/ml
APIDRA (3ML OPTISET)	solution	100 U/ml
APIDRA (3ML SOLOSTAR)	solution	100 U/ml
APIDRA SOLOSTAR	subcutaneous injection	300 U/3ml
INSULIN RECOMBINANT HUMAN (inhaled)		
AFREZZA	powder for inhalation	4 U/inhalation
AFREZZA	powder for inhalation	8 U/inhalation

## Annex 5. Patent applications filed by US universities

Title	Owner of IP	Jurisdiction	Filing date	Inventor	Brief Description
HALOGEN-STABILIZED INSULIN	CASE WESTERN RESERVE UNIVERSITY	US	01.01.2015	Michael Weiss	An insulin analogue comprises a B-chain polypeptide incorporating a halogenated phenylalanine at position B24, B25 or B26. Halogen substitution-based stabilization of insulin may enhance the treatment of diabetes mellitus in regions of the developing world lacking refrigeration
THERAPEUTIC AGENTS COMPRISING ELASTIC PEPTIDES	Duke University	US	19.03.2015	Ashutosh Chilkoti	The present invention provides therapeutic agents and compositions comprising elastic peptides and therapeutic proteins. Such peptides exhibit a flexible, extended conformation. In some embodiments, the therapeutic protein is insulin, including functional analogs. The therapeutic agents have improvements in relation to their use as therapeutics, including, inter alia, one or more of half-life, clearance and/or persistence in the body, solubility, and bioavailability.
SITE 2 INSULIN ANALOGUES	CASE WESTERN RESERVE UNIVERSITY	US	18.09.2014	Michael Weiss	An insulin analogue contains one or more modifications at a distinct protein surface comprising one or more of the residues at position B13, B17, A12, A13, and/or A17. A method of treating a patient with diabetes mellitus comprises administering a physiologically effective amount of the insulin analogue to a patient by means of intravenous, intraperitoneal, or subcutaneous injection.
N-TERMINAL TRUNCATED INSULIN ANALOGUES	CASE WESTERN RESERVE UNIVERSITY		31.07.2014	Michael Weiss	An insulin analogue contains a foreshortened B-chain polypeptide lacking residues B1-B3 and optionally contains an additional substitution in the C-terminal B23-B30 segment of the B-chain.
LONG-ACTING SINGLE-CHAIN INSULIN ANALOGUES WO	CASE WESTERN RESERVE UNIVERSITY	US	08.05.2014	Michael Weiss	A single-chain insulin analogue containing a basic side chain at position A8 (Arginine, Histidine, Lysine, or Ornithine), a basic side chain at position B29 (Arginine, Histidine, Lysine, or Ornithine), and a foreshortened C-domain of length 6-11 residues is provided.
INSULIN ANALOGUES CONTAINING PENTA-FLUORO-PHENYLALANINE AT POSITION B24	CASE WESTERN RESERVE UNIVERSITY	US	08.05.2014	Michael Weiss	An insulin analogue comprises a B-chain polypeptide incorporating a halogenated phenylalanine at position B24, B25 or B26. Halogen substitution-based stabilization of insulin may enhance the treatment of diabetes mellitus in regions of the developing world lacking refrigeration.
INSULIN ANALOG DIMERS	INDIANA UNIVERSITY RESEARCH AND TECHNOLOGY CORPORATION	US	03.04.2014	Richard Dimarchi	Insulin analog dimers having unique insulin receptor agonist activity based on insulin polypeptide sequences, the site of dimerization and the length of the dimerization linker that connects the two insulin polypeptides.

CTP-BASED INSULIN ANALOGS FOR TREATMENT OF DIABETES WO	INDIANA UNIVERSITY RESEARCH AND TECHNOLOGY CORPORATION	US	27.06.2013	Richard Dimarchi	A peptide sequence of greater than 18 amino acids is used as a linking moiety to link human insulin A and B chains, or analogs or derivatives thereof, to provide high potency single chain insulin analogs. In one embodiment the linking moiety comprises one or more glycosylation sites. Also disclosed are prodrug and conjugate derivatives of the insulin analogs.
ULTRA-CONCENTRATED RAPID-ACTING INSULIN ANALOGUE FORMULATIONS	CASE WESTERN RESERVE UNIVERSITY	US	02.05.2013	Michael Weiss	A pharmaceutical formulation comprises insulin having a variant insulin B-chain polypeptide containing an ortho-monofluoro-Phenylalanine substitution at position B24 in combination with a substitution of an amino acid containing an acidic side chain at position B10, allowing the insulin to be present at a concentration of between 0.6 mM and 3.0 mM.
NON-STANDARD INSULIN ANALOGUES	CASE WESTERN RESERVE UNIVERSITY	US	17.01.2013	Michael Weiss	An insulin analogue comprises a B-chain polypeptide containing a cyclohexanylalanine substitution at position B24 and optionally containing additional amino-acid substitutions at positions A8, B28, and/or B29.
AMIDE-BASED INSULIN PRODRUGS	INDIANA UNIVERSITY RESEARCH AND TECHNOLOGY CORPORATION	US	29.12.2011	Richard Dimarchi	Prodrug formulations of insulin and insulin analogs are provided wherein the insulin peptide has been modified by an amide bond linkage of a dipeptide prodrug element.
NOVEL STABILIZED INSULIN AGONISTS	INDIANA UNIVERSITY RESEARCH AND TECHNOLOGY CORPORATION	US	22.12.2011	Richard Dimarchi	An A chain and a B chain sequence wherein the native alpha helical secondary structure has been stabilized in one or both of said A chain and B chain sequences by substitutions and/or additions of the native sequence with alpha, alpha disubstituted amino acids (e.g., amino isobutyric acid, Aib) or with amino acids that foster intramolecular interactions between amino acid side chains.
SINGLE CHAIN INSULIN AGONISTS EXHIBITING HIGH ACTIVITY AT THE INSULIN RECEPTOR	INDIANA UNIVERSITY RESEARCH AND TECHNOLOGY CORPORATION	US	22.12.2011	Richard Dimarchi	Single chain insulin analogs are provided having high potency and specificity for the insulin receptor, wherein the carboxy terminus of the B25 amino acid of the B chain is linked to the amino terminus of the A1 amino acid of the A chain via the intervening linking moiety.
LONG-ACTING INSULIN ANALOGUE PREPARATIONS IN SOLUBLE AND CRYSTALLINE FORMS	CASE WESTERN RESERVE UNIVERSITY	US	25.08.2011	Michael Weiss	A pharmaceutical formulation comprises an insulin analogue or a physiologically acceptable salt thereof, wherein the insulin analogue or a physiologically acceptable salt thereof contains an insulin A-chain sequence that contains paired Histidine substitutions at A4 and A8, and optionally a substitution at A21.

INSULIN ANALOGUES OF ENHANCED RECEPTOR-BINDING SPECIFICITY	CASE WESTERN RESERVE UNIVERSITY	US	10.03.2011	Michael Weiss	A method of treating a patient includes administering a physiologically effective amount of an insulin analogue, which contains an insulin A-chain sequence modified at positions selected from the group consisting of A0, A1, A4, A8, and A21.
ISOFORM-SPECIFIC INSULIN ANALOGUES	CASE WESTERN RESERVE UNIVERSITY	US	29.10.2009	Michael Weiss	A method treating a mammal by administering a physiologically effective amount of an insulin analogue where the insulin analogue displays more than twofold greater binding affinity to insulin receptor isoform A (IR-A) than insulin receptor isoform B (IR-B).
MEAL-TIME INSULIN ANALOGUES OF ENHANCED STABILITY	CASE WESTERN RESERVE UNIVERSITY	US	22.10.2009	Michael Weiss	A method treating a patient includes administering a physiologically effective amount of a fibrillation-resistant insulin analogue or a physiologically acceptable salt thereof to the patient, which an insulin A-chain sequence modified at position A8 and an insulin B-chain sequence or an analogue thereof.

## Annex 6. Patent applications filed by individual companies

Company	Document	Subject Matter	Additional Comments of the authors	Patenting Activity
BIOCON	(WO2007007345) PROCESS FOR THE PREPARATION OF INSULIN CONJUGATES	Method of making insulin that is linked to various other organic compounds	Designed to improve "survival in the intestine ..." due to gastric and pancreatic enzymes and so on and low membrane permeability, limiting its ability to pass from the lumen into the bloodstream.	Granted: United States, India, Korea, European Union In process: Israel, Japan, Mexico
BIOCON	(WO2007043059) PROCESS FOR THE PREPARATION OF INSULIN CONJUGATES.	Method of making insulin that is linked to various other organic compounds.	Designed to improve "survival in the intestine ..." due to gastric and pancreatic enzymes and so on and low membrane permeability, limiting its ability to pass from the lumen into the bloodstream.	Granted: United States, Korea In process: Israel, Japan, Mexico, India, China
BIOCON	(WO2009050738) AN ORALLY ADMINISTERABLE SOLID PHARMACEUTICAL COMPOSITION AND A PROCESS THEREOF	This is an improved spray-drying process	For making solid insulin compositions for oral delivery.	Granted: Korea In process: Australia, Canada, Egypt, Japan, New Zealand, Russia, Ukraine
BIOCON	(WO2009104199) A METHOD OF OBTAINING PURIFIED HETEROLOGOUS INSULINS EXPRESSED IN YEAST	The invention is supposed to permit selective purification of the product (especially insulin glargine) from the impurities	As one of the major disadvantages of expressing insulin in yeast cells is the post-translational modification of resulting proteins which later exist as impurities in the final product that is difficult to purify	Granted: US In process: China, Israel, Japan, Korea, Malaysia, Russian Federation
BIOCON	(WO2013144685) SECRETION OF FUNCTIONAL INSULIN GLARGINE DIRECTLY INTO THE CULTURE MEDIUM	Is in relation to a process of expressing a fully folded functional two chain insulin glargine that require no further processing to make it functionally active.	Is this innovative?	In process: US, European Patent Office
WOCKHARDT	(WO2014102623) PHARMACEUTICAL COMPOSITION	Discloses the use of amino acids in combination with a halogenide to increase the stability of the insulin preparations by reducing aggregation as well as decreasing glass	Several attempts to provide stable insulin formulations have been described previously. However, there still exists a need to develop formulations wherein the insulin does not undergo chemical transformation and remains stable for a sufficiently	In process: Australia

		adsorption.	long period of time. Insulin is any human or analogue insulin	
WOCKHARDT	WO2014096985) A STABLE AQUEOUS COMPOSITION COMPRISING HUMAN INSULIN OR AN ANALOGUE OR DERIVATIVE THEREOF .	Insulin plus solubility-enhancing agent selected from urea, amino acids and/or surfactants with pH modifying agents	insulin preparations having better solubility and chemical stability can be obtained	In process: Australia
WOCKHARDT	(WO2011121496) COMPOSITION COMPRISING INSULIN AND HERBAL OIL FOR TRANSDERMAL OR TRANSMUCOSAL ADMINISTRATION	insulin, insulin analog and derivatives suited specially for non-invasive routes such as transdermal or transmucosal routes,	inventors have "surprisingly" found that when herbal oil is added to insulin solution, the insulin, which when applied on skin results in rapid systemic absorption, i.e. less than 1 hour, of insulin across skin.	In Process; European Patent Office, Canada
WOCKHARDT	(WO2005115303) PURIFICATION OF INSULIN-LIKE MATERIAL BY REVERSE PHASE CHROMATOGRAPHY	Polystyrenic resins for the purification of insulinlike materials from solutions that contain impurities, including closely related ones like polypeptides.	Polystyrenic resins provide several advantages over silica based ones due to their stable polymeric structure	In Process; India, United States Withdrawn: European Patent Office
WOCKHARDT	(WO2004050672) PROCESS FOR THE EXTRACTION AND ISOLATION OF INSULIN FROM RECOMBINANT SOURCES	Conditions for the extraction of insulin, to increase its recovery in solution	Procedure to combine extraction, medium clarification and chromatography, to effect the simultaneous isolation and purification of "in solution" as well as "particulate-residue-bound insulin".	Granted: European Patent Office, United States In process: India
WOCKHARDT	(WO2004024862) YEAST PROTEIN EXPRESSION SECRETION SYSTEM	The present invention describes the expression of insulin, particularly human insulin, B and A chains as a fusion protein,	The fusion polypeptide is very efficiently produced and secreted from yeast cells.	Granted: India In process: United States
TONGHUA	(WO1999050302) CHIMERIC PROTEIN CONTAINING AN INTRAMOLECULAR CHAPERONE-LIKE SEQUENCE AND ITS	Develop a recombinant process for obtaining human insulin with correctly linked cysteine bridges with fewer	One major problem in the production of human proinsulin or its derivatives in microorganisms such as E. coli is the incorrectly linked structure	Granted: Australia, European Union, South Korea In process: Canada, China, Mexico,

	APPLICATION TO INSULIN PRODUCTION	necessary procedural steps, and hence resulting higher yield of human insulin.		United States
ZHUHAI UNITED	(CN103694339) RENATURATION METHOD OF INSULIN GLARGINE PRECURSOR.	The invention discloses a renaturation method of an insulin glargine precursor, and belongs to the field of biomedical protein folding.	According to the method, the renaturation reaction time is shortened, the correctly folded protein content is increased, the renaturation efficiency is improved to be 51%-62%, the production cost is reduced, and the large-scale industrialization production and application are facilitated.	In process: China

## Annex 7. Patent applications and issued patents found in Indian patent office

No.	Company	Document	Subject Matter	Additional Comments of the Authors	Expiration Date	Contained in INPADOC	Contained in WIPO PatentScope
1	ELI LILLY	Patent 263855	Pegylated insulin lispro compounds	Polyethylene glycol pegylated insulin lispro compounds, are highly soluble at physiological pH, have an extended duration of action. The invention also relates to methods of providing such molecules, to pharmaceutical compositions containing them, and to their therapeutic uses.	25 November 2030	This patent appears to be related to an INPADOC family that includes WO2009152128; however, there is no record specific to India	Under WO2009152128, there is a record for India with a national number of 2512/MUMNP/2010, but no application or grant date are provided.
2	ELI LILLY	Patent 257510	Insulin analogue formulation	Various parenteral formulations, which comprise: human insulin analogues in a hexamer conformation, zinc ions, and at least three molecules of a phenolic derivative selected from the group consisting of m-cresol, phenol, or a mixture of m-cresol and phenol. The formulation provides a rapid onset of action	14 June 2015	This patent appears to be related to an INPADOC family with a priority of US19940260634 19940616; however, there is no WO filing nor a record specific to India	There appears to be a related national route filing under US5474978, but no national level data are available.
3	SANOFI	Patent Application	A pharmaceutical formulation comprising acidic insulin	The present invention relates a pharmaceutical formulation comprising	18 June 2022	This patent appears to be related to an INPADOC family that includes	Under WO2003105888, there is a record for India with a national number of 2807/CHENP/2004 and a patent grant date

				GIy(A2I), Arg(B31), Arg(B32)-human insulin; at least one chemical entity chosen from polysorbate 20 and polysorbate 80; at least one preservative; and water, wherein the pharmaceutical formulation has a pH in the acidic range from 3.5 to 4.5.		WO2003105888; however, there is no record specific to India	of 19.09.2008
4	SANOFI	Patent Application	Zinc free and low zinc insulin formulations having improved stability	The present invention relates to a pharmaceutical formulation, which does not contain any zinc, or only a small quantity of zinc, and which comprises improved stability. The invention also relates to the production of insulin preparations	23 March 2021	This patent appears to be related to an INPADO family that includes WO02076495; however, there is no record specific to India.	Under WO2002076495, there is a record for India with a national number of 488/CHENP/2003 and a patent grant date of 31.12.2008
5	SANOFI	Patent 210667	A procedure for the end-polishing of an insulin in an insulin purification process	Improved procedure for the chromatographic purification of insulins	11 August 2019	This patent appears to be related to an INPADO family that includes WO0011030; however, there is no record specific to India.	Under WO2000011030, there is a record for India with a national number of IN/PCT/2001/231/CHE and a patent grant date of 08.10.2007
6	SANOFI	Patent Application	A process for the preparation of mature insulin or a mature insulin derivative	The present invention relates to a process for the preparation of mature insulin or a mature insulin derivative	9 April 2019	This patent appears to be related to an INPADO family that includes WO0061727; however, there is	Under WO0061727, there is a record for India with a national number of IN/PCT/2001/1334/CHE and a patent grant date of 10.10.2008.

						no record specific to India	
7	SANOFI	Patent Application	Improved process for obtaining insulin precursors having correctly bonded cystine bridges	The present invention relates to an improved process for obtaining a precursor of insulins or insulin derivatives having correctly bonded cystine bridges in the presence of cysteine or cysteine hydrochloride and of a chaotropic auxiliary.	August 18, 2017	This patent appears to be related to an INPADO family with a priority of DE1999115938 19990409; however, there is no WO filing nor a record specific to India	There appears to be a related national route filing under US6380355, but no national level data are available.
8	SANOFI	Patent Application	An insulin derivative	The present invention relates to insulin derivatives which in comparison to human insulin, have an accelerated onset of action, to a process for their preparation and to their use, in particular in pharmaceutical preparations for the treatment of diabetes mellitus.	June 20, 2017	This patent appears to be related to an INPADO family with a priority of DE1997126167 19970620; however, there is no WO filing nor a record specific to India	There appears to be a related national route filing under US 6221633, but no national level data are available.
9	NOVO NORDISK	Patent Application	Process for preparing insulin compounds	The present invention relates to a process for preparing an insulin compound wherein no isolation of the intermediate product is performed	November 19, 2021		
10	NOVO NORDISK	Patent 211570	An aqueous insulin formulation for pulmonary	The present invention relates to a concentrated aqueous insulin	April 10, 2021		

			delivery	formulations of high physical and chemical stability are disclosed. The formulations are suitable for pulmonary delivery. The object has been accomplished by providing an insulin formulation in which the concentration of chloride is kept below 50 mM			
11	NOVO NORDISK	Patent Application	Method for making insulin precursors and insulin precursor analogs	The present invention relates to an insulin precursor or an insulin precursor analogue comprising the formula; B(l-27)-X2-X3-Xi-Y-A(l-21)	December 29, 2019		
12	NOVO NORDISK	Patent 209529	A chemically stable aqueous insulin preparation	This invention relates to a chemically stable aqueous insulin preparation comprising: AspB28 human insulin, glycerol and/or mannitol, 5 to 100 mM of a halogenide	June 19, 2017		
13	NOVO NORDISK	Patent 209528	An aqueous insulin preparation having superior physical stability	Comprising dissolved and/or precipitated human insulin or an analogue or derivative thereof, and a water-soluble reduced or non-reducing carbohydrate	June 19, 2017		

				containing at least 4 carbon atoms			
14	NOVO NORDISK	Patent 220879	Process for preparing insulin compounds	The present invention relates to protracted human Insulin derivatives in which the A21 and the B3 amino acid residues are, independently, any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys	March 16, 2015		

## Annex 8. Patent documents, Indian Patent Office, filed by other organisations

Patent Owner	Patent Number	Title	Expiration Date
BIOCON	259104	A method for producing biologically active polypeptide having insulinotropic activity	21 June 2026
SEMBIOSYS GENETICS	256154	Methods for the production of insulin in plants	12 January 2026
BIOCON	253674	Preparation of insulin conjugates	8 January 2028
RELAINCE LIFESCIENCES LTD	236079	Method for synthesis of human recombinant insulin with improved process efficiency	26 March 2024
RELAINCE LIFESCIENCES LTD	232442	Improved method for production of insulin by constitutive expression in pichia pastoris	26 March 2024
SHANGHAI INST. BIOCHEMISTRY	232282	Monomeric analogue of human insulin	25 February 2022
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY	229649	A process for the preparation of oral insulin microcapsules	16 January 2022
SAVIENT PHARMACEUTICALS LTD	228703	A method for producing insulin	22 July 2019
TRANSLATIONAL RESEARCH LTD	224408	Composition of insulin for nasal administration	6 February 2024
ITOHAM FOODS INC.	222568	Process for producing recombinant insulin from novel fusion proteins	8 November 2021
L.M. COLLEGE OF PHARMACY	208600	A pharmaceutical formulation of chromium insulin injections (suspension) and its preparation	19 November 2024

## Annex 9. Patent filings in China for other organisations

No.	Company	Document	Subject Matter	Additional Comments of the Authors	Expiration Date
1	BIOTECHNOLOGY RES CT SHANDONG ACADEMY OF AGRICULTURAL SCIENCES	Patent Application CN104017809A	Expression gene and method for modified human Insulin protein	The expression method comprises the steps of expressing a gene fragment of an easily-expressed human Insulin protein in a peanut oil body protein system	5 May 2034
2	AN SHENGJUN;CHAI XIQING;WANG KUNSHENG	Patent Application CN102268451B	Human insulin gene-containing expression vector and construction method and application thereof	The plant expression vector pBINOI disclosed by the invention is obtained by inserting a fusion protein expression box which is driven by a rape oil body protein gene promoter and consists of peanut oil body protein genes and human insulin genes	30 May 2031
3	UNIV JILIN AGRICULTURAL	Patent Application CN101037692A	Method for expressing human insulin by using plant seed oil body	The invention uses plant bio reactor to produce human insulin avoiding harm of animal pathogen and endotoxin of coliform bacteria, and can simplify departing and purification process of goal proteins to reduce cost and good for industrialization of human insulin	28 December 2026
4	SHANDONG DONGXING HUIZHI BIOTECHNOLOGY CO LTD	Patent Application CN103969234A	Method capable of detecting four kinds of type I diabetes autoimmune antibodies simultaneously	The invention provides a method capable of detecting four kinds of type I diabetes autoimmune antibodies simultaneously, and belongs to the technical field of medical testing	17 April 2034
5	SHANGHAI JINGTAI BIOTECHNOLOGY	Patent Application CN1448724A	Type 1 diabetes related antigen-antibody simultaneous detection	The present invention is protein chip for simultaneous detection of type-I diabetes relevant antigen and antibody.	13 May 2023
6	CHAOYING RES AND DEV OF BIOMED	Patent Application CN1173182C	Albumen chip for detecting autoimmunity antibody of diabetes, as well as preparation and detection method	This invention relates to preparation of and detection method for diabetes autoimmune antibody using a protein chip	Not stated
7	UNIV NINGBO	Patent Application	Method for growing protein	The prepared insulin fiber as a nano-material has extensive application	31 March 2032

		CN103360610A	fiber on surface of substrate	prospects in future biological electronic materials	
8	MING ZHANG;ZHENGRUI XI	Patent Application CN101020063A	Vaccine for preventing and/or treating autoimmune disease	The present invention discloses one kind of vaccine for preventing and/or treating autoimmune diseases. The vaccine has as an active component an antigen such as insulin, heat shock protein, etc.	26 March 2027
9	UNIV HUAZHONG SCIENCE TECH	Patent Application CN1220705C	Alpha-lipoic acid and its derivative modified insulin and preparing method thereof	The invention is an oral medicine able to cure diabetes - alpha-protogen or alpha-protogen derivative bio-modified insulin as well as preparing method.	17 October 2023
10	MING ZHANG;ZHENGRUI XI	Patent Application CN104217133A	Medicament reutilization method based on omics data	Method for integrating data analysis results of human diabetes-associated whole-genome association analysis, proteomics and metabonomics, screening human diabetes-associated risk proteins, and integrating pathogenesis information of human diabetes through a public database.	26 August 2034