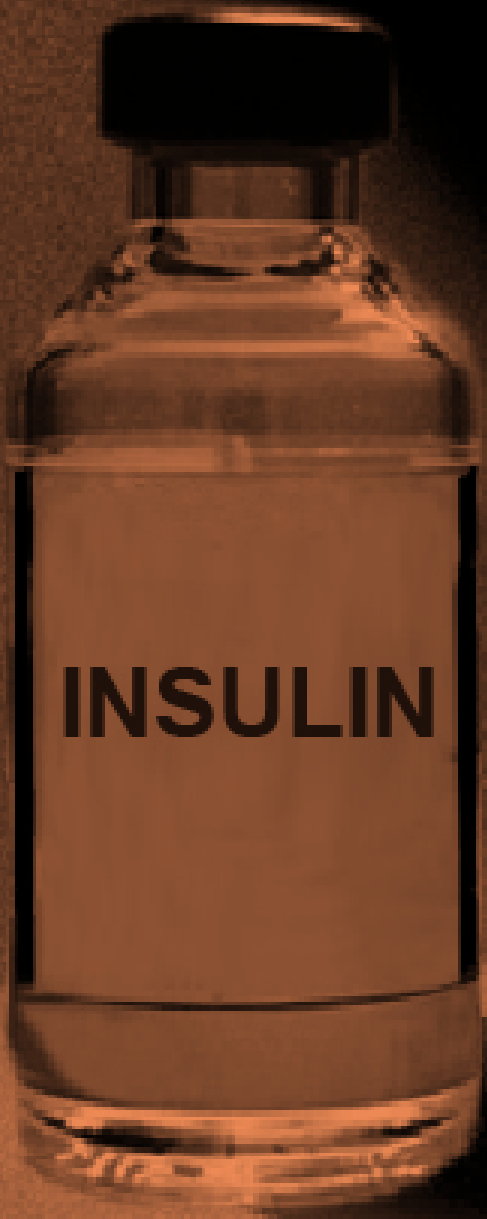
INSULIN MARKET PROFILE

April 2016



acciss
Addressing the Challenge and Constraints of Insulin Sources and Supply

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INSULIN MARKET PROFILE

April 2016

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Acronyms

WHO	World Health Organization
EML(s)	Essential Medicines List
ACCISS	Addressing the Challenge and Constraints of Insulin Sources and Supply
ATC	Anatomical Therapeutic Classification
LMIC	Low-and middle-income countries
RL	Reimbursement Lists
NMRA	National Medicine Regulatory Authorities
AFRO	WHO African Regional Office
AMRO	WHO Americas Office
EMRO	WHO Eastern Mediterranean Regional Office
EURO	WHO European Office
EMA	European Medicines Authority
SEARO	WHO South East Asian Regional Offic
WPRO	Western Pacific Regional Office
EU	European Union
EEA	European Economic Area
INN	international non-proprietary name
SFDA	Chinese equivalent of the FDA
WHO MEML	WHO Model Essential Medicine List
NEMLs	National Essential Medicene List
NPH	Neutral protamine hagedorn
HbA1c	Glycated haemoglobin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
OAD	Oral antidiabetic agents

Executive Summary

The aim of this profile is to describe key aspects of the insulin market in order to contribute to a better understanding of supply and demand of insulin globally. Each section of the profile presents findings from a particular aspect of the market: manufacturing, registration, inclusion in the national essential medicines list, and promotion. It also features two literature reviews, one on the latest evidence on the clinical efficacy of human versus analogue insulin and one of the consumption of insulin in patients with type 2 diabetes.

According to an extensive review of market intelligence information, including market reports, there are about 40 smaller manufacturers with largely local markets apart from the three largest global insulin manufacturers –Novo Nordisk, Sanofi, and Eli Lilly. Southeast Asia and Latin America are regions with higher numbers of smaller manufacturers than other regions. Little is known about these smaller manufacturers in terms of their product portfolio including prices, their supply channels (largely public or private sector), and main clients. Given the scarcity of publically available information on license agreements it is difficult to ensure that these smaller manufacturers are in fact all independent from the large three global producers of insulin. More research is needed to obtain a comprehensive picture of global supply.

The analysis of 75 national medicines regulatory authorities websites shows that there is a difference between the types of insulin products registered between high- and middle-income country markets: a larger number of analogue products are licensed in high-income markets compared to middle-income countries. The variation between countries may be partially explained in the prevalence of diabetes and by the differences in purchasing power – analogue insulin products are often substantially higher priced than human insulin ones. Other factors are likely to be related to the regulatory framework in each country (e.g. fees to register a product, time until registration, process to register), which may present barriers to manufacturers that attempt to register their products.

The analysis of 100 national essential medicines lists from low-and middle-income countries demonstrates that with very few exceptions all countries list both short-acting and intermediate-acting insulin, which are recommended by the World Health Organization (WHO) Model List. This means that other factors, aside from the inclusion of insulin on the national Essential Medicines Lists (EMLs), are likely to be more relevant barrier to access. More research is needed to identify the reasons for not listing insulin, particularly in countries with a significant burden. Countries in the Middle East are overall more likely to list analogue insulin which is likely due to a combination of factors such as high prevalence of diabetes and higher healthcare spending than countries in several other regions. The results on the inclusion of medicines in the national EMLs need to be discussed in conjunction with the analysis of the reimbursement list of countries to see whether the absence or listing of medicines on that list is associated with reimbursement.

In order to create demand for insulin products manufacturers use advertisement and market campaigns. An analysis of breaches of the national codes of medicines promotion in three high-income and seven middle-income countries revealed that marketing breaches were related to the recently launched products from the three main manufacturers of insulin. An exception was Pfizer, with breaches related to its inhalable insulin. For all middle-income countries except China no reports on market breaches of interest to the study were available. More analysis of promotion of insulin in middle-income countries is warranted.

The systematic literature review of the last five years on comparative efficacy and safety of insulin analogue versus human insulin shows that analogue insulins protect from nocturnal hypoglycaemic events but the studies do not demonstrate that this reduction is clinically significant (e.g. protection from severe hypoglycaemic events reducing morbidity and mortality). It is noteworthy that none of the studies that we identified examine the long-term clinical effects of diabetes or diabetes mortality rates. According to the second systematic literature review of the prevalence of insulin consumption in type 2 diabetes in the last 15 years, 15 percent to 23 percent of patients with type 2 diabetes use insulin in the United States (US) with a large variation between studies outside the US (2.6 to 36 percent). Only three out of 11 studies included show an increase in prevalence of consumption of insulin indicating insufficient evidence of an overall increasing prevalence of insulin consumption in type 2 diabetes. Comparing studies is difficult due to the variation in patient population (different age groups) studied and healthcare settings (primary care versus hospital data).

1. Introduction

1.1 The 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 Insulin Market Profile is a result of the mapping work completed 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 The Insulin Market Profile

Business market and industry reports used by the private sector describe the supply and demand of insulin, market shares, and market growth. However, this literature is largely inaccessible to public health practitioners, policy experts, and insurance administrators in low and middle income countries. The most specific market reports are extremely expensive, and much of the literature is focused on the larger diabetes markets in high income countries. Information about the markets in low- and middle-income countries is especially limited, increasing the difficulty of addressing the issues of access in those geographical areas.

The purpose of this report is to present the result of the Insulin Market Profile within the scope of the ACCISS study:

- Characterisation of the insulin manufacturers (Section 2),
- Registration of insulin products (Section 3),
- Insulin analogue market share (Section 4),
- Inclusion of insulin products in the national essential medicines lists and reimbursement lists (Section 5)
- Market practice of insulin manufacturers (Section 6),
- Clinical efficacy of human insulin versus analogue insulin (Section 7) and
- Prevalence of insulin use in type 2 diabetes (Section 8).

2. Characterisation of the insulin manufacturers

2.1 Background

The goal of this profile is to gain a more comprehensive understanding of the global insulin market by identifying opportunities and challenges in access to insulin, particularly in low and middle income countries. In doing this, we hope to make a first step into conducting more public-health focused market research to improve global access to medicines.

The first objective of the profile was to describe the supply and demand of insulin at the global level. While others have written about the dominance of the three major insulin manufacturers (Novo Nordisk, Eli Lilly, and Sanofi) and their role in the insulin market (1), there is not much research on other companies involved in insulin manufacturing.

The second objective was to create a list of all insulin manufacturers, both multinational companies and smaller insulin suppliers. In addition, we aimed to identify licensed manufacturers, subsidiaries, and distributors related to insulin manufacturers and involved in the global insulin market.

The third objective was to look at country markets, focusing on describing local insulin suppliers. Typically, these are not captured adequately in the grey and peer-reviewed literature. These country profiles, particularly those countries with the largest populations of people with diabetes, help us understand the markets with the highest demand for insulin.

These three objectives allowed us to accomplish the last objective, to identify regions particularly impactful to the global insulin market and potential opportunities in improving access to insulin. The regions identified as important to the global insulin market could indicate possible markets, countries, and manufacturers that would provide opportunities to improve access to insulin. This could direct policies and programs which would promote affordable insulin supplies in low-and middle-income countries.

2.2 Methods

To respond to the objectives of our profile, we conducted a literature review of publications about the global insulin market. These methods were divided in five parts: general global market review, specific country market and industry report review, pharmaceutical company review, medicine regulatory authority review, and descriptive analysis.

2.2.1 General Global Market Review

In the general market review, we included documents published in English from 2005 to the present. We consulted three databases in our review: LexisNexis Academic (2), ProQuest (3), and Frost & Sullivan (4). After conducting the searches, we considered the search results and titles of resulting documents and consulted results that were both relevant and specific to our research. Additional documents for specific background information collected through handsearches were also included.

Our first set of searches focused on variations of the terms “global insulin market,” and some included criteria for information about manufacturers, diabetes, or market reports (Annex 1.1). The results from the searches were then downloaded in full-text. We developed a data extraction

matrix where we recorded information on the prevalence of diabetes, the size and value of the global insulin market, and the main manufacturers.

2.2.2 Specific Country Market and Industry Report Review

A second set of searches focused on specific countries, searching for the country name with variations of "insulin market", some including criteria for the country's market share by volume or value. To study specific country markets, we accessed industry reports on the pharmaceutical markets provided by Business Monitor International in ProQuest (ABI/INFORM Complete) (5). The two most recent market reports for each country were collected (usually Q1 and Q2 for 2014). If neither document contained a reference to insulin or diabetes, the most recent reports containing one of the search terms was also included. We did not include pharmaceutical industry reports published before 2010 or after Q2 2014.

Within each report, we searched for the terms "insulin" and "diabetes," as well as the names of the three major companies in the insulin market, "Sanofi," "Novo Nordisk," and "Eli Lilly." After reviewing the report for each country, we extracted the following information:

- Prevalence and recent changes in prevalence of diabetes;
- Value of the diabetes and insulin markets in terms of sales and if available, volume;
- Market growth rate in terms of sales and, if available, volume;
- All insulin manufacturers present in the country;
- Other important pharmaceutical manufacturers present in the region that were potentially related to insulin manufacturers (license agreement, subsidiary, distributor, or similar);
- Information about Novo Nordisk's, Sanofi's, and/or Eli Lilly's involvement in the country; and
- Other important relevant information about the diabetes and the insulin market in the country.

Important sections of the market reports were analysed further and the previously indicated information was recorded in the data extraction matrix.

In order to identify and verify manufacturers providing insulin to each country, we contacted public health professionals using the Essential Drugs email forum (6). We asked members to contact us with a list of the insulin manufacturers supplying their country or their region of expertise. This was done both to verify our results and to collect data on countries, particularly smaller countries and low-and middle-income countries, for which there was little market data available. Data on manufacturers was checked and then included in our results and analyses. Following the initial review of the Business Monitor International Pharmaceuticals & Healthcare Reports, we used the Global and Chinese Insulin Industry Report 2014, published by Beijing Hengzhou Bozhi International Information Consulting Co., Ltd (QY Research) (7) to verify our findings on insulin manufacturers involved in the market and data on the market shares by volume and value of insulin manufacturers, global supply and demand of insulin, and global insulin production and capacity.

2.2.3 Pharmaceutical Company Review

Following our country market analyses, a further set of searches looked for company specific information, searching the name of an identified insulin manufacturer along with specific

country locations. Relevant documents were included as additional information to gain a clearer understanding of a country's market, a country's role in the global insulin market, and a manufacturer's role in the global insulin market.

Since the market reports were not always clear in distinguishing among insulin manufacturers, licensed manufacturers, subsidiaries, distributors, and non-insulin manufacturers, we performed Google searches (8) on each of the companies mentioned in the most recent Business Monitor International Pharmaceuticals & Healthcare Report for each country and in IMS Health (9) data on insulin manufacturers and distributors (10). The available websites for each identified manufacturer and additional relevant sources were recorded in the matrix for reference.

We determined each company's role as manufacturer, licensed manufacturer, subsidiary, distributor, or other (e.g. no involvement in the insulin market) based on product listings, other summary information, and references to insulin production on the company websites. When the company websites either could not be found or did not give a clear indication of the company's involvement in the insulin market, additional sources, including news articles, gained from Google searches, and other database searches were used to supplement information. We contacted companies where we could not find additional information to inquire about insulin production. Companies for which no information could be found were disregarded for the purposes of our review.

To verify the list of global insulin manufacturers, specifically looking for additional relationships between manufacturers, licensed manufacturers, subsidiaries, distributors, and additional players in the global insulin market, Google and database searches were conducted. Search terms included the name of the company and variations of "insulin", "licence", "partnership", "subsidiary", "manufacturer", and the name of another insulin manufacturer. In reviewing the search results, we looked for references to other insulin manufacturers, analyses of competition in the market, or licencing agreements with other companies. For those companies which little information was available regarding their role in the insulin market or for which there was conflicting or vague information, the final categorisation was based on available information. If insulin products were not easily found, if the company appeared to be a part of the diabetes market but not the insulin market, or if the company's description implied it was selling other companies' products, it was categorised as a licenced manufacturer, subsidiary, or distributor. If insulin products were apparent or further descriptions could not be found, the default categorisation at this stage was manufacturer.

We identified manufacturers for which we did not find any indication of a manufacturing license, distribution agreement, or other arrangement with another insulin manufacturing company as "independent". This final list of independent insulin manufacturers was used in our analysis and is referred to as manufacturers with insulin products registered and/or sold in a country.

2.2.4 Medicine Regulatory Authority Review

To further search for smaller insulin manufacturers and identify the locations of product registry, we looked at the available websites for the medicine regulatory authorities and ministries of health for each country. These were found using a list of medicine regulatory authorities from the WHO (11) and by searching in Google, using the country name and "drug regulatory authority", "medicine regulatory authority", or "list of registered medicines" as search terms.

On each website, we looked for the most recently updated list or database of registered human medical products in the country. After searching for "insulin" or the Anatomical Therapeutic Classification (ATC) code, we recorded the manufacturer of each human insulin product registered in the country. When distributors and manufacturer were identified, we only recorded the manufacturer of their product.

2.2.5 Descriptive Analysis

After categorising insulin manufacturers as independent and licensed manufacturers, subsidiaries, and distributors, we began geographical analyses of the global insulin market. For each country, we counted:

- The total number of insulin manufacturers with insulin products either registered and/or sold in the country, disaggregated into all such entities including Novo Nordisk, Eli Lilly, and Sanofi and all such entities excluding Novo Nordisk, Eli Lilly, and Sanofi; and
- The number of insulin manufacturers with corporate headquarters in the country, determined according to the information on the company websites.

We then grouped countries into categories based on the number of insulin manufacturers involved in the local market and graphed them on a world map in order to look for geographical trends in the global spread of insulin manufacturers.

We selected the six top middle-income countries in terms of number of people with diabetes using populations and national prevalence data from the sixth edition of the International Diabetes Federation's Diabetes Atlas (12). For those countries, we more specifically described the local markets.

2.3 Results

2.3.1 The Global Supply and Demand of Insulin

There was not a lot of easily available information on the supply and demand of insulin. Some market reports provided data on the insulin production of individual factories or companies in each country, but there was not consistent, comparable data on supply in this format.

The Global and Chinese Insulin Industry Report 2014 did provide one source of data on the global supply, demand, and shortage of insulin (7). Although the prevalence of diabetes is increasing globally and access to insulin continues to be a problem, it does not appear currently that the problem is lack of global supply. According to the report, there was a surplus of insulin of 67.6 million pieces (vials) in 2014 (7) (Table 1).

Table 1. Global supply, demand, and surplus of insulin 2012-2014. (7)

	2012	2013	2014
Demand (Million Pieces)	1580.0	1850.0	2150.0
Production/ Supply (Million Pieces)	1828.9	2000.0	2217.6
Surplus (Million Pieces)	248.9	150.0	67.6

While the global demand and production of insulin has been increasing, the global surplus of insulin has decreased by more than half from 2013 to 2014 (7). If this trend continues into the future, supply could serve as a barrier to access to insulin. However, at the moment, production

has been able to sustain the increase in demand.

The problem with access may be more a result of infrastructure and local policies as opposed to a lack of insulin supply. Thus, it is even more important to understand the role of insulin manufacturers in the global and local markets to address the problem of access to insulin.

2.3.2 The Global Insulin Market

We were able to collect data on the manufacturers with insulin products registered and/or sold in 121 countries. These 121 countries represent 96.3 percent of the world's population with diabetes (12).

With the worldwide prevalence of diabetes increasing at a compound annual growth rate of 7.6 percent, the insulin market is growing as well, at a rate of 12.9 percent sales increase in 2012 (12). The global insulin market was valued at approximately $20.8 billion USD in 2012, consisting of numerous human insulin and recombinant products (13). Interestingly, all the market reports we reviewed lack information on insulin sales volume, although the Global and Chinese Insulin Industry Report had market share based on pieces (vials) produced by each manufacturer (7).

Despite the size of the global market in terms of value, it is largely dominated by three pharmaceutical companies: Danish-based Novo Nordisk, French-based Sanofi, and American-based Eli Lilly, shown in Table 2. All three companies operate on all six continents, both independently and through licensed manufacturers, subsidiaries, and distributors, selling many different insulin products. Of the 121 countries studied in our review, Novo Nordisk had its insulin products registered and/or sold in 111 countries, Sanofi had its products registered and/or sold in 101 countries, and Eli Lilly had its insulin products registered and/or sold in 94 countries. They were the only insulin manufacturers with products registered and/or sold in 55 percent of the countries studied and are the sole providers of all of the insulin products in many of the world's countries, especially in high income countries in Western Europe. Furthermore, these three companies held an 88.7 percent value share in the global insulin market in 2012 (10). We identified a total of 42 independent insulin manufacturers worldwide, shown in Annex 1.2. Twenty-three of the manufacturers only sell their products in one country, almost all of them being local manufacturers selling to the country in which they are based. The list included seven companies selling their insulin products in only two countries, with only the top eleven companies with their products registered and/or sold in more than two countries. The top three manufacturers, Novo Nordisk, Sanofi, and Eli Lilly, all had their insulin products registered and/or sold in 90+ countries studied. Following the three major companies, there are four companies with products registered and/or sold in 10-30 countries: Bioton, Wockhardt, Biocon, and Julphar, and shown in Table 2, and four companies with insulin products registered and/or sold in 3-10 countries. One company was identified as an insulin manufacturer but no locations of products sales or registration were identified. Since compiling this list, we received additional information which changed some of our categorizations, although the total number of potentially independent insulin manufacturers remains at 42.

In addition to the independent insulin manufacturers, 62 companies were identified as licensed manufacturers, subsidiaries, or distributors selling insulin for one of the independent insulin manufacturers. This list is not considered exhaustive, but includes many insulin providers; the companies and the manufacturers for which they are connected to (if known) are listed in Annex 1.3.

Table 2. The top seven global insulin manufacturers.

Rank in World Market	Company Name	Headquarters Country	Number of Reviewed Countries Where They Sell Insulin	Percent of Insulin Market (by revenue)[2]	Percent of Insulin Market (by production)[9]	Major Insulin Products [13,14,15,16,17,18,19]
1	Novo Nordisk	Denmark	111	41%	52%	Actrapid®, Insulatard®, Mixtard®, NovoLog®/ NovoRapid®, NovoMix®
2	Sanofi	France	101	32%	17%	Apidra®, Insuman®, Lantus®
3	Eli Lilly	United States	94	20%	23%	Humalog®, Humilin®
4	Bioton	Poland	26	Unknown	Unknown	Gensulin™, SciLin™
5	Wockhardt	India	17	Unknown	Unknown	Wosulin®
6	Biocon	India	17	Unknown	Unknown	Basalog®, Insugen®
7	Julphar	United Arab Emirates	13	Unknown	Unknown	Jusline®

The top seven insulin manufacturers are ranked by a combination of the number of countries where they have insulin products registered or sold, their percent share of the insulin market by revenue, and literature sources. Based on this data source, insulin manufacturers outside of Novo Nordisk, Sanofi, and Eli Lilly comprise less than 7 percent of global insulin market value and 8 percent of global insulin market volume.

2.3.3 Global Spread of Insulin Manufacturers

Perhaps more important than the identity of the companies' manufacturing insulin are their locations and the distribution of the companies. Along with identifying the companies that manufacture insulin and in what country their headquarters are located, we recorded the number of manufacturers with insulin products registered or sold in each country. The manufacturers with insulin products registered and/or sold in country are shown in Annex 1.5. These manufacturers are separated into the presence of the big three insulin manufacturers (Novo Nordisk, Sanofi, and Eli Lilly) in each country and the presence of additional manufacturers (any of the other 39 manufacturers) in each country. This best demonstrates trends with the presence of smaller manufacturers and problems with access to insulin, as well as the dominance of major insulin manufacturers and problems with access to insulin.

In order to visualise the geographic trends in the spread of insulin manufacturers, we graphed the presence of insulin manufacturers on world maps. These maps allowed us to identify regions of interest or opportunity based on high numbers of insulin manufacturers present in a region of the world.

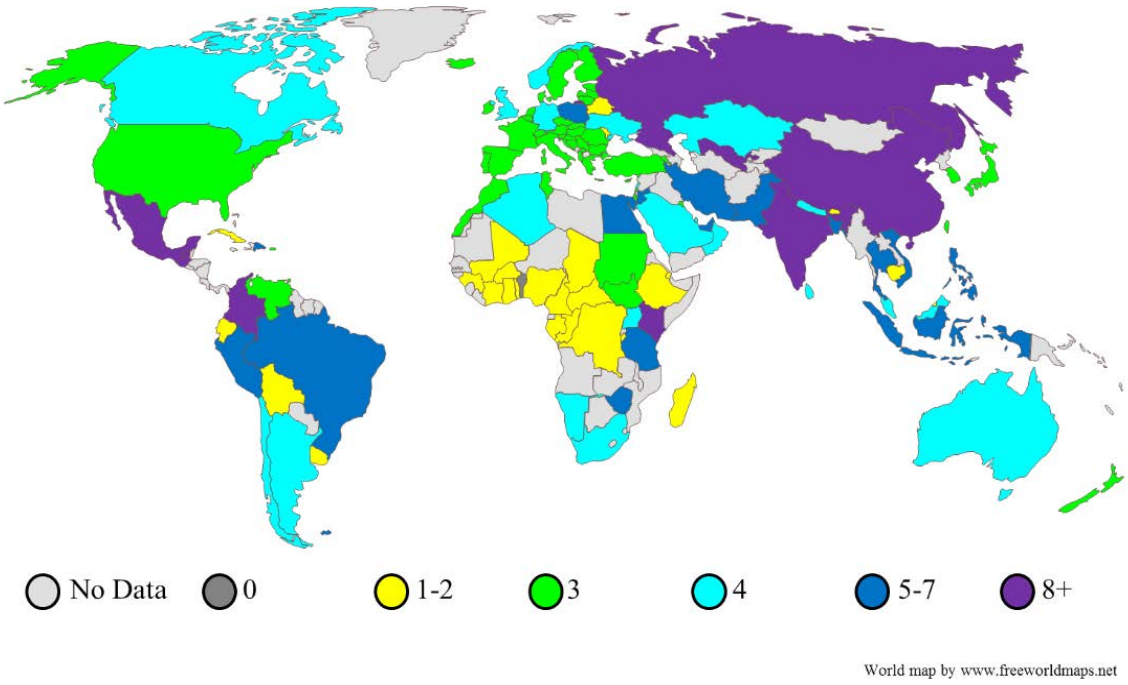
Graphed in Figure 1 is the total number of independent insulin manufacturers with insulin products registered and/or sold in each country. The particular countries included in each range and number of companies present is shown in Annex 1.4. While the range of number of

companies is quite large, it is clear that there are a higher number of manufacturers with insulin products registered and/or sold in Asia, the Middle East, Central America, and South America.

When excluding Novo Nordisk, Sanofi, and Eli Lilly, it becomes apparent that the highest number of insulin manufacturers have their products registered and/or sold in Asia, particularly in Southeast Asia (see Figure 2 for graphical display). This was also supported when graphing the number of insulin manufacturers according to their headquarter country, shown in Figure 3. The largest number of insulin manufacturers, the majority of them local manufacturers, have their headquarters in Asia, particularly Southeast Asia, and the Middle East. A large number are also based in high income countries.

Comparing Figure 1 and Figure 2, it is clear that many low and middle income countries, particularly those in sub-Saharan Africa, are supplied insulin by only one or two of the big three insulin manufacturers. Fewer small insulin manufacturers supply insulin to these low resource settings. These regions also have very few, if any, manufacturers with their main headquarters located in their country.

Figure 1. Number of independent insulin manufacturers with insulin products registered and/or sold in each country.



Asia and Latin America have the highest number of insulin manufacturers with insulin products registered and/or sold in countries in the region. The majority of high-income countries have only three or four insulin manufacturers, primarily being Novo Nordisk, Sanofi, and Eli Lilly.

Figure 2. Number of independent insulin manufacturers with insulin products registered and/or sold in each country (excluding Novo Nordisk, Sanofi, and Eli Lilly).

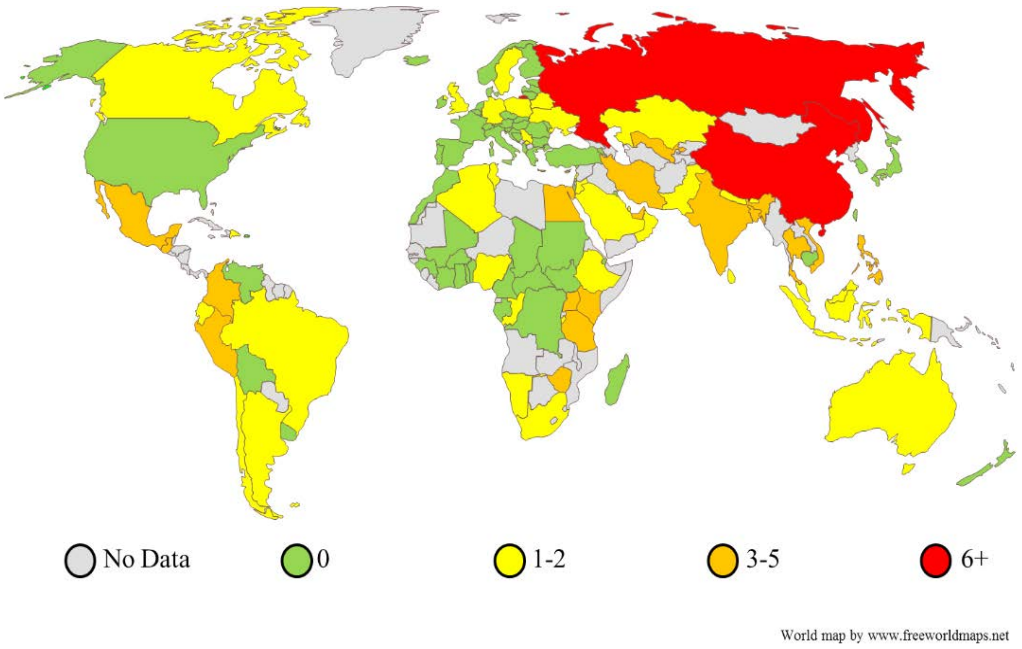
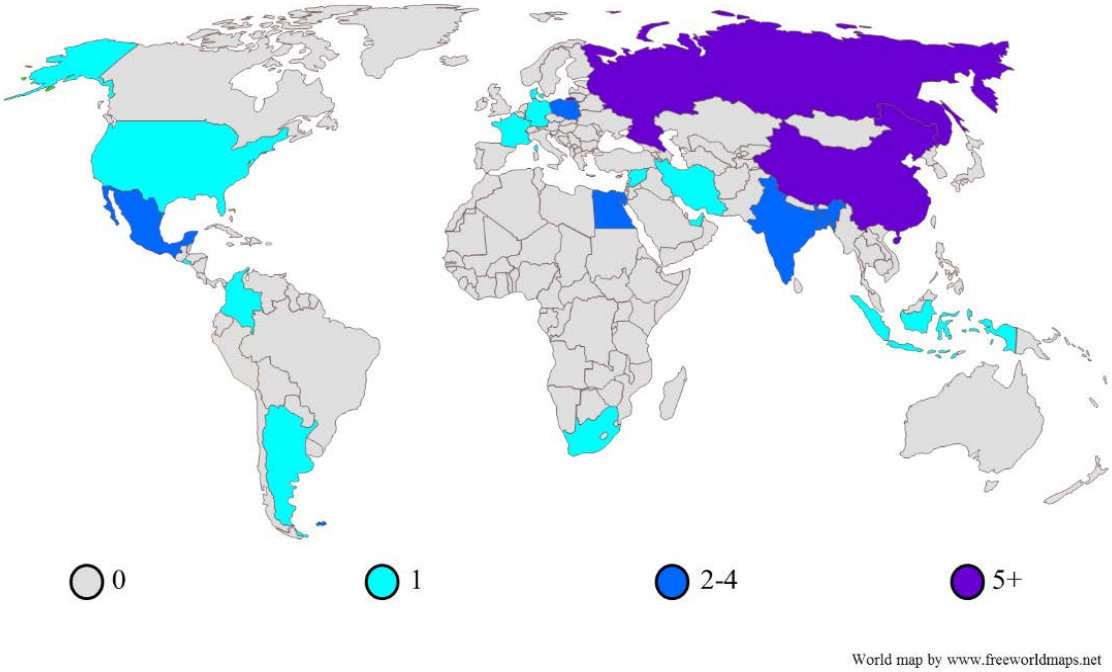


Figure 3. Number of independent insulin manufacturers with corporate headquarters in each country.



2.3.4 Insulin Market Profiles of Six Middle Income Countries

In order to gain the best understanding of the insulin market dynamics, we further analysed the insulin markets of the six middle-income countries with the largest number of persons with diabetes (12), as opposed to those countries with the highest prevalence but smaller populations which therefore make a smaller market impact. Profiles of these countries, which are all included in the top ten largest populations of people with diabetes (12), and the insulin markets of these are summarised in Table 3. The three major insulin manufacturers have a large share of the insulin market in these middle income countries, but there are also several manufacturers, including local manufacturers.

Table 3. Profiles of insulin markets in six middle-income countries.

Country	Percentage of World's Population with Diabetes in 2013	List of Independent Insulin Manufacturers with Products Registered and/or Sold in Country	Number of Manufacturers with Corporate Headquarters in Country
China	25.8	Novo Nordisk, Sanofi, Eli Lilly, Beier, Bioton, Hongye Biochem, Jinhua, Nanjing Xinbai, Shanghai Biochemical Research, Shanghai Biomedical, Shanghai Fosun, Tonghua Dongbao, Union, United Laboratories	10
India	17.1	Novo Nordisk, Sanofi, Eli Lilly, Biocon, Bioton, Polfa Tarchomin, USV, Wockhardt	3
Brazil	3.1	Novo Nordisk, Sanofi, Eli Lilly, Aspen, Wockhardt	0
Mexico	2.3	Novo Nordisk, Sanofi, Eli Lilly, Laboratorios Antibioticos, Laboratorios Cryopharma, Pisa, Probiomed, Wockhardt	4
Indonesia	2.2	Novo Nordisk, Sanofi, Eli Lilly, Bioton, Sanbe	1
Egypt	2.0	Novo Nordisk, Sanofi, Eli Lilly, Amoun Pharmaceuticals, SEDICO, Vacsera	3

These middle-income countries with the highest populations of people with diabetes show that more insulin manufacturers often supply countries with high demand. Because these countries have more infrastructure than some other low and middle income countries, these trends and local markets could help us identify ways to create programs to improve access.

2.4 Discussion

This profile supports previous knowledge that the global insulin market is dominated by three major manufacturers: Novo Nordisk, Sanofi, and Eli Lilly. These three companies had insulin products registered and/or sold in the majority of the 121 countries for which we had data and all except two countries reported at least one of these three companies having insulin products registered and/or sold there.

However, our study adds to the public health literature on access to insulin and insulin markets by identifying additional insulin manufacturers, the location of their headquarters, and their locations of product registry and/or sales, and additional licensed manufacturers, subsidiary companies, and distributors. While other multinational insulin manufacturers were identified, the overwhelming majority of them only have their products registered and/or sold in one

country. The documents we reviewed did not provide information on the major clients of the manufacturers. The manufacturers could supply only to public health providers such as the Ministry of Health or social security or they may be small local pharmaceutical companies manufacturing for local consumers. Future studies are needed to analyse these manufacturers and their role at country level in more detail.

We were also able to identify geographical regions particularly important to the global insulin market. While the three major insulin manufacturers are headquartered in high income countries, many other significant manufacturers have their headquarters in middle income countries. Many of these middle-income countries have particularly large populations with diabetes, including China, India, and Mexico. Since these countries have a high demand and many local insulin manufacturers, in depth analyses of the markets in these countries could demonstrate where the problems with access to insulin arise.

Regional analyses also gave insight onto the global insulin market. While we expected more insulin manufacturers to be based in high-income regions, this was not the case. Southeast Asia had the highest number of both insulin manufacturers with products registered and/or sold in countries as well as the highest number of insulin manufacturers with their headquarters in a country in that region. Central America, including Mexico, also had a higher number of insulin manufacturers than Western Europe, which was surprising. Start-ups would be attracted to the high insulin prices, which could explain the large number of smaller insulin manufacturers identified in these regions and globally. If there are many suppliers in these regions, why are there still challenges in affordable access? Regional analyses may also be helpful in understanding important market dynamics.

In short, there is an overall lack of available information about markets for the purposes of public health research. Furthermore, accessing information is difficult, as many market reports are very expensive or not specific enough to insulin markets. There is a disparity regarding the relative ease of finding data on middle and high income countries versus the difficulty in finding data for many low income countries and small income countries. Moreover, data on sales in terms of volume (Table 4) is not available. We also lacked information on the smaller insulin manufacturers, particularly their percent market shares in terms of both value and volume. In order to get a complete understanding of the global insulin market, filling these information gaps would be essential.

Table 4. Summary of information needed for public health market research.

Usually Available	Sometimes Available	Rarely Available
Companies involved in local market	Disease prevalence	Local Market Shares
Changes in local market (news)	Market Value	Market Volume
Presence of local manufacturing facilities	Market Growth Rate	Value and volume of smaller insulin manufacturers

The table summarises the information needed for public health-focused market research, organised on its availability in the pharmaceutical and healthcare market reports accessed through databases.

In addition to the lack of market data available for public health research, this study demonstrated the lack of transparency on the part of many pharmaceutical companies. While some manufacturers release data on their market share by value or volume and their rank in the global insulin market, the vast majority do not. These pharmaceutical companies also do not

release much information about the companies which have licenses to manufacture and distribute their products, making it more difficult to identify these relationships and describe competition in pharmaceutical markets. This study demonstrates the lack of transparency in the pharmaceutical industry and an area in which they can improve.

2.4.1 Limitations

We were limited by lack of complete publically available information and information available through Boston University. We were able to access many pharmaceutical market reports, but funds restricted us from being able to review more specific reports on the insulin market globally and nationally and we were only able to acquire one report specific to the global insulin industry at the end of this study. We are aware that there are market reports that market intelligence and pharmaceutical companies produce and purchase, but their prices are very high, making it difficult for academic institutions to study the insulin market. Because of information access restriction, our data is incomplete on the percentage of the insulin market that each company represents, by volume, value, and revenue both globally and nationally. This was shown to be particularly problematic for countries with detailed lists of registered medicines, such as Kenya, Uzbekistan, Guatemala, and Colombia, where there are many insulin manufacturers registered in the country but relatively low diabetes prevalence. We know that the insulin market in Kenya, for example, is dominated by Eli Lilly, who has a 90 percent market share (20).

Although there are a large number of companies, we see that in this case they make up a very small part of the market as a whole. In addition, the Global and Chinese Insulin Industry Report 2014 that we accessed was not very transparent in its data sources, methods, or methods of validation. This is a barrier to verifying and standardizing our research findings and ensuring the accuracy of the information in these reports. Complete market share data and standardized lists of registered medicines in each country would give us a clearer understanding of the insulin market as a whole and limit the outliers and inaccuracies in some of our data points.

The other main limitation in our study was defining insulin manufacturers as “independent”. Because we wanted to understand the competitiveness of the global insulin market, we wanted to exclude distributors, licensed manufacturers, and subsidiaries that were not adding additional products and competition to the market from our geographical analyses. However, we found it extremely difficult to determine with certainty whether a company was independent or a contract manufacturer, distributor, and/or subsidiary. Some companies were easily identified as distributors for primary insulin manufacturers, were reported to be owned by another manufacturer, or clearly showed they were selling the products of another company on their website. Other companies, such as Saidal and M.J. Biopharm, have links to major insulin manufacturers (Saidal with Novo Nordisk (21) and M.J. Biopharm (22) with Bioton), but at first appear to have their own independent insulin manufacturing and products; the categorization of these companies and companies for which there was little or conflicting information available was particularly difficult. Others buy insulin crystals from another insulin manufacturer and produce their own product. We were also unable to access databases of license agreements between companies. Because of this, it is possible that some agreements were missed, some companies were incorrectly categorised, and our list is not solely “independent” manufacturers, thereby influencing our analyses.

This study could be improved by more complete market data and greater information about agreements between pharmaceutical companies. However, despite these limitations, we feel that we have developed a list of relevant global insulin manufacturers and a qualitatively good

understanding key players, global distribution, and important geographical regions in the global insulin market by using business databases and market reports. This research will provide a platform to continue research on the global insulin market, looking for opportunities to broaden the market competition in some regions, as well as a first step towards a public health focused market analysis.

2.5 Conclusions

Apart from three major insulin manufacturers representing 88.7 percent of the global insulin market as of 2012, there are many smaller insulin manufacturers that produce for the local market. While many small local manufacturers only provide insulin to one country, there are some relevant regional and global insulin manufacturers. Four manufacturers in Europe, Asia and the Middle East have recently increased their market share substantially: Biocon, Wockhardt, Bioton, and Julphar. Their relevance might increase as more patients in low and middle income countries require access to affordable insulin.

Regionally, the global insulin market is not concentrated only in high-income countries. Countries in Asia, particularly Southeast Asia, have the highest number of insulin manufacturers with insulin products registered and/or sold in the country, with many manufacturers also in Central America. These regions may be particularly important in increasing insulin production to fill the gap in the insulin market. This research can be used to further our understanding of the global insulin market and identify further opportunities and challenges in providing equitable access to insulin.

3. Insulin Product Registrations Worldwide

3.1 Objective

This section summarises the results of the review of registries from National Medicine Regulatory Authorities (NMRA) websites of countries of the following WHO regions: WHO Eastern Mediterranean Regional Office (EMRO), Western Pacific Regional Office (WPRO), WHO South East Asian Regional Office (SEARO), WHO African Regional Office (AFRO) and WHO European Office (EURO) and WHO Americas Office (AMRO).

The objective of this review is to collect and generate a database of registered insulin products using publicly available information obtained from websites in order to understand the current status of registers containing insulin products around the globe.

3.2 Methods

3.2.1 Data Sources

Using the list of NMRA websites available from the WHO each NMRA website was searched for information on the currently registered, insulin-containing products. The procedure to collect registered, insulin-related products is as follows:

- For countries with NMRA websites and database of registered products, a scan was performed using the term “insulin” in the active ingredient field (where available) to obtain a filtered list of insulin-related products:
    - Information such as brand name, generic name/active ingredient, registration date, strength, cost of insulin product were collected, where available; if the product was not registered in English, the local brand and generic names also were recorded and later translated using Google;
    - For information without the aforementioned fields, “N/A” was labelled in the spreadsheet to specify information on registered insulin containing products was not available;
- Additionally, NMRA websites of countries with WHO Pharmaceutical Sector Country Profiles and Data (23) available were examined to find registries of medicines that may have not been included in the previously mentioned list of NMRA websites. Specifically, item 5.01.02 in the WHO Pharmaceutical Sector Country Profiles and Data was recorded to see if an NMRA existed within the country; item 5.01.07 in the Country Profile also was examined to see if a NMRA website existed, and sub-item 5.01.07.01 in the Profile showed the URL of the NMRA website, where available.
- For countries with established and working NMRA URLs, but no easy access to a list of registered drug products through the homepage, a Google search was performed on respective country’s Ministry of Health website;
- Notes were taken of countries without established NMRA websites.

3.2.2 Exclusion Factors

Any registered products that did not state insulin (human or analogue) as its main active pharmaceutical ingredient were excluded. These included items such as immunoassay kits, antibodies, human hormone, and blood sugar reduction tablets.

3.2.3 Definitions

Products
Each unique insulin product is defined as a good with a distinct type of presentation. Products may have the same brand name, but was counted as two unique items because of different presentation of dose, strength or application form. Products with the same brand name, same presentation but different registration dates are not considered unique for this project.

Income level
Income level assigned to each product corresponded to the original country's NMRA website. The income level was based on data from the 2015 World Bank income classification (24).

Company
When analysing the products' company, subsidiaries of companies with the same umbrella name in different countries were grouped and counted as one organisation. For example, "Novo Nordisk N/A" and "Novo Nordisk (China) Co., Ltd." are considered the same company. This also was true for "Eli Lilly & Company" and its subsidiaries such as "Lilly France".

Classification
After a list of the registered products was collected from NMRA websites, products were sorted by classification categories (27) in accordance with Annex 2.1, international non-proprietary name (INN), and origin of insulin (i.e. human, analogue, or animal).

If any of the above fields were initially unknown, the researcher carefully analysed other fields such as brand name, generic name, company to deduce a logical option. For instance, if the description of the product provided by the NMRA said regular recombinant human insulin it was classified as such in the database.

Special classification consideration was taken for products identified as "insulin degludec and insulin aspart", commonly sold under the brand name Ryzodeg. As this class of insulin product was not classified in Annex 2.1, the researcher classified it as an "intermediate-acting basal" analogue insulin product.

3.3 Results

The detailed listing of each NMRA with functioning links from the regions reviewed can be found in Annex 2.2.

(1) Total number of NMRA reviewed: 195
(2) Total number of NMRA with functioning links reviewed: 118 (118/195= 60.5 percent)
(3) Total number of countries with publicly available, registered insulin products: 75 (75/195= 38.4 percent)

Only 40.0 percent of all NMRA had publically accessible information on the registered insulin products. Table 5 below displays the data by region. The region with the highest percentage of NMRA that had publically available information on registered insulin products were Europe, followed by the Southeast Asia and Americas. The region with the lowest publically accessible information on registered insulin products was Africa.

Table 5. Number of countries with national medicines regulatory authorities by characteristics on accessibility of information.

		AFRO	AMRO	EMRO	EURO	SEARO	WPRO	Total
Total number of NMRA		46	35	23	53	11	27	195
Total number of NMRA with functioning links (=100%)		15	22	12	49	8	12	118
Total Number of countries with publicly available, registered insulin	HI	0	4	2	31	0	5	42
	UMI	3	8	1	6	0	3	21
	LMI	2	1	3	2	4	1	13
	LI	0	0	0	0	0	0	0
% of NMRA with publicly available information on insulin products		10.9%	37.1%	26.1%	73.5%	36.4%	33.3%	40.0%

The total number of insulin products obtained from publicly available in-country databases was 2020. Table 6 shows the total number of insulin products per region and per country. Europe stands out with 732 products, followed by the Western Pacific (n=464) and the Americas region (n=364). A total of 1992 products within 55 countries (excluding the EMA registrations) translating into a mean of 36 products per country. As shown, for none of the low-income countries information on registered insulin products was available. In terms of ratio analogue to human insulin products Europe had the highest (0.77), followed by Western Pacific (0.71) and the American region (0.69). The lowest ratio analogue versus human insulin was found in the African region (0.15).

Table 6. Total registered insulin products by region and per country.

Region (*)	Country	Income level	No. of human insulin products	No. of analogue insulin products	No. of animal products	Unknown	Ratio analogue /human insulin product	Total
AFRO (5)			**112**	**17**	**4**	**5**	**0.15**	**138 (mean 28)**
	Algeria	UMI	3	1	0	0		4
	Botswana	UMI	5	0	0	0		5
	Kenya	LMI	35	8	3	1		47
	Nigeria	LMI	65	7	1	1		74
	South Africa	UMI	4	1	0	3		8
AMRO (13)			**192**	**134**	**31**	**7**	**0.69**	**364 (mean 28)**

	Brazil	UMI	6	0	1	1		8
	Canada	HI: OECD	17	18	2	0		37
	Chile	UMI	8	0	0	0		8
	Colombia	UMI	20	2	0	1		23
	Costa Rica	UMI	9	8	0	0		17
	Cuba	UMI	4	3	0	0		7
	Dominican Republic	UMI	35	21	0	0		56
	Guatemala	LMI	35	21	0	3		59
	Mexico	UMI	16	11	0	0		27
	Panama	UMI	0	1	0	0		1
	Peru	UMI	15	18	0	0		33
	Trinidad and Tobago	HI: non-OECD	6	1	0	0		7
	USA	HI: OECD	21	30	28	2		81
EMRO (6)			**121**	**81**	**3**	**3**	**0.67**	**208 (mean 35)**
	Egypt, Arab Republic	LMI	54	13	1	3		71
	Lebanon	UMI	11	0	0	0		11
	Morocco	LMI	19	22	1	0		42
	Oman	HI: non-OECD	9	23	0	0		32
	Saudi Arabia	HI: non-OECD	16	22	1	0		39
	Sudan	LMI	12	1	0	0		13
EURO (19)			**406**	**311**	**10**	**5**	**0.77**	**732 (mean 39)**
	Armenia	LMI	19	13	0	0		32
	Azerbaijan	UMI	12	17	0	0		29
	Belarus	UMI	8	1	0	0		9
	Croatia	HI: non-OECD	12	12	0	0		24
	Estonia	HI: OECD	71	60	0	0		131
	European Medicine Agency	N/A	19	13	0	0		32
	Finland	HI: OECD	73	56	0	2		131

	Iceland	HI: OECD	9	13	0	0		22
	Israel	HI: OECD	9	17	0	0		26
	Latvia	HI: non-OECD	51	41	0	0		92
	Lithuania	HI: non-OECD	5	0	0	0		5
	Malta	HI: non-OECD	3	0	0	0		3
	Moldova	UMI	19	9	0	0		28
	Montenegro	UMI	6	9	0	0		15
	Norway	HI: OECD	21	13	0	1		35
	Serbia	UMI	20	26	0	0		46
	Sweden	HI: OECD	31	0	0	0		31
	Switzerland	HI: OECD	4	11	3	0		18
	United Kingdom	HI: OECD	14	0	7	2		23
SEARO (4)			**69**	**41**	**2**	**2**	**0.59**	**114 (mean 29)**
	Bangladesh	LMI	22	3	0	0		25
	India	LMI	28	16	2	2		48
	Indonesia	LMI	4	5	0	0		9
	Sri Lanka	LMI	15	17	0	0		32
WPRO (9)			**263**	**186**	**11**	**6**	**0.71**	**464 (mean 52)**
	Australia	HI: OECD	24	13	2	0		39
	Brunei Darussalam	HI: non-OECD	5	8	0	0		13
	China	UMI	141	80	0	3		224
	Fiji	UMI	3	0	0	0		3
	Japan	HI: OECD	4	27	0	0		31
	Malaysia	UMI	3	0	0	0		3
	New Zealand	HI: OECD	64	30	7	3		104
	Philippines	LMI	7	8	0	0		15
	Singapore	HI: non-	12	20	0	0		32

		OECD						
Total (55)			**1163**	**770**	**59**	**28**	**0.66**	**2020***

(*) = Number of countries within a region, excluding EMA countries; ** n=1988 excluding the 32 products listed in the EMA countries

In terms of country income level nearly half of all products identify (n=964; 48.5 percent) are registered within the high-income countries, about one quarter in upper-middle and one in lower-middle income (Table 7). As mentioned before information for low income countries was not available.

Table 7. Total registered products by income levels.

Income level	Total count	% total registered products
High income (both OECD and non-OECD)	964	48.5%
Upper middle income	529	26.6%
Lower middle income	495	24.9%
Total*	**1988**	100.0%

*Excludes products centrally registered by the EMA

In terms of products per manufacturer (or market authorisation holder) Novo Nordisk lead the ranking with a little more than one third of the products (36.2 percent) followed by Eli Lilly and Sanofi-Aventis (Table 8). These three companies account for 78 percent of all products identified through our search. There are many manufacturers with a small number of products. Except Wockardt these smaller manufacturers are exclusively marketing their products in upper-middle and lower-middle income countries.

Table 8. Top 20 companies with registered insulin products by income level.

Company	High income	Upper middle income	Lower middle income	Total	% all registered insulin products
Novo Nordisk	431	153	135	719	36.2%
Eli Lilly/Lilly & Company	232	124	114	470	23.6%
Sanofi-Aventis	222	78	61	361	18.2%
Bioton	0	26	3	29	1.5%
Biocon	0	10	16	26	1.3%
Wockhardt	9	4	12	25	1.3%
Wanbang Biopharmaceuticals	0	19	0	19	0.96%
MJ Biopharma	0	1	18	19	0.96%
Tonghua Dongbao	0	14	3	17	0.86%
Laboratorias Pisa	0	8	3	11	0.55%
Gan & Lee Pharma	0	10	0	10	0.50%
Incepta Pharma. Ltd.	0	0	10	10	0.50%
Popular Pharma. Ltd.	0	0	9	9	0.45%
Hoechst	0	3	5	8	0.40%
Probiomed	0	7	1	8	0.40%

Vacsera	0	0	8	8	0.40%
Aristopharma Ltd.	0	0	6	6	0.30%
Julphar	0	3	2	5	0.25%
Shreya Life Sciences	0	0	5	5	0.25%
United Laboratories Co., Ltd.	0	5	0	5	0.25%
Unknown	46	5	63	114	5.7%
Grand total	**964**	**529**	**496**	**1988**	--

Regarding the types of insulin products registered one third of them are premixed insulin products, followed by regular insulin and long-acting basal insulin (Table 9). It is interesting to note that the distribution by income level shows that regular insulin products are about equally distributed between the income groups: whereas particularly for rapid acting insulin products there is a largely unequal distribution: nearly double the amount of rapid-acting products are registered in high-income versus upper-middle income and only about one quarter of the number of products registered in high-income countries are registered in lower-middle income countries. Hundred-and-fourteen of all products could not be classified due to lack of information.

Table 9. Total registered insulin products by classification.

Type of insulin product	High income	Upper middle income	Lower middle income	Total	% all registered insulin products
Premixed	348	137	141	626	31.5%
Regular	127	114	108	349	17.6%
Long-acting basal	171	73	83	327	16.5%
Intermediate-acting basal	120	88	84	292	14.7%
Rapid-acting	159	74	47	280	14.1%
Unknown	39	43	32	114	5.7%
Total	**964**	**529**	**495**	**1988**	**100.0%**

Table 10 lists out the total number of registered insulin products by international non-proprietary name. Human insulin is the most common substance in registered products compared to other types of insulin such as animal insulin and analogue insulin. Insulin lispro is the most commonly registered analogue insulin product at 12.3 percent. Similar to the previous findings the distribution of human insulin more similar between income groups than the one of animal or analogue insulins. For analogue insulin products about half or more of all products are registered in high-income countries.

Table 10. Registered products by active substance and income levels.

	High income	Upper middle income	Lower middle income	Total	% all registered insulin products
Insulin (human)	488	318	317	**1123**	**56.5%**
Insulin lispro	135	66	44	**245**	**12.3%**
Insulin aspart	117	45	30	**192**	**9.7%**

Insulin glargine	60	37	37	**134**	**6.7%**
Insulin detemir	41	16	12	**69**	**3.5%**
Insulin glulisine	35	18	13	**66**	**3.3%**
Insulin (pork)	29	1	7	**37**	**1.7%**
Insulin degludec	19	9	4	**32**	**1.6%**
Insulin degludec and insulin aspart	9	7	0	**16**	**0.8%**
Insulin (beef)	16	0	0	**16**	**0.8%**
Insulin (beef) and insulin (pork)	3	0	0	**3**	**0.2%**
Unknown	12	12	31	**55**	**2.8%**
Grand Total	964	529	495	**1988**	**100.0%**
	48.5%	26.6%	24.9%	100.0%	

Note: There are small differences in the number of insulin types between Table 6 and 10 due to the difficulty of categorizing some of the products into subcategories. For instance, it is clear from the data that the product is animal insulin but it is unclear whether it is pork or beef.

Products under the brand names of Humalog (premixed), Mixtard (premixed), and NovoMix (premixed) were the top three registered brand names follow by Lantus (insulin glargine) and NovoRapid (insulin aspart) (Table 11).

Table 11. Top five registered brand name products.

Brand name	Count	% total registered products
Humalog (premixed)	106	5.3%
Mixtard (premixed)	96	4.8%
NovoMix (premixed)	89	4.4%
Lantus (insulin glargine)	86	4.3%
NovoRapid (insulin aspart)	83	4.1%

3.4 Discussion

Registration of insulin products globally provides insight into the supply and demand of insulin. Caution is need in generalising the results across the globe as only a little more than one third of all the NMRA websites had information on registered insulin products; for instance, information about registered insulin products in low-income countries could not be identified. These limitations indicate relevant gaps in the transparency and completeness of information about product registration. Other authors found similar results analysing the completeness and user-friendliness of the information provided by NMRA (25).

Among other factors, demand (prevalence of diabetes) and purchasing power influence registration. For instance, more analogue products are being registered in certain countries which is likely related with purchasing power.

However, other results are harder to explain such as the number of insulin products per country. For instance, Estonia and Finland have a large number of products whereas countries with a larger pharmaceutical market have less. National requirements to register products may be one of the reasons for this variation between countries.

With respect to the type of products, those containing human insulin are most common.

Accessing NRMA websites

During the search and data collection phase of the project, the search methods showed a large disparity in the availability of resourceful, up-to-date, and accurate registration of insulin products from all NRMA websites.

For example, in upper-middle income countries of Algeria and South Africa in the AFRO region, only five and eight registered insulin products, respectively, were found. Meanwhile, in the same income level, China in the WPRO region had 79 registered products.

Many countries' NRMA websites did not have clear or easily accessible links to their registries of medicines available to the public. In many cases, the investigator had to either find the database using queries in Google or the website's search application. Even in high-income countries, such as Canada, United Kingdom, and Australia, with detailed NRMA websites, it was difficult to find their searchable database of medicines without extensive examination of the website's site map. It is important to note that the project also did not find any registered products from low-income countries and their NMRA websites.

Searching the registry

When NRMA websites had a searchable or downloadable database, the investigator used the term "insulin" in the active ingredient search field. This allowed for a more detailed and accurate search of the database. Not all NRMA websites, however, allowed one to search this accurately. For example, the registry of drug products in Belgium only allowed searching by brand name. This became difficult as the investigator did not know all of the available insulin product names in the country.

Display of registered products

Display of registered products was also a variable amongst different countries around the world. For example, countries in EMRO such as Egypt and Lebanon used downloadable Excel spreadsheets—making data extraction easier to manage and analyse.

In the WPRO region, countries like China and Australia displayed the information in a clean, web page format. The difficulty in this format was that data extraction was harder as not all fields (e.g. generic name, classification, company/distributor) were displayed on the table. One had to click on the individual brand names of the registered insulin product in order to get more details.

Furthermore, Japan on their English website only included their registered products in tables contained within Portable Document Format (PDF) file type, separated by month. This made searching difficult as the researcher needed to download each individual file and use the search function to encompass all of the registered insulin products.

Language

Language was also a barrier to finding registered products on NRMA websites. Some countries (e.g. Azerbaijan, Belarus, Russian, and Uzbekistan) in Eastern European region only had NRMA website in the Russian interface. This may have impeded the ability of investigator to find their complete registry of medicines.

While some countries such as China, Maldives, South Korea, and Japan offered English-facing websites, only the country's primary language website contained informative, detailed, up-to-date, and descriptive information on registered insulin products. In many situations, the English website only contained a section on general information regarding diabetes and descriptions of

some public health programs and services available to citizens. On many occasions, the investigator had to rely on Google Translate to figure out where the registry of drugs was located on the non-English website.

Misclassification

The issue of misclassification has two facets: misclassification of products by generic name and misclassification of products available by country.

Some countries would classify products in a detailed manner, providing the type of insulin (e.g. lispro or biphasic aspart [30 percent rapid acting aspart / 70 percent intermediate aspart protamine]). Other countries would simply classify some products under the "insulin" umbrella. This made it difficult to analyse the types of insulin products registered without further organization of the data. Despite these challenges, it was possibly to deduce some of the products based on either company/manufacturer or the brand name of the drug.

Issues with classifying drugs registered through European Medicines Authority

As the European Medicines Authority (EMA) centrally approves medicinal products across all countries in the European Union (EU) and European Economic Area (EEA), this meant a clear and consistent understanding of registered products in the region. Each country in the EU/EEA, however, has their own NMRA and the sovereignty to approve individual products for use within their individual country. It became difficult to differentiate the drugs that were approved centrally for usage across all member states versus those that were nationally-approved for individual EU/EEA countries. While the EMA maintains a clear centralised database of registered medicines, countries within this area, however, can regulate and approve drugs for national use. Only Lithuania provided clear distinction to which drugs were nationally or centrally regulated. Countries like Iceland and Finland grouped their registry of drugs together.

Inability to classify

At the time of writing this report, there were still some countries that needed to be classified, but were unable to be completed because of lack of information from NMRA website. For example, in India, there were a few instances of products without any identifiers such as brand or generic names. They merely included descriptions such as "Soluble Insulin Injection I.P." which made it extremely difficult to classify in accordance to Annex 2.1.

Incompleteness

Incompleteness of data found on NMRA websites also was an issue. Especially in countries such as India, there simply was not enough information available on the insulin itself. The researcher had to deduce the product based on either brand name or manufacturer in order to classify the insulin product. This increased the chances of misclassification and human error. Many of the countries lacked information on price so from an initial scan of NRMA websites, many of the structured fields in the database are left either as empty cells or filled in with "N/A".

Product count

Counting of insulin products need to be standardised across the database, as some countries (e.g. countries under the jurisdiction of the EMA, Norway, and Mexico) only counted the different brand names of insulin products. Other countries provided an exhaustive list of every type of product available within each brand name (e.g. in Finland where Actraphane in 40 IU/mL and Actraphane in 100 IU/mL were counted as different products). This is attributed to the greater number of products registered in countries such as Finland and Estonia.

The authors tried to compensate for this dilemma by looking at all forms of registered insulin products. Despite this effort, some countries may not have reported their complete set of insulin products in all forms on the NMRA website.

In terms of recommendations, a detailed, but generalisable, checklist could help to pre-screen NRMA websites for legitimacy, clarity, accuracy, relevance, and resourcefulness. This checklist could be used by other researchers and scholars who might be interested in finding out pharmaceutical offerings in certain countries across the globe.

For AFRO region some key personnel of NRMAs without a website or registered insulin products were contacted to obtain their database. However, very few people replied. The authors will continue to contact key personnel in countries with WHO Pharmaceutical Sector Country Profile and Data available to increase the number of countries for which data can be obtained.

Since many countries did not provide all fields for their registered insulin products, other registries or sources need to be examined to procure the pricing of insulin products in countries that are already in the database.

4. Inclusion of Insulin Products into the National Essential Medicines Lists and Reimbursement Lists

This section of the report will first present the time sequence of inclusion of insulin in the WHO Model Essential Medicine List (WHO MEML) and second present the results of a comparison between the National Essential Medicines Lists (NEML) of low and middle-income countries in the following WHO Regions: EMRO, SEARO, WIPRO, AFRO and AMRO. Finally, the report will present findings of comparing reimbursement lists of high income countries.

4.1 Inclusion of Insulins in the WHO Model List of Essential Medicines

The WHO MEML has a long history of updates with regards to medicines for various diseases. For diabetes, Figure 4 illustrates the timeline and key changes of insulin on the WHO MEML throughout the years of its bi-annual updates.

1985
Insulin was first added on the third version of the WHO MEML in 1985. The two types added were the soluble human insulin and intermediate-acting insulin that currently remain on the WHO MEML. The different forms added were 40 IU/ml in 1D-ml vial, 80 IU/ml in 1D-ml vial , 40 IU/ml in 10-ml vial, 80 IU/ml in 1D-ml vial (as compound insulin zinc suspension or isophane insulin.

1988
In 1988, the l00-IU/ml product presentation/form of soluble insulin and intermediate-acting insulin were added to the WHO MEML since many countries were adopting it.

1998
It took a decade for the deletion of 80 IU/ml soluble and intermediate-acting formulations of insulin since they were no longer the recommended standard dosages of insulin. The other product presentations remained on the WHO MEML.

2003
In 2003, an application was made for the inclusion of intermediate amorphous (100 percent) porcine insulin suspension (insulin semilente) to the WHO MEML since the Model List did not specify the origin (i.e. human or animal) nor the type (i.e. zinc suspension or isophane insulin) of insulin.

The arguments for the inclusion of the intermediate-acting semilente form were that it has more favourable pharmacokinetic properties than other intermediate-acting insulins and the incidence of both nocturnal hypoglycaemia and early morning hyperglycaemia is lower. However, the committee concluded that there are no clinically significant differences between insulins, therefore, the choice should be based on cost. Moreover, given that that intermediate-acting insulin was on the WHO MEML, there was insufficient evidence to recommend a specification of insulin.

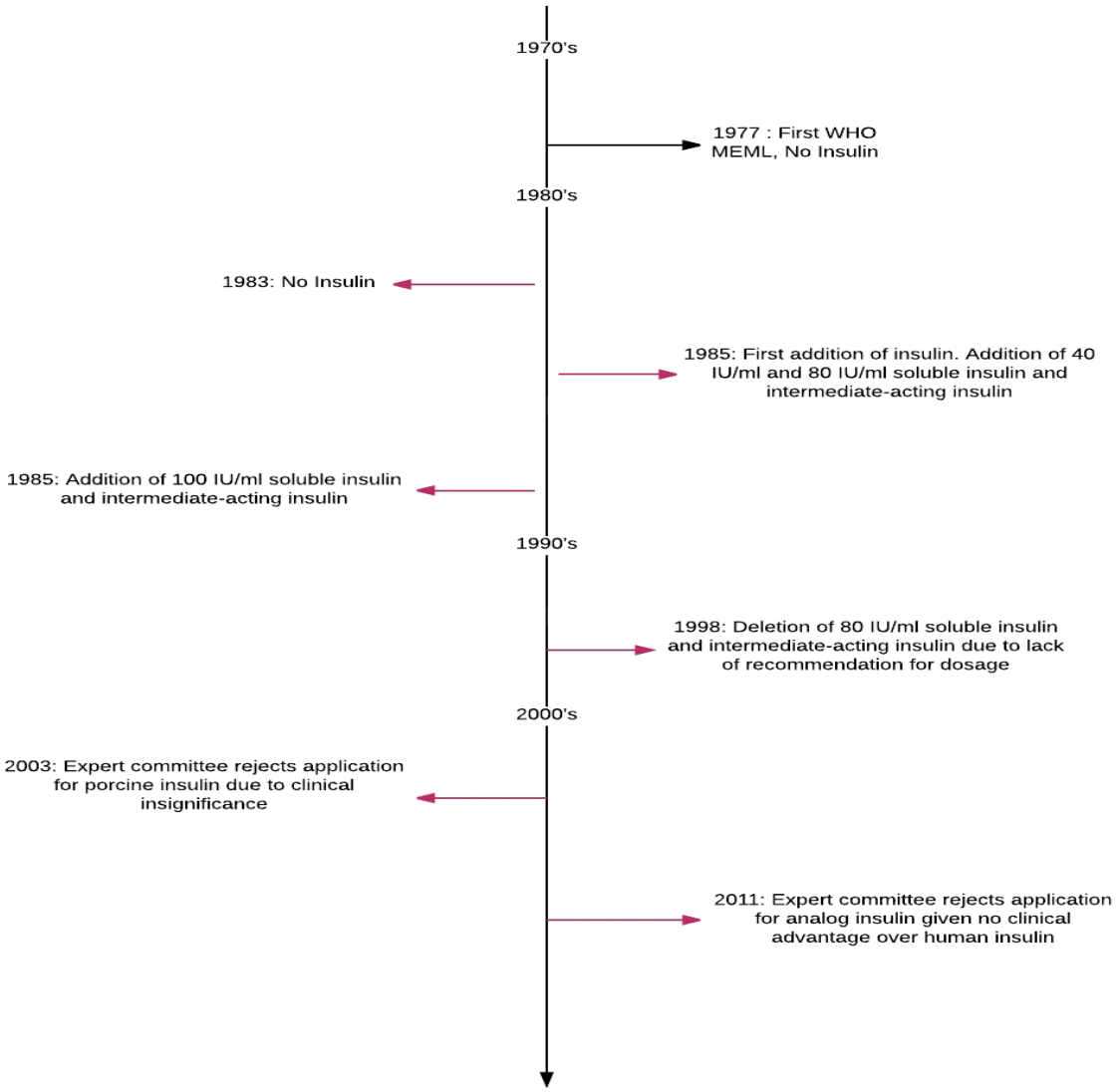
Since the 2003 application for review, no changes have been made to insulin on the WHO MEML to date and no specifications have been made for insulin.

2011

In 2011, the WHO 18th Expert Committee on the Selection and Use of Essential Medicines reviewed the application for analogue insulin based on its comparative effectiveness and cost–effectiveness of its various types: glargine, detemir, aspart, lispro, and glulisine insulins in contrast to human insulin.

The application was rejected based on no evidence of a clinically significant difference in between analogue and human insulins. The Committee concluded that types of analogue insulin currently do not offer any clinical advantage over recombinant human insulin and there is still concern about possible long-term adverse.

Figure 4. Historic time of inclusion of insulin on the WHO MEML.



4.2 Inclusion of Insulin Products on NEMLs

The objective of this section is to present the comparison of NEML for low- and middle-income countries (LMIC) with respect to insulin.

For this study all LMIC were eligible for the preliminary analysis. Countries were grouped by region.

The WHO Model Essential Medicines List published in October 2013 was used to perform the comparative analysis (27).The Diabetes Medications section (Section 18) of the WHO MEML[i] includes 2 human insulin presentations. As mentioned in Section 5.1 analogue insulin is not included in the WHO MEML. The classification on insulin types can be found in Annex 2.1. The comparative analysis comprises three steps:

- Comparison of all essential insulin presentations included in WHO MEML with the NEML
  - The percent of WHO medicines listed on the NEML out of total WHO EML insulin presentations (100 percent = 2 diabetes medications are on the WHO MEML).
- Identification of medicines not listed in the WHO MEML by ATC Analysis:
  - A matrix was used to identify the number of countries with insulin listed in each of the five different categories (rapid, short, intermediate, long-acting and mixed insulins). No insulin listed would indicate a gap in the selection while choosing more than two or more would indicate that selection is not restricted to the most essential medicines.

Table 12 presents an overview of the countries with a National Essential Medicines List accessed for the purpose of the study. It also includes the year of the NEML, which was included in this analysis. There are several countries for which no list was accessible.

Table 12. WHO region countries and availability of the NEML for low- to middle-income countries.

WHO Region	WHO EMRO (n=19)	WHO SEARO (n=11)	WHO WPRO (n=17)	WHO AFRO (n=31)	WHO PAHO (n=22)
NEML Medicine + Product Presentation Listed	Afghanistan (2014) Iran (2013) Djibouti (2007) Oman (2009) Pakistan (2007) Morocco (2012) Egypt (2012) Libya (2005) Lebanon (2014) Yemen (2009) Sudan (2014) Iraq (2010) Saudi Arabia	Bhutan (2012) DPR Korea (2012) India (2011) Indonesia (2011) Maldives (2009) Myanmar (2010) Nepal (2011) Sri Lanka (2009) Thailand (2012) Timor-Leste (2010)	Cambodia (2012) China (2012) Cook Islands (2008) Fiji (2013) Kiribati (2009) Malaysia (2012) Mongolia (2009) Niue (2006) Papua New Guinea (2002) Solomon Islands (2010) Vanuatu (2007)	Angola (2014) Algeria (2006) Botswana (2012) Burkina Faso (2007) Burundi (2012) Cameroon (2009) Chad (2007) Congo (2013) Cote d'Ivoire (2013) Democratic	Argentina (2005) Bolivia (2013) Brazil (2010) Dominican Republic (2005) Ecuador (2009) Guyana (2010) Haiti (2012) Honduras (2011) Jamaica (2008)

[i] Core essential medicines satisfy the basic needs for a health-care system, and consist of safe and cost-effective medicines for priority conditions.

	(2012) Somalia (2003) Palestine (2012)		Vietnam (2008) Republic of Korea (2012)	Republic of Congo (2010) Ethiopia (2010) Eritrea (2010) Ghana (2010) Kenya (2010) Lesotho (2010) Madagascar (2008) Mali (2008) Mauritania (2007) Mozambique (2012) Namibia (2008) Niger (No year) Nigeria (2010) Rwanda (2010) Zambia (2013) Senegal (2008)	Mexico (2009) Nicaragua (2009) Paraguay (2009) Peru (2010) Suriname (2014) Trinidad and Tobago (2010) Venezuela (2004)
NEML Derived from National Formulary	Jordan (2011) Bahrain (2009) Tunisia (2008)	-	Palau (2006) * Hospital Marshalls Island (2007) Philippines (2008) Tonga (2007) Tuvalu (2010)	Guinea (2013) Lesotho (2005) Liberia (2011 Malawi (2009) South Africa (2012) Tanzania (2007) Zimbabwe (2011)	Belize (2011) Barbados (2012) Chile (2005) Colombia (2006) Uruguay (2011)
NEML Medicine Listed Only without specifying the product presentations (dosage,	Syria (2008)*	Bangladesh (2008)	-	-	El Salvador (2011)

tablet, etc.)					
No NEML available			American Samoa Brunei French Polynesia Guam Lao People's Democratic Republic Japan (2012)[ii] Micronesia Nauru New Caledonia Northern Mariana Island Samoa Tokelau Wallis and Futuna	Benin Cabo Verde Comoros Equatorial Guinea Gabon Gambia Guinea Bissau Mauritius Sao Tome and Principe	Antigua and Barbuda Bahamas Costa Rica Cuba Dominica Grenada Guatemala Panama St. Kitts St. Lucia

*Exclusion criteria: Countries not specifying the type of medicines listed were excluded from the analysis. For example, Syria was the only country excluded from the insulin analysis since it did not specify the type of insulin –such as short or intermediate.

Out of 138 possible NEML and formularies 100 were available (Table 13).

Table 13. Number of NEML or formularies available and total number of countries in the regions.

WHO Region	NEMLs or Formularies available	Total number of LMIC per region	Percentage of LMIC analysed
AFRO	31	42	71%
EMRO	19	19	100%
SEARO	11	11	100%
WPRO	17	33	52%
AMRO	22	33	67%
Total	**100**	**138**	**Average 73%**

4.2.1 Results

Table 14 describes the number of countries listing insulin. Soluble insulin injection was listed by 98 countries and intermediate-acting human insulin was listed by 97 countries. Syria was excluded from the insulin analysis since it did not specify any insulin type. Burundi and Djibouti from the WHO AFRO and EMRO regions are the only two countries that do not list soluble insulin injection. Across the 100 countries, Bangladesh, from the WHO SEARO region, is the only country that does not list intermediate-acting human insulin.

[ii] Japan's Healthcare Insurance is used for the comparison. Currently in process of translations

Table 14. Number of countries listing WHO MEML recommended insulin presentations.

WHO Recommended Medicine	Number of countries with medicine	List of Countries Without Medicine
Insulin injection(soluble)[iii]	98	Burundi, Djibouti,
Intermediate-acting insulin (as cpd insulin zinc suspension or isophane inulin)[iv]	97	Bangladesh

*Lists were excluded from the analysis because classification of insulin type was not possible due to insufficient information presented

Figure 5 shows a comparison of the percentage of different insulin products listed in the NEML by region. Predictably, the two human types of insulin on the WHO MEML are the most frequently listed on the NEMLs studied. WHO WPRO and PAHO countries always list both types. SEARO countries always list soluble insulin injection.

Many countries, on average 30 percent, also list mixed insulin products. WHO EMRO is the region with the highest percentage of countries listing all different types of insulin, including rapid and long-acting analogue insulin. In other regions less than 25 percent of countries list analogue insulin on their NEML.

[iii] Syria has been excluded from the since it does not specify the insulin category; Many countries list “Insulin rapid acting” that has been classifies as insulin soluble due to translation.
DPR Korea lists "insulin” and “intermediate acting”. “Insulin” has been classified has insulin short acting (soluble).

[iv] Syria has been excluded from the analysis since it does not specify the insulin category.
Many countries list “Insulin long acting” or “insulin lente” that has been classified as insulin intermediate acting due to translation.
Kenya lists “insulin intermediate, biphasic” that has been classified as insulin intermediate actin

Figure 5. Percentage of insulin types included in the NEML amongst different WHO Regions.

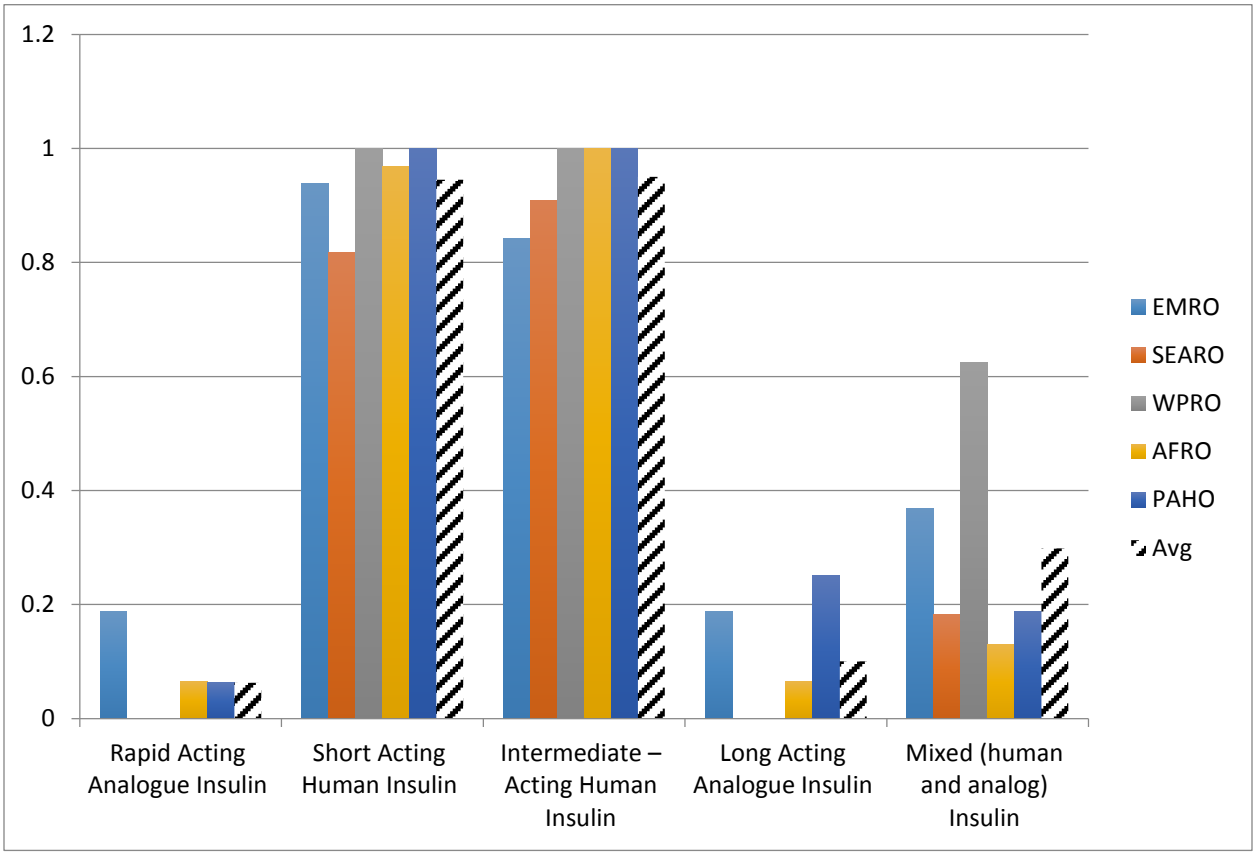


Table 15 describes the countries listing analogue insulin as part of their NEML. Overall, amongst 100 countries studied, only 15 countries list either or both rapid and/or long-acting analogue insulin. Saudi Arabia, Colombia and Mexico list the highest number types of rapid acting analogue insulin with each country at (n=3). Jordan, Saudi Arabia, Tunisia, Colombia, Mexico and Ghana list the highest number types of long acting analogue insulin with each country at (n=2).

Table 15. Number of different types of analogue insulin among LMIC.

Countries (n=16)	Analogue Insulin Rapid-Acting	Analogue Insulin Long-Acting	WHO Region
Bahrain	0	1	EMRO
Iran	1	1	EMRO
Iraq	0	0	EMRO
Jordan	0	2	EMRO
Oman	0	1	EMRO
Saudi Arabia	3	2	EMRO
Tunisia	1	2	EMRO
Argentina	1	0	AMRO
Colombia	3	2	AMRO
Ecuador	0	1	AMRO
Honduras	0	0	AMRO
Jamaica	0	1	AMRO
Mexico	3	2	AMRO

Trinidad and Tobago	0	1	AMRO
Uruguay	2	0	AMRO
Ghana	2	2	AFRO
Total countries listing analogue either rapid or long acting insulin	**9**	**13**	-

Among the different types of analogue insulin, long acting glargine insulin is the most frequently listed (n=10) (Table 16). The least listed type of analogue insulin is aspart (n=4). The long acting insulin detemir and rapid acting insulin are listed by approximately 40 percent of countries.

Table 16 describes the countries listing specific rapid and/or long acting analogue insulin as part of their NEML. Only the AFRO, EMRO and PAHO countries list analogue insulin on their NEML. Among the different types of analogue insulin, long acting glargine insulin (n=14) and rapid acting insulin *lispro a*re the most frequently listed (n=9) (Table 16). The analogue insulin least listed is the long acting detemir and rapid acting glusiline is listed by approximately 40 percent of countries.

Table 16. Analogue insulin types amongst LMIC.

Countries (n=16)	Rapid Acting Analogue Insulin			Long-Acting Analogue Insulin		
	Glulisine	**Aspart**	**Lispro**	**Detemir**	**Glargine**	**WHO Region**
Algeria	**0**	**1**	**1**	**0**	**2**	**AFRO**
Ghana	**0**	**1**	**1**	**1**	**1**	**AFRO**
Bahrain	0	0	0	0	1	EMRO
Iran	1	0	0	0	1	EMRO
Iraq	0	0	1	0	0	EMRO
Jordan	0	1	0	1	1	EMRO
Oman	0	0	1	0	1	EMRO
Saudi Arabia	1	1	1	1	1	EMRO
Tunisia	1	0	0	1	1	EMRO
Argentina	1	0	0	0	0	PAHO
Colombia	1	1	1	1	1	PAHO
Ecuador	0	0	0	0	1	PAHO
Honduras	0	0	1	0	0	PAHO
Jamaica	0	0	0	0	1	PAHO
Mexico	1	1	1	1	1	PAHO
Trinidad and Tobago	0	0	0	0	1	PAHO
Uruguay	0	1	1	0	1	PAHO
Total	**6**	**7**	**9**	**6**	**14**	-
% Total	**37.50%**	**43.75%**	**56.25%**	**37.50%**	**87.50%**	-

4.3 Inclusion of Insulin Products on Reimbursement Lists

The following part summarises the results of the comparison of Reimbursement Lists (RL) for high-income level countries with respect to the different types of insulin.

The most recent and available reimbursement lists for countries that are part of EMRO, WPRO, SEARO, AFRO, and EURO were eligible for the preliminary analysis. First, a comparison of all types of insulin included and excluded in WHO MEML with the RL was carried out. Second, the frequency and percentage of WHO medicines listed on the RL out of total WHO EML diabetes medications (100 percent = 2 insulin types are on the WHO MEML) was obtained. Finally, all insulin product presentations (volumes, dosages, etc.) of all types of insulin included in the RL were compared between different countries.

Table 17 shows the number of the most recent RL available in relation to the total number of countries in each region.

Table 17. Available RLs by WHO Region.

WHO Region	Available RL	Total number of HIC countries	Percentage of HIC countries analysed	Available RL in Countries
EURO	19	57	33%	Austria, Belgium, Croatia, Denmark, Estonia, Finland, France, Germany, Iceland, Ireland, Latvia, Netherlands, Norway, Poland, Romania, Serbia, Slovakia, Slovenia, Sweden
EMRO	1*	6	0%	Morocco (UMIC)
SEARO	0	0	-	N/A
WPRO	3	5	60%	Australia, New Zealand, South Korea
AFRO	1*	0	-	Ghana (UMIC)
AMRO	1	2	50%	Canada
Total	22	68	32.4%	

***included in the pilot study to perform comparison between RL and NEML

With few exceptions the high-income country reimbursement lists include all different types of insulins including analogue (Figure 6). This is very different from LMIC NEML as mention in the previous section.

Figure 6. Percentage of RLs that include insulin products.

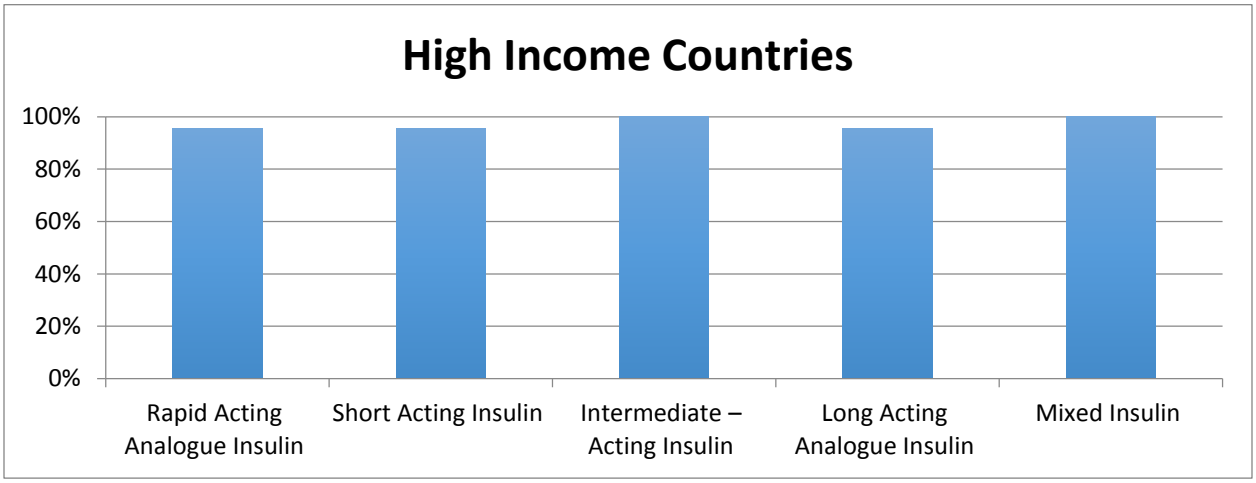


Table 18 describes the six countries omitting one or more types of insulin. Germany is the only country without any analogue insulin on its reimbursement list. Estonia is the only countries that do not list intermediate acting insulin.

Table 18. Insulin groups not reimbursed by high-income countries.

Countries (n=6)	Rapid Acting Analogue Insulin	Short Acting Insulin	Intermediate Acting Insulin	Long Acting Analogue Insulin	
Estonia	3	1	0	2	no human intermediate acting insulin
Finland	2	1	1	2	no glulisine
New Zealand	3	1	1	1	no detemir
Poland	3	1	1	1	no detemir
South Korea	3	1	1	1	no detemir
Germany	0	1	26	0	no rapid or long acting analogue insulin

Table 19 illustrates the total number of products among the different high-income countries based on insulin types. On average, each country lists about 47 types of insulin product forms, with mixed-insulin and rapid acting insulin having the highest average among all other types. The least frequently listed product presentation is from the human short acting insulin category.

Table 19. All insulin product presentations types amongst high-income countries.

Countries (n=23)	Total number of product presentations	Rapid Acting Analogue Insulin	Short Acting Insulin	Intermediate – Acting Insulin	Long Acting Analogue Insulin	Mixed Insulin
Australia	36	9	6	6	4	11
Austria	33	9	6	9	4	5
Belgium	39	9	10	4	4	12
Canada	35	9	4	4	5	11

Croatia	20	5	2	2	3	8
Denmark	54	21	5	9	3	13
Estonia	17	6	1	2	3	5
Finland	33	9	4	5	7	5
France	54	8	8	11	6	21
Germany*	265	0		26	0	
Iceland	19	7	1	4	4	3
Ireland	48	13	3	7	11	14
Latvia	19	6	2	3	3	5
Netherlands	60	15	7	7	5	23
New Zealand	27	8	4	4	3	8
Norway	25	11	2	4	4	4
Poland	40	5	7	4	3	18
Romania	33	7	5	5	4	12
Serbia	24	5	3	4	3	9
Slovakia	39	8	5	5	7	11
Slovenia	33	7	3	6	4	11
South Korea	25	9	1	2	3	6
Sweden	89	24	7	11	30	13
Average	**46.4**	**9.13**	**4.36**	**6.26**	**5.35**	**10.4**

*It is unclear if the RL of Germany provides comprehensive information (verification pending)

4.3 Discussion

4.3.1 Listing of Insulin Products on the NEMLs

Amongst the 138 LMICs countries in all five WHO Regions available for our study, we were able to access NEMLs for 73 percent (n=100) of the countries; making it one of the largest studies on a comparative analysis for diabetes medicines on LMICs.

Almost all LMICs list intermediate human insulin and short acting human insulin. It indicates that most countries give priority to these medicines for the treatment of diabetes, which is positive. At the same time, it is clear that the barriers to access to insulin are not due to its exclusion from the NEML.

Of the 100 countries in the LMIC study, 16 percent (n=16) listed analogue insulin as part of their NEML with WHO EMRO countries having the highest numbers of rapid and long acting insulin. The higher prevalence of diabetes and the relative wealth of the countries in comparison to other regions may explain the higher percentage. Amongst the countries with analogue insulin, Colombia, Saudi Arabia, Mexico and Ghana list more than one of each type suggesting that these countries are less selective in listing analogue. Except Ghana these are high- or upper-middle income countries with more resource available than lower middle income countries.

Since reimbursement lists for LMICs were not easily accessible this analysis focused on NEMLs. However, it needs to be acknowledged that NEMLs are limited in providing information on medicines procured and hence available under pre-paid financial schemes.

Our analysis is also limited by the quality of the information provided in the NEML. In about one percent of cases the type of insulin was not specified which is why we had to exclude those countries from the analysis (e.g. Syria). This is in line with the findings by Bazargani et al 2014 also found that some lists did not provide sufficient information on the insulin type (26).
The authors did a pilot comparative analysis on the difference between the listing of diabetes medicines on the RL in contrast to the NEMLs (Annex 3). Among the two countries analysed,

Ghana and Morocco, there were many discrepancies evident. Morocco tends to reimburse more medicines, including analogue insulin, whereas Ghana only includes analogue insulin as part of its NEML and no inclusion on its national RL. This suggests the disparities between the two lists, it concurs with previous evidence regarding the limited information that NEML can provide and how medicines might be procured or reimbursed differently at provincial or health care centre level (26).

It is recommended that NEMLs have greater consistency with respect to the way in which they denominate different insulin products. We suggest using the WHO ATC code framework. This could reduce misclassification errors due to the variety of NEMLs.

Although the large majority of countries include essential insulin to treat diabetes there are some areas for improvement. Many countries in the EMRO and AMRO region list a large number of human and analogue insulin products. With regards to insulin, NEMLs should avoid duplications; selection of only one medicine from a therapeutic class is usually recommended.

4.3.2 Insulin Products on the Reimbursement Lists

Overall, high income countries reimburse all types of insulin marketed which suggest that these countries have more resources and can afford being less selective about the inclusion of insulin products in the RL.

It is surprising that some countries do not list particular types of insulin. More research is needed into the reasons for not listing this essential type of insulin.

All RL analysed include the essential insulins recommended by WHO MEML. In contrast to low resource settings there is large number of products that each country has decided to reimburse. Under the assumption that analogue insulin is clinically equivalent to recombinant human insulin (27) limiting the inclusion to only human insulin could result in more efficient use of resources. Germany for instance, includes analogue insulin only if their price is comparable to human insulin products.

The sample in this report included only a selected number of high-income countries (n=20) which are not representative of high-income countries as a whole. For some countries it is unclear if the information is complete (e.g. Germany only human insulin reimbursed).

The inclusion of essential medicines for the treatment of diabetes is only the first step toward access. The majority of countries include insulin. There is room for improvement in terms of information on the type of insulin included.

5. Analogue Insulin versus Human Insulin Market Share

5.1 Introduction

A protocol had been developed and submitted to IMS Health to request data on insulin consumption (Annex 4). However, the authors of this report were unable to obtain the requested data. Only a small study on the percentage of analogue insulin out of total insulin market in high-and-middle income countries could be carried out.

5.2 Methods

The percentage analogue insulin consumption by year was calculated dividing the volume of analogue insulin in standard units by the total volume insulin consumption per year.

A stratified analysis was conducted by high- and middle-income countries. The underlying hypothesis was the following: country wealth measured by income would influence analogue consumption whereby high-income countries consume more analogue insulin.

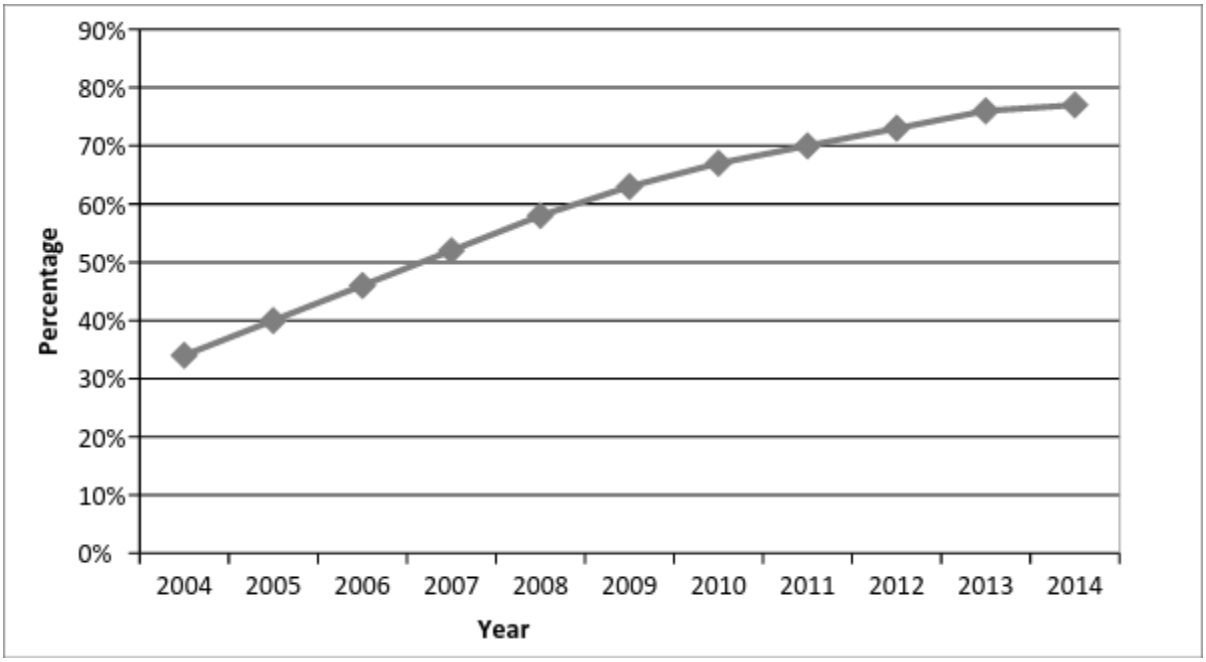
For middle-income countries public sector data is often not available. Hence, we confined the analysis to the out-of-pocket segments of the market assuming that private markets would be conform to out-of-pocket payment.

5.3 Results

Figure 7 and 8 present the percentage analogue insulin by country income group and reimbursement status. Key findings were:

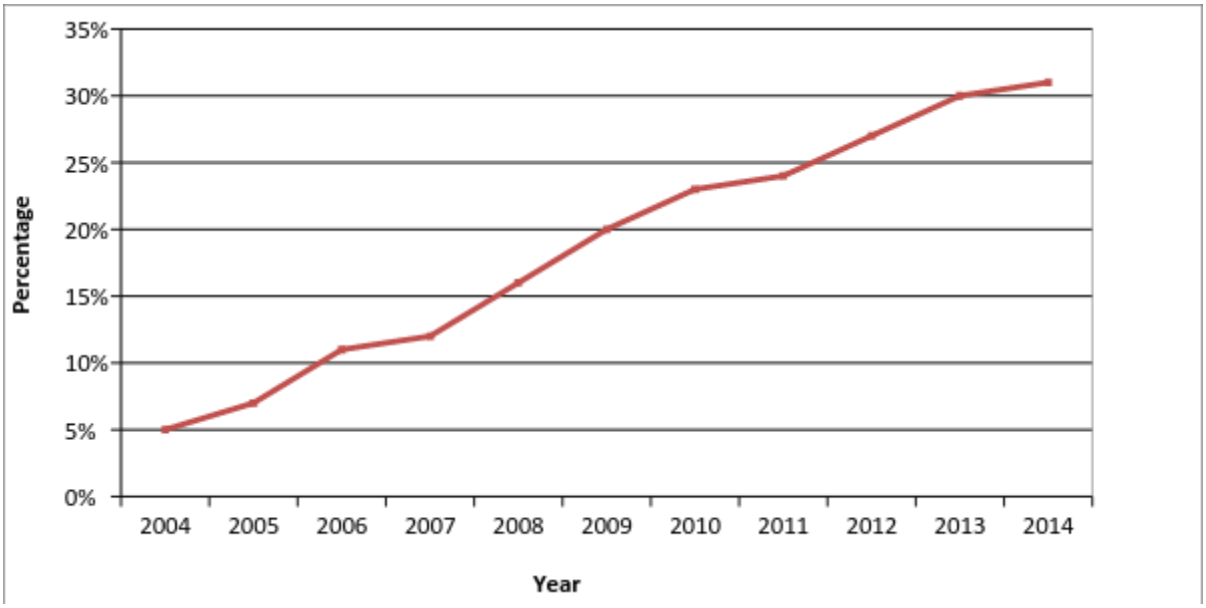
- Percentage analogue insulin consumption increases over time in high income countries from about 32 percent to nearly 80 percent between 2004 and 2014.

Figure 7. Percentage of analogue insulin sales by reimbursement status in a sample of high-income countries.



- Percentage of analogue insulin consumption is higher in high-income countries (more than double) than in middle-income countries.

Figure 8. Percentage of analogue insulin sales in a sample of middle-income countries.



5.4 Discussion

The findings presented needs to be interpreted with caution. Whereas for high-income countries IMS Health data captures reimbursed products, for middle income countries data covers largely private sectors where products are paid out-of-pocket. Hence, data of high and middle income markets are not directly comparable since they look at different market segments.

Consumption of analogue insulin products are increasing in all market segments. Given that in most settings analogue insulin products are more expensive than human insulin health expenditures have increased which results in higher tax burden, insurance premiums or individual household expenditures.

More analysis is needed to identify the drivers for increased consumption of analogue insulin in spite of the disagreement about their clinical benefits compared to human insulin.

6. Marketing Breaches
6.1 Introduction

The following analyses reports of the breaches of national marketing codes in ten countries: the US, the UK, South Africa, China, India, Russia, Australia, Columbia, Jordan, Thailand, and Kenya. While the UK and, to a lesser extent the US and Australia, have been praised for their effective regulatory system, other nations often lack much of the basic governmental and regulatory framework necessary to enforce their drug promotion guidelines. This is particularly important as Russia and India are both pharmerging markets, and represent two of the world's fastest growing economies and purchasers of pharmaceutical products. As these markets continue to expand, the ability of their regulatory agencies to adequately enforce drug policy will play a key role in controlling cost and access to medicine.

Together, approximately 209 million individuals with type 1, type 2 or gestational diabetes live in the countries included in this study (12). This makes up roughly 54 percent of people living with diabetes. China makes up nearly half of this sample, with just over 96 million of its citizens living with some form of diabetes, while the country with the lowest diabetic population included is Kenya, with 183,000 individuals affected (12).

Due to the high prevalence of diabetes in most of these countries, it is very important to ensure the appropriate use of insulin there. This paper aims to identify insulin-related drug promotion code breaches and their outcomes as a first step in this direction.

6.2 Methods

This study investigates insulin-related reported breaches in marketing codes by pharmaceutical companies in the UK, US, South Africa, China, India, Russia, Australia, Columbia, Jordan, Thailand, and Kenya. We conducted a systematic review of available news articles, legal documents and official press releases using both Google and the "cases" section of Lexis Nexis.

To standardise our search, we developed a series of key phrases that we used in the search process for each country. Each key phrase began with the words "[country name] insulin" and ended with the word "marketing", "breach", "lawsuit", "bribe", "illegal", and "corruption". In addition, we also incorporated as ending words company names, "Novo Nordisk", "Eli Lilly" and "Sanofi-Aventis", the world's three largest insulin producers, as well as insulin types "lispro", "aspart", "glulisine", "regular", "NPH", "glargine" and "detemir" (Annex 5). Furthermore, for our search focused on Columbia, we included the Spanish words "promoción" (promotion), "publicidad" (advertising) , "ilegal" (illegal), "cohecho" (bribe) and "corrupción" (corruption).

Documents were included in our data set whether or not the corresponding case went to trial, and whether or not a trial was won by the insulin-producer involved. The first one hundred Google results and all cases appearing in Lexis Nexis (2) were examined for each search.
The UK was an exception to this search method, as marketing breaches occurring in the country are publically available beginning in 2004 via the PMCPA (Prescription Medicines Code of Practice Authority) website (28).

Australia runs a regulatory authority similar to the PMCPA, the Therapeutic Goods Administration, but its publically available promotion complaint records extend only as far back as 2011. While these were considered, none of them related to insulin.

Google and Lexis Nexis search results were examined over a ten-year period from 1st January 2004 to 31st December 2014. Qualitative analytic categories for marketing breaches were created by one of the authors using the UK PMCPA code as a guideline. These categories are “drug promotion”, “representative conduct”, “information and claims”, and “marketing authorization”. Available data on code breaches were then filtered into the most appropriate categories.

6.3 Results

Our systematic review revealed four results from the US, ten results from the UK and two results from China (Table 20). No results were found from India, Brazil Russia, South Africa, Columbia, Thailand, Kenya, Jordan, or Australia, possibly because either the regulatory or reporting frameworks in these countries are not sufficient to consistently identify breaches and make data on the publicly available. The company most often in breach of marketing codes with regard to insulin products was Novo Nordisk with five breaches over the period of our review.

United States

Two lawsuits in the US, one involving Novo Nordisk and the other implicating Aventis, fell under the “information and claims” category. Novo Nordisk was sued by rival Sanofi in 2006 for disseminating false information in relation to Levemir, while Aventis was sued in 2008 by patients in claiming that they were not informed of the risks of developing tumours as a result of using Lantus. In both cases, the companies were cleared of any wrongdoing.

A second lawsuit filed against Novo Nordisk in 2005, categorized under both “drug promotion” and “representative conduct”, alleged that company sales representatives had paid Rite Aid pharmacists for the names of patients with diabetes in order to pitch them Novolog and Novolin. Novo Nordisk settled by paying the federal government $897,000 and the Medicaid plans of the four states involved $828,000 with three percent interest for four years.

Finally, a former Sanofi employee sued the company in 2014 for allegedly contracting Accenture and Deloitte consultants to induce pharmacists to buy Sanofi brand insulins in what she believed amounted to an illegal kickback scheme. This lawsuit is ongoing.

United Kingdom

Five complaints under the PMCPA code in the UK were related to “information and claims”. Three of these were filed in 2007 against Pfizer in relation to their Exubera product line. Exubera was an inhalable insulin product that was discontinued by the company in 2007. Two of these complaints were filed by general practitioners, one alleging that a promotional letter to physicians looked misleadingly like a communication from the National Institute of Health and Clinical Excellence, and a second complaining that an advertisement for the product did not accurately represent how large the product was. Only the second of these complaints was ruled a breach of code upon review by the PMCPA. The third complaint against Pfizer alleged that Exubera promotional material claimed with little supporting evidence that the product helped patients with diabetes maintain “long-term glycaemic control”. This complaint was eventually considered a breach of code. Fourth and fifth complaints in the “information and claims” category were filed against Novo Nordisk in 2006 and 2012, respectively. The first was issued after the company sent a letter to physicians beginning with the unreferenced phrase, "As you are probably aware the vast majority of patients with diabetes who require insulin are now initiated on analogue insulins", while the second involved the complainant receiving an unsolicited email for a symposium promoting the off-label use of Victoza in combination with

Levemir. A breach was ruled by the PMCPA in the first case, while no breach was found by in the second.

Two complaints were categorized under "representative conduct". The first, occurring in 2007, was filed against Eli Lilly after a sales representative threatened to discontinue funding for a hospital educational post unless sales of Eli Lilly products, including insulins, increased. This was ruled a breach. The second, also occurring in 2007, was brought against Sanofi-Aventis after a representative presented a flowchart from the American Diabetic Association suggesting that basal insulins such as Lantus second-line to metformin in patients with type 2 diabetes. No breach was ruled as the complainant had no proof the flowchart was shown.

One breach from the UK was related to the "marketing authorization" category. This was filed against Novo Nordisk in 2006 after the company ran an ad in Diabetes Breakthrough Magazine, which is sent to both general practitioners and non-physicians, with the phrase, "You need to be able to count on the company that supplies your medicine." This was not ruled a breach.

Two UK breaches related to two complaint categories. One, categorised under both "representative conduct" and "drug promotion", was filed against Eli Lilly in 2009 following a representative conducting a six-day diabetes training course at a local physician practice without the permission of the local diabetes treatment team and focused primarily on Eli Lilly insulins. The representative also took local physicians out for free meals. This was ruled a breach by the PMCPA. As second, categorised under both "representative conduct" and "information and claims", was filed against Sanofi in 2012 after a representative quoted unpublished evidence to hospital administrators that Novo Nordisk's Levemir had failed a non-inferiority trial with Sanofi's Lantus, and thus should be not be prescribed. The PMCPA ruled this as a breach.

China

Both cases identified in China were categorized under "drug promotion". Eli Lilly was probed in 2013 by the Chinese government after a whistle-blower suggested the company maintained a fund for bribing physicians to use its Humalog insulin product. That same year, the Chinese pharmaceutical firm Gan & Lee was the subject of a separate government probe for using a similar bribery tactics. No data were found as to the outcome of either of these cases.

India, Brazil, Russia, Columbia, South Africa, Thailand, Kenya, Jordan, and Australia

Under our methodology, there were no data found for insulin-related marketing breaches in these countries occurring between 2004 and 2014.

Table 20. Market breaches by type, country, and outcome.

Breach Category	Country	Company	Product(s)	Year	Description	Outcome	Breach/Lawsuit/Settlement
Representative conduct; Drug promotion	US	Novo Nordisk	Novolin & Novolog	2005	Realtor filed lawsuit on behalf of federal government and several states claiming sales	Company paid federal government $897,000 and state Medicaid $828,000 plus 3% interest for four years.	Lawsuit & Settlement

					representatives in four states paid Rite Aid pharmacists for names of patients with diabetes so they could pitch Novolin & Novolog to them.		
Drug promotion	US	Sanofi	All Sanofi insulin products	2014	Former employee claims being fired after refusing to sign contracts she believed were illegal kickback schemes. The contracts paid consultants Accenture and Deloitte to induce pharmacists to prescribe Sanofi branded insulins rather than generics.	Ongoing	N/A
Information and claims	US	Novo Nordisk	Levemir	2006	Sanofi sues Novo Nordisk for disseminating false claims including that Levemir is "a 24-hour insulin", is a "once-daily insulin", is "predictable" and causes less weight gain than NPH.	Court finds that the complaints by Sanofi are not legally founded and that Novo Nordisk's marketing should not be corrected.	Denial of preliminary injunctive relief to Sanofi.
Information and claims	US	Aventis	Lantus	2008	Plaintiffs claim Aventis failed to inform consumers of risk of Lantus, and that use of the drug caused a tumour that	Court finds that Avantis did adequately inform consumers.	Motion for summary judgement by Aventis is granted.

					eventually killed one of the plaintiffs.		
Information and claims	UK	Novo Nordisk	All Novo Nordisk insulin products	2006	Novo Nordisk sent a letter to physicians announcing discontinuation of animal insulin products and beginning with the phrase "As you are probably aware the vast majority of patients with diabetes who require insulin are now initiated on analogue insulins". This is arguably untrue and could promote other Novo Nordisk insulin products.	Prescribing information was provided. The claim did not refer to a published study, and thus did not need to be referenced.	No breach
Marketing authorisation	UK	Novo Nordisk	All Novo Nordisk insulin products	2006	Novo Nordisk ran an advertisement in Diabetes Breakthrough Magazine stating "you need to be able to count on the company that supplies your medicine." Complaining party stated that because this was not solely sent to healthcare professionals, it was a form of DTC advertising.	The advertisement did not encourage patients to ask their doctor to prescribe a specific medicine, although it did endorse Novo Nordisk insulin products.	No breach
Representat	UK	Eli Lilly	All	200	Due to sales	Representative was	Breach

ive conduct			Eli Lilly insulin products	7	pressure, representative threatened discontinuation of funded educational post if UK hospital did not increase sales of Eli Lilly insulin products.	dismissed and educational post was funded for two additional years. Lilly successfully claimed rep. acted independently of company knowledge.	
Information and claims	UK	Pfizer	Exubera	2007	Promotional material claimed Exubera maintained "long-term glycaemic control", despite limited evidence to support this statement.	N/A	Breach
Representative conduct	UK	Sanofi-Aventis	Lantus (glargine), Acomlia (rimonabant)	2007	Complaining party was concerned with a representative presenting a flowchart from American Diabetic Association that advised the use of basal insulins like Lantus second line to metformin in patients with type 2 diabetes.	Complaining party had no proof representative presented flowchart or provided unsubstantiated information.	No breach
Information and claims	UK	Pfizer	Exubera	2007	General practitioner complained that a promotional letter for Exubera looked like an official communication from the National	The product logo was used on the letter, and the colour scheme was not similar to NICE communications. The letter contained the phrase "promotional material enclosed."	No breach

					Institute for Health and Clinical Excellence. The letter also did not clearly lay out the restrictions for Exubera use.		
Information and claims	UK	Pfizer	Exubera	2007	General practitioner complained that a full-page advertisement for Exubera was misleading because it did not give an accurate impression of how large and inconvenient the inhaler device was.	The size of the inhaler was not accurately portrayed by the advertisement. It was displayed next to a woman's head that took up most of the page, making it look relatively small.	Breach
Representative conduct; Drug promotion	UK	Eli Lilly	Eli Lilly type 2 diabetes insulin products	2009	Eli Lilly representative set up a six-day diabetes training course at a physician practice without the permission of the local diabetes treatment team. Trainers discussed primarily Eli Lilly products. Representatives also took physicians out for free meals.	Concern regarding inappropriate educational practices, especially concerning the inordinate promotion of Eli Lilly products.	Breach
Information, claims	UK	Novo Nordisk	Detemir (Levemir), Victoza	2012	Complaining party received unsolicited email from Novo Nordisk promoting a symposium that suggested the off label use	Concern regarding the reception of unsolicited promotional materials. However, the symposium was ruled not to promote off labelled use of drugs.	Breach

					of Victoza in combination with Levemir. No prescribing information was provided for Levemir.		
Representative conduct; Information and claims	UK	Sanofi	Levemir (detemir, Novo Nordisk), Lantus (glargine, Sanofi)	2012	Sanofi representative disparaged Levemir (Novo Nordisk) and quoted unpublished evidence at a hospital diabetes meeting. Representative stated that Levemir had failed a non-inferiority trial against Lantus, and thus should not be prescribed.	Concern regarding lack of clinical evidence and representative's statement that "Lantus should be the only choice when a once-daily basal insulin is needed."	Breach
Drug promotion	China	Eli Lilly	Humalog	2013	Probe by government and whistle-blower find that Lilly had $5 million fund for bribing Shanghai doctors to prescribe Humalog. Doctors were paid from $33 to $49 per new patient.	N/A	Breach
Drug promotion	China	Gan & Lee	All Gan & Lee insulin products	2013	Probe by government and whistle-blower suggested that company spent $130 million in bribes to doctors since 2008.	N/A	Breach

6.4 Discussion

Our results clearly show a number of reported insulin marketing breaches in the United States and the United Kingdom. While these countries have shown the willingness to punish companies in breach of drug promotion codes, the huge financial rewards of outcompeting competitor products in these markets nevertheless makes them a likely location for code breaches to occur.

Due to the political realities the power of the Chinese equivalent of the FDA (SFDA) to regulate effectively is determined in part by the political will behind the ruling party's anti-corruption measures. Both of the cases included in this study occurred during a broader government crackdown on corruption in the healthcare industry. No results were available regarding the outcome of either case, and it is not known if either company involved was punished – and if so, how severely – for their actions. Consequently, it is difficult to determine whether our lack of results is because of poor regulatory oversight, or whether companies promoting insulin in China are not frequently breaching the country's drug promotion code.

No results were found for India, Brazil, Russia, Colombia, South Africa, Thailand, Kenya, Jordan, and Australia. This makes it difficult to determine whether the regulatory frameworks in these countries are insufficient to provide effective oversight, or if the companies operating within their borders are not violating drug promotion guidelines with regard to insulins.
Of the 16 cases identified, five (31 percent) involved Novo Nordisk. This is not surprising, as Novo Nordisk is the world's largest producer and supplier of insulin, and may have more opportunities and incentives to market products aggressively. While three cases (19 percent) involved Pfizer, all of these related to its discontinued Exubera inhaled insulin product. No currently marketed Pfizer insulin products were involved in promotional code breaches. Eli Lilly was also involved in three cases (19 percent), all of which were found to be breaches of national drug promotion codes. Sanofi was cited twice (13 percent), while Aventis, Sanofi-Aventis and the Chinese pharmaceutical firm Gan & Lee were all cited once (6 percent).

Seven (45 percent) of the 16 identified breaches were categorised solely under "information and claims", making this the most common form of code violation. Three (19 percent) related to "drug promotion", including both cases in China, while two (12 percent) were placed in the "representative conduct" category. Two additional cases (12 percent) fell into both the "drug promotion" and "representative conduct" categories simultaneously. One case (6 percent) was identified in the "marketing authorization" category, as well as in the "representative conduct" and "information and claims" categories simultaneously.

While our search was extensive, there were limitations. Primarily, we used only two search engines, limiting the results of our study.

Further studies are needed to evaluate and analyse the effectiveness of the regulatory mechanisms within the countries included in this study, specifically with regard to their ability to uphold strict drug promotion guidelines. Analysis of appropriate use of medicines for diabetes, as well as of the quality of drugs available to patients on a national level, should be considered in order to complement research on promotion code breaches.

7. Comparison of the Efficacy and Safety of Analogue versus Human Insulin

7.1 Introduction

Insulin is broadly divided into two categories: conventional and analogue. Conventional insulins - neutral protamine hagedorn (NPH), regular human insulin - are generally less expensive than many types of analogue, but do not mimic the pattern of basal and postprandial endogenous secretion of insulin naturally found in the human body. Insulin analogues, although generally more expensive, do not have this limitation. Additionally, analogues are available within the body for both a shorter time insulin lispro, insulin aspart, and insulin glulisine, and a longer time insulin glargine and insulin detemir, - than conventional insulins are, potentially allowing for greater patient convenience during treatment. However, some concerns exist regarding the long-term safety of analogue insulins, particularly regarding the potential association between insulin glargine and a rise in cancer risk. While systematic reviews and meta-analyses of the comparative effectiveness and the short and long-term safety of both categories of insulin have been published, the literature is limited. This paper aims to update the existing meta-analysis literature by reviewing existing meta-analyses and individual trials comparing conventional and analogue insulins conducted between January 2011 and April 2015.

7.2 Objective

To conduct a systematic review of the literature comparing the clinical efficacy and both short- and long-term safety of types of insulin analogue to regular human insulin in patients with type 1 and 2 diabetes.

7.3 Methods

A systematic review of the literature was performed in accordance with PRISMA guidelines.

Keywords

Clinical efficacy and short-term safety studies were identified via a comprehensive search using combinations of keywords, including “lispro”, “aspart”, “glulisine”, “detemir”, “degludec”, glargine”, “human”, “regular”, “NPH”, “Type 1 diabetes”, “Type 2 diabetes” and “head-to-head”. Long-term safety studies were identified using the phrase “long-term safety” followed by the names of analogue and human insulins.

Databases

The databases searched for the review were PubMed Central, Medline, and Google Scholar.

Publication Period

Studies performed between January 2011 and April 2015 were included in the review, as were six pre-existing meta-analyses from 2009 to 2014.

Limits

Studies and meta-analyses were included without language restrictions.

A reviewer initially selected the studies and pre-existing meta-analyses by reviewing available titles and abstracts. The studies included randomized control trials and crossover trials of

patients of all ages with either type 1 or type 2 diabetes receiving either human or analogue insulin. Types of analogue were rapid acting (lispro, aspart or glulisine) or long acting (glargine, detemir, or degludec).

A reviewer also performed data extraction for relevant studies in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (29) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Extracted data included title, journal, year, study design, type of diabetes, drug regimen, outcome measure(s), study sample and population, and outcome(s).

Two primary outcome measures were extracted from the literature: clinical efficacy, defined as a change in glycated haemoglobin (HbA1c) concentration from study start to study termination, and safety, including overall hypoglycaemia episodes and nocturnal hypoglycaemia episodes. These were defined by the number of patients with at least one episode during a study for long-acting insulin, or the number of patients with at least one episode during a month for short-acting insulin.

7.4 Results

Meta-analyses

We initially identified six meta-analyses comparing the efficacy and safety of human insulin to analogue insulin (Table 21).

Two meta-analyses included patients with type 1, type 2 and gestational diabetes. Singh et al. (2009) found *minimal* benefits in HbA1c concentrations across comparison groups. Differences in hypoglycaemic event reduction were also inconsistent (30). Siebenhofer et al. (2009) also found inconsistent benefits for both HbA1c concentration and hypoglycaemic event occurrence (31). Both studies concluded their data was insufficient to recommend analogue over human insulin.

Two reviews including only type 2 diabetic patients separately concluded that, while types of analogue did decrease severe and nocturnal hypoglycaemia, they did not decrease HbA1c compared with human insulin (32,33).

Finally, one review including only type 1 diabetic patients found no benefits in HbA1c or hypoglycaemic event reduction for types of analogue (34).

Contrary to other meta-analysis Tricco et al., 2013 found statistically significant reductions in both (35). However, one of the HbA1c benefits reached the 0.5 percent benchmark for clinical efficacy, and hence, cannot be used to recommend analogue insulin use. Moreover, differences in HbA1c concentration have not been shown to reduce macro-vascular complications in randomised control trials. The differences were not statistically significant when including predictive trials and the studies included in the meta-analysis were brief, with a mean duration of 14 to 26 weeks, and a low of four weeks. Additionally, 20 of 27 the randomised controlled trials (RCTs) included in this meta-analysis received funding from pharmaceutical companies. Finally, the study pooled results from randomised and non-randomised trials, which was not discussed by the authors as a potentially problematic issue.

Individual Trials

We also identified 15 head-to-head randomized control or crossover trials conducted between January 2011 and April 2015 comparing human insulin to long- and short-acting types of analogue (Table 22). Six studies compared glargine with NPH, five studies compared detemir with NPH, one comparing aspart to regular human insulin and four comparing more than one analogue insulin against NPH and/or regular human insulin. Of the 15 studies, six reported receiving industry funding, while a pharmaceutical company supplied one additional study with free insulin.

Glargine vs. NPH

All identified studies found no significant differences in HbA1c concentration after treatment with glargine compared to NPH. Glargine was consistently shown to provide greater protection against both severe and nocturnal hypoglycaemic events. One study found that glargine caused greater weight gain among type 2 diabetes patients.

Detemir vs. NPH

None of the identified studies showed a significant difference in HbA1c concentration between detemir and NPH treatment groups. Two studies found that severe and nocturnal hypoglycaemic were significantly less common on detemir, while one did not find a significant difference. A fourth study did not consider this outcome.

Aspart vs. Regular Human

One study showed 48-hour mean glucose levels to be lower with aspart compared to regular human insulin in 12 hospitalised patients with type 2 diabetes. No patients experienced severe hypoglycaemia on either treatment regimen.

Long-term Safety

We identified two systematic reviews and meta-analyses of the available literature addressing the long-term use of analogue insulins and a rising risk of cancer incidence (Table 23). One review examining type 2 diabetes patients found no clear evidence of an increased risk of cancer incidence, especially considering the confounding effect obesity (36). The second review did find an increase in the risk of breast cancer for insulin glargine users compared to users of other insulins, including types of analogue and human insulin, but also found a decreased risk of colon cancer for insulin glargine users (37). Both reviews recommended further studies before drawing clinical conclusions.

We also included five individual trials – four large cohort studies and one large retrospective cohort study all using either national registries or hospital discharge records - examining this potential association. Two large cohort studies comparing cancer incidence among insulin glargine and human insulin users found no significant difference between the two groups (38,39). A third cohort study also comparing glargine with human insulin found a lower risk of general malignancy amongst glargine users, but a heightened risk of breast cancer incidence. The final included cohort study, examining women over the age of 40 with type 2 diabetes, found no difference in cancer risk between glargine and other insulins for the first five years after initiation of a therapy, but did find a significant difference during the next five years. The included retrospective cohort study, also examining type 2 diabetes patients, found no significant different in cancer risk between glargine and long/intermediate acting human insulins.

7.5 Discussion

Analysis of the trials included in our review suggest that conventional insulins and types of insulin analogue minimally different in the treatment of type 1, type 2 and gestational diabetes. None of the other 14 studies comparing either detemir or glargine insulins to NPH showed significant difference in HbA1c levels. One study comparing aspart and regular human insulin did report slightly higher HbA1c levels with conventional insulin. However, this study observed an unusually small sample of 12 patients, all of whom were hospitalised throughout the study. Additionally, the difference in HbA1c concentration between the analogue insulin and conventional insulin groups in this study was smaller than the minimally required difference to establish clinical significance.

We did observe from the studies advantages for types of analogue insulin compared to conventional insulins in preventing severe and nocturnal hypoglycaemic events. Glargine consistently protected against these events compared to NPH, while two of three studies comparing detemir to NPH found detemir to be significantly more effective in preventing them. A small study comparing aspart to regular human insulin did not report any severe hypoglycaemic events for either treatment regime.

From reviewing the trials we did not observe consistent, significant long-term safety issues regarding analogue insulin in comparison with intermediate or long-term human insulins. While cancer incidence is commonly studied in relation with long-term insulin use, neither of the systematic reviews and meta-analyses we identified found a significantly higher risk of malignancies among analogue users compared to human insulin users. Moreover, of the five individual trials we identified, three did not find a significantly higher risk of cancer incidence. Of the two that did, one found a higher cancer risk among glargine users compared to users of other analogue or human insulins, but only five years or more after beginning therapy. The other found a lower risk of malignancies in general amongst glargine users compared to human insulin users, and a higher risk of breast cancer. The variation in these results, combined with the confounding issues caused by the common diabetic comorbidities including obesity, suggest this is an important area for further study.

VigiAccess, a medicine database run by the WHO Collaborating Centre for International Drug Monitoring lists 34,351 adverse drug reaction records for insulin glargine, compared with 19,726 for human insulin. However, it is not clear from the database which of these adverse reactions are short-term and which are long-term.

One study found that glargine caused greater weight gain among type 2 diabetes patients compared to NPH. None of the other included studies examined this variable.
None of the included studies examined the long-term clinical effects of diabetes or diabetes mortality rates.

Table 21. Systematic reviews and meta-analyses of the clinical efficacy and safety of analogue versus human insulin.

Title	Journal	Year	Product(s)	Outcome Measure(s)	Sample Size	Outcome(s)
Efficacy and safety of insulin analogues for the	CMAJ	2009	Aspart, Lispro, Detemir, Glargine, NPH,	Change in HbA1c level, hypoglycaemia control, complications and	68 randomized controlled trails comparing	Minimal HbA1c differences between rapid-acting analogues and regular human insulin in adults with type 1 diabetes (lispro: -0.09%,

managem ent of diabetes mellitus: a meta-analysis. (30)			Regular Human	adverse effects.	rapid-acting insulin analogues to conventional insulins, and 49 randomised control trials comparing long-acting insulin analogues to conventional insulins. All studies were conducted before April 2007.	aspart: -0.13%) and type 2 diabetes (lispro: -0.03%, aspart: -0.09%). Very small differences between long-acting analogues and NPH among adults with Type 1 diabetes (glargine: -0.11%, detemir: -0.06%) and Type 2 diabetes (glargine: -0.05%, detemir: 0.13%). Hypoglycaemia reduction an control benefits overall were inconsistent.
Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus (31)	Cochra ne Library	200 7	Lispro, Aspart, Glulisine, Regular Human	Change in HbA1c level, number of severe (requiring help) and non-severe hypoglycaemic episodes, quality of life assessment	8274 participants across 49 RCT's and crossover trials for type 1 and type 2 diabetes. Studies were included if they were conducted before 20th September 2005	In patients with Type 1 diabetes, mean difference in HbA1c was -0.1% (95% CI -0.2 to -0.1) in favour of analogues. In patients with Type 2 diabetes, mean difference in HbA1c was 0.0% between insulin analogues and regular insulin. Incidence of severe hypoglycaemic episodes was not significantly different between insulin analogues and regular insulin for either type 1 or type 2 diabetes.
Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus (32)	Cochra ne Library	200 7	Glargine, Detemir, NPH	Change in HbA1c level, severe and nocturnal hypoglycaemia events.	8 RCT's or crossover studies (2001 – 2006), 6 using glargine and 8 using detemir, investigating 2293 patients (mean age 55-62 years) with type 2 diabetes. Studies lasted between 24 and 52 weeks.	Insulin glargine and insulin detemir almost identically effective compared to NPH insulin in HbA1c control. Significantly fewer severe or nocturnal hypoglycaemic episodes with treatment with glargine or detemir compared to NPH.
Newer agents for	Heath Technol	201 0	Glargine, Detemir,	Change in HbA1c level, frequency of	15 trials for glargine and 4	Glargine and detemir were equivalent to NPH in terms

blood glucose control in type 2 diabetes: systematic review and economic evaluation (33)	ogy Access		NPH	hypoglycaemic events, nocturnal hypoglycaemia, cost.	for detemir, both in comparison with NPH.	of glycaemic control (HbA1c), but showed statistically significant improvements in severe and nocturnal hypoglycaemia events. NPH was cheaper than either analogue, costing 468 pounds annually compared to 634 and 714 pounds for glargine and detemir respectively.
Insulin analogues versus human insulin in type 1 diabetes: direct and indirect meta-analysis of efficacy and safety (34)	BJPS	2013	Glargine, Detemir, Aspart,Llistpro, Glulisine, NPH, Regular Human	Change in HbA1c level and overall safety measures (# of patients with hypoglycaemia episodes or nocturnal hypoglycaemia episodes during study (long-acting) or a during a month (short-acting).	16 articles for long-acting insulin analogues. Includes 5,733 patients receiving short-acting analogue and 4,771 patients receiving long-acting or NPH insulin.	No significant changes in HbA1c values for once-daily glargine and detemir compared to NPH and glargine vs. detemir. Lower HbA1c values for twice-daily detemir vs. NPH. No significant differences btw. Detemir and glargine alone. Aspart more effective compared with regular insulin, but lispro and glulisine are not. No significant safety differences.
Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and meta-analysis (35)	BMJ	2014	glargine, detemir, NPH	Change in HbA1c level, severe hypoglycaemia episodes, weight gain.	39 articles (27 RCT's including 7496 patients from 4 to 104 weeks in length) for glargine vs. NPH (10), detemir vs. NPH (11) or detemir vs. glargine (3). Mean age 28 to 47 years.	Glargine, detemir once daily and detemir twice daily all decreased HbA1c compared to NPH (mean difference -0.39%). Long-acting insulins significantly decrease severe hypoglycaemic events compared to NPH and resulted in differences in weight gain.

Table 22. Individual head-to-head trials on the clinical efficacy and safety of analogue versus human insulin.

Title	Journal	Year	Product(s)	Outcome Measure(s)	Sample Size	Outcome(s)
Comparison of daily glucose excursion by continuous glucose monitoring between type 2 diabetic patients receiving biphasic insulin aspart 30 or biphasic human insulin 30 (40)	Journal of Diabetes Investigation	2011	Aspart, Regular Human	48-hour mean glucose levels and mean amplitude of glucose excursions	12 hospitalised patients with Type 2 diabetes	Average glucose level and mean amplitude of excursions significantly lower with aspart, including postprandial. Hypoglycaemia not observed with either treatment.
Comparison of human insulin analogues on hypoglycaemia and metabolic variability in type 1 diabetes using standardized measurements (HYPO score and Lability Index) (41)	Acta Diabetologica	2013	Aspart, Glargine, NPH, Regular Human	HYPO score, Lability Index, HbA1c % change, nocturnal and non-nocturnal hypoglycaemic events	47 patients (21 human insulin: mean age 35, mean HbA1% 7.5; mean HYPO score 223, mean LI 89.8; 26 analogue insulin: 36, 7.5%, 149, 77.4).	HYPO score was significantly lower in analogue group. Nocturnal and non-nocturnal hypoglycaemic events were significantly lower in analogue group. LI was not significantly different. HbA1c % change was not significantly different.
Addition of insulin glargine or NPH insulin to metformin monotherapy in poorly controlled type 2 diabetic patients decreases IFG-I bioactivity similarly (42)	Diabetologia	2012	Glargine, it's metabolites, IGF-I, NPH	HbA1c % change, IGF-I bioactivity and total serum IGF-I levels measured via IGF-IR KIRA Assay	110 poorly controlled, insulin-naïve, type 2 diabetes patients previously receiving Metformin monotherapy.	HbA1c % change was similar in both treatment groups. IGF-I bioactivity was similar in both treatment groups at both baseline and at study termination.
Cerebral Blood Flow and Glucose Metabolism in Appetite-Related Brain Regions in type 1 Diabetic Patients After Treatment with Insulin Detemir and NPH Insulin	Diabetes Care	2013	Detemir, NPH	HbA1c % change, fasting insulin, blood glucose levels, weight gain, CBF, CMRglu	28 males with well-controlled Type 1 diabetes (mean age = 36.9 years, BMI = 24.9, A1c = 7.5)	HbA1c % change, fasting insulin and blood glucose levels were statistically similar across treatments at study termination. CBF was higher

(43)						in brain regions involving appetite regulation. No difference in CMRglu observed.
Maternal Efficacy and Safety Outcomes in a Randomized, Controlled Trial Comparing Insulin Detemir with NPH Insulin in 310 Pregnant Women with Type 1 Diabetes (44)	Diabetes Care	2012	Detemir, NPH	Change in HbA1c levels, fasting plasma glucose, major (patient unable to treat self) and minor (patient able to treat self) hypoglycaemic events - all measured at 36 weeks	310 type 1 diabetes, pregnant women. All subjects had been treated with insulin for at least 12 months prior to randomisation.	Change in HbA1c levels and frequency of major and minor hypoglycaemic events were not statistically different across treatments. Detemir resulted in significantly lower fasting plasma glucose.
A Retrospective Study Comparing Neutral Protamine Hagedorn Insulin with Glargine as Basal Therapy in Prednisone-Associated Diabetes Mellitus in Hospitalized Patients (45)	Endocrine Practice	2012	Glargine, NPH	Fasting blood glucose, mean daily blood glucose concentration, median daily blood glucose concentration, number of hypoglycaemic episodes	120 hospitalised patients over age 18 receiving prednisone (60 NPH, 50% w/ type 2 diabetes; 60 Glargine, 52% Type 2 diabetes)	Results across treatment groups were similar regarding all key outcomes. No statistically significant differences. NPH doses were lower than Glargine doses.
Starting bedtime glargine versus NPH insulin in poorly controlled Type 2 diabetic patients with various hyperglycaemia types (fasting type or postprandial type) (46)	Acta Diabetologica	2014	Glargine, NPH	Change in HbA1c level, body weight, final insulin dose	109 type 2 diabetic patients (mean age = 56 years) given metformin with either NPH (n=49) or Glargine (n=60) at bedtime. Doses were raised until reaching target fasting plasma glucose levels (<5.5 mmol/l). Groups were further subdivided	No difference between glargine and NPH regarding changes in HbA1c levels. Hyperglycaemia subdivision not helpful in predicting which type of insulin will be more appropriate.

					into "fasting type" (fasting plasma glucose/ glycosylated haemoglobin ratio > 1.3) or "postprandial type) (<1.3)	
Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: insulin glargine versus neutral protamine hagedorn insulin in insulin-naïve people with type 2 diabetes (47)	Diabetes, Obesity and Metabolism	2015	Glargine, NPH	Change in HbA1c level, nocturnal hypoglycaemia events.	701 patients (mean age = 57 years, BMI = 29.8, HbA1c level = 8.2%), 349 on NPH and 352 on Glargine	No significant differences in HbA1c values at treatment end between NPH and glargine patients. Significantly lower (48% less) nocturnal hypoglycaemia events for glargine patients.
A Randomized Clinical Trial of Insulin Glargine and Aspart, Comparted to NPH and Regular Insulin in Children with Type 1 Diabetes Mellitus. (48)	Iranian Journal of Pediatrics	2014	Aspart, NPH, Glargine, Regular Human	Change in HbA1c levels, mean fasting blood glucose, lipid profile	40 patients, all receiving NPH and regular insulin pre-trial. Twenty randomised to either glargine and aspart (mean age = 8.1) or NPH and Regular (mean age = 8.6).	No significant differences in HbA1c changes, mean fasting blood glucose changes, or lipid profile changes between treatment groups.
Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with Type 1 diabetes mellitus (49)	Pediatric Diabetes	2011	Detemir, NPH	HbA1c change, number of nocturnal and non-nocturnal hypoglycaemic events, fasting plasma glucose levels, adverse events	82 subjects (Detemir: 42, mean age 4.3; NPH: 40, mean age 4.5) ages 2- 5 yr with Type 1 diabetes.	No statically significant differences in glycaemic control (HbA1c). Greater fasting glucose reduction, hypoglycaemia episode rates and adverse event rate than NPH.
Insulin glargine compared to NPH among insulin-naïve US inner city, ethnic	Diabetes Research and Clinical	2011	Glargine, NPH	HbA1c levels, mean fasting and pre-supper glucose	85 subjects randomised to receive bedtime NPH (n=30, mean	No significant differences in changes in HbA1c, fasting or pre-supper

minority Type 2 diabetic patients (50)	Practice			readings, nocturnal hypoglycaemia episodes and weight gain.	age 53.2), bedtime glargine (n=30, mean age 50.3) or morning glargine (n=25, mean age 53.0). 82% of subjects Hispanic, but subgroups randomised by race.	glucose readings between treatments. Weight gain greater with glargine compared to NPH.
A randomized trial comparing the rate of hypoglycaemia - assessed using continuous glucose monitoring - in 125 preschool children with Type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study) (51)	Pediatric Diabetes	2013	Glargine, NPH	HbA1c changes, event rate of composite hypoglycaemia (symptomatic hypoglycaemia, low CHM excursions (<3.9 mmol/L)) or low finger stick blood glucose. Primary endpoint was non-inferiority of glargine with NPH.	125 patients (mean age 4.2 years) randomized to either glargine (n=61, mean HbA1c = 8.0%)) or NPH (n=64, mean HbA1c = 8.2%)). Glargine patients received once-daily injections. NPH patients usually received twice-daily injections.	No statistically significant differences in outcome measures across treatments. 95% CI's for incidence ratios all include 1.00. Non-inferiority not established.
Efficacy of insulin detemir comparted to insulin NPH on glycaemic control in Indian children with Type 1 diabetes (52)	Journal of Diabetology	2014	Detemir, NPH	HbA1c levels, mean fasting blood glucose, mean glucose levels, number hypoglycaemic episodes	100 Indian children with type 1 diabetes randomized to either detemir once-daily (n=50, mean age 8.02) or NPH twice-daily insulin (n=50, mean age 8.1).	No statistically significant differences in HbA1c levels, mean fasting glucose or mean blood glucose levels between groups at study endpoint. Hypoglycaemic events were significantly less common on detemir.

Table 23. Individual studies and reviews on the long-term safety of analogue insulins.

Title	Journal	Year	Study Type	Product(s)	Outcome Measure(s)	Sample Size	Results
Glargine safety, diabetes and cancer (36)	Expert Opinion on Drug Safety	2013	Systematic review and meta-analysis	Any insulin products	Cancer incidence	Relevant meta-analyses and individual studies from 2009 to 2013 examining the association between Type 2 diabetes, insulin use and cancer	There is no clear evidence that insulin use in Type 2 diabetes causes a significant increase in cancer risk, especially considering the confounding effect of obesity
Use of insulin and insulin analogues and risk of cancer – systematic review and meta-analysis of observational studies (37)	Current Drug Safety	2013	Systematic review and meta-analysis	Any insulin products (analogues and non-analogues)	Cancer incidence	34 studies examining the risk of insulin use on cancer incidence	Glargine insulin users had an increased risk for breast cancer and a decreased risk of colon cancer compared to non-glargine insulin users.
Cancer Incidence Among Those Initiating Insulin Therapy With Glargine Versus Human NPH Insulin (38)	Diabetes Care	2013	Cohort	Glargine, NPH	Cancer incidence (defined as having 2 claims for cancer within 2 months)	43,306 patients initiating glargine and 9,147 initiating NPH from the MORE[2] Registry followed for 1.2 years. Subjects did not have an insulin prescription for 19 months prior to the study.	Patients initiating glargine did not have a significantly increased risk of any kind of cancer compared to those initiating NPH over the same period.
Insulin glargine and risk of cancer: a	Diabetologia	2012	Cohort	Glargine, NPH	Cancer incidence,	A random 1/97 permanent	There was no excess risk of

cohort study in French National Healthcare Insurance Database (39)					mortality incidence	sample of the French national healthcare insurance system database from January 2003 to June 2010 including only patients with type 2 diabetes. Subjects used either glargine (2,273-3,125 patient years) or NPH (614-2,341) exclusively	cancer in type diabetic patients on insulin glargine alone compared with those on NPH alone.
Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: results from a large population-based follow-up study (53)	Diabetologia	2012	Cohort	Any insulin	Cancer incidence	19,337 insulin (analogues and human) users enrolled using hospital discharge records in the Netherlands.	Glargine use was associated with a lower risk of malignancies in general compared to human insulin. However, a higher risk of breast cancer was also found.
Cancer Risk Associated with Insulin Glargine among Adult Type 2 Diabetes Patients – A Nationwide Cohort Study (54)	PLoS One	2011	Retrospective cohort	Glargine, Intermediate/long -acting human insulin	Cancer incidence	Patients with type 2 diabetes initiated with either glargine (10,190) or human insulin (49,253) with an average of 526 and 754 days of follow up, respectively.	Insulin glargine did not significantly increase the risk of overall cancer incidence compared with human insulin.
Long-term effects of	Diabetologia	2011	Cohort	Glargine, other	Breast cancer	15,227 women -	The risk of breast

insulin glargine on the risk of breast cancer (55)				insulins	incidence	4,579 glargine on glargine, 10,648 on other insulins - from the UK General Practice Research Database over the age of 40 with ypye 2 diabetes followed for four years.	cancer is not increased during the first five years of insulin glargine use. Longer-term use may increase this risk.

8. Systematic Literature Review of the Prevalence of Insulin Use in Type 2 diabetes

The worldwide burden of diabetes mellitus is steadily growing, with type 2 diabetes accounting for most cases. This review intends to address the following questions: are there differences in the prevalence in consumption of insulin in type 2 diabetes between regions and over time? Are some types of insulin more prevalent than others? Is insulin prescribed as monotherapy, or do physicians prefer to recommend insulin in combination with other antidiabetic medications? The characterisation of insulin consumption provides an input to estimate insulin need in patients with type 2 diabetes. Differences in these characteristics could indicate differences in medical practice and potential barriers to access.

8.1 Objectives

To conduct a systematic literature review of published population data in order to characterise insulin consumption over the last 15 years.

8.2 Methods

8.2.1 Criteria for Considering Studies for this Review

Types of Studies

Cross-sectional database studies, case series and cohort studies containing outcome data from any period between 2000 and 2015.
While we aimed to exclude studies conducted at levels lower than national consumption, we altered our inclusion criteria to accept subnational studies when national studies were unavailable in the geographic region of interest.

Types of participants

Participants of any age, sex or ethnicity that fulfilled one or both of two criteria:

- Type 2 diabetes diagnosis
- One or more diabetes medication prescriptions

Types of interventions

- Insulin monotherapy
- Insulin-oral diabetes medication combination therapy

Types of outcome measures

Primary outcomes

- Prevalence of insulin consumption amongst type 2 diabetes patients
- Prevalence of insulin consumption among all diabetes patients (type unspecified)
- Prevalence of insulin consumption used in combination therapy

Secondary outcomes

- Comparison of analogue and human insulin consumption levels
- Comparison of insulin monotherapy and combination therapy
- Longitudinal trends of insulin consumption prevalence
- Geographic trends of insulin consumption prevalence

Covariates, effect modification and confounders

- Age
- Economic status
- Level of care (for example, general practitioners or outpatient hospital departments)
- Health care coverage/insulin costs to patient

8.2.2 Search Methods for Identification of Studies

We used PubMed for the identification of relevant literature. [Pending to include Annex with full search criteria].

8.2.3 Data Collection and Analysis

Selection of studies

To determine the studies to be assessed further, abstracts, titles, or both of every study identified were scanned. All potentially relevant articles were evaluated as full text with the exception of Chen et al 2014 (56) which was only available as an abstract. When determination of relevance was unclear, articles were evaluated by a second author.

Data extraction and management

For studies that fulfilled inclusion criteria, relevant study characteristics using standard data extraction templates were collected. For details see "Characteristics of included studies."

Assessment of risk of bias in included studies

The risk of bias of the included trials was assessed by examining exposures, data quality, and sampling error. Risk of bias assessment of all included studies was performed..

Measures of insulin consumption

To maximise potential results, we included studies that varied in their reporting of insulin consumption levels. Inclusion in this review required measures of prevalence; measures of incident insulin consumption were excluded from our analysis.

Prescription data

For prescription data, insulin consumption levels were reported as a percentage of total diabetes prescriptions.

Patient data

For patient data, insulin consumption levels were either reported as a percentage of total diabetes patients, a percentage of diabetes patients receiving one or more diabetes medicine, or a percentage of diabetes patients receiving one or more oral diabetes medicine.

Alexander et al 2008, Holden et al 2014, and Sarayani et al 2014 used insulin consumption measures unique to our review (57, 58, 59). The database used in Alexander et al 2008 reported "treatment visits," which were defined as physician visits "for patients diagnosed as having diabetes and treated with at least 1 medication." During the study, the mean number of treatment visits per patient ranged from 2.9 in 1994 to 2.4 in 2007 (57); because of this, we can expect the Alexander et al 2008 data to be higher than studies that use annual patient data. Studies using patient data will count each person's prescription for insulin only once per year, while Alexander et al2008 may count it multiple times for each treatment visit in which the patient was told to begin or continue insulin injections (57).

Holden et al 2014 measured the prevalence of insulin use amongst the entire population of their database of interest, the Clinical Practice Research Database (58). Because of this, the majority of its data is calculated based on a number of all patients in this database, not just those with diabetes. However, Holden et al 2014 did report that 15 percent of the type 2 diabetes patients in its database used insulin (58), both in the "Results" and "Discussion" section. This is the value we used for our analysis.

The majority of the Sarayani et al 2014 paper discusses insulin consumption in terms of defined daily doses (DDDs) per 1000 inhabitants per day (59). This measure is not comparable to our other studies; however, the paper also reported that "insulin utilisation only comprised 17 percent of total A10 consumption" in its "Discussion" section, making it possible to include it in our analysis.

Data synthesis

Studies were first separated into one of three categories based on the primary outcomes outlined above. Studies which did not separate those with type 1 from type 2 diabetes but that estimated the type 1 diabetes prevalence in their study population to be <1 percent were included in the type 2-specific primary outcome group. Data was further separated based on its measure of insulin consumption (prescription data or patient data). Separate data synthesis was performed for the secondary outcomes described above without regard to the categorisation required for primary analysis.

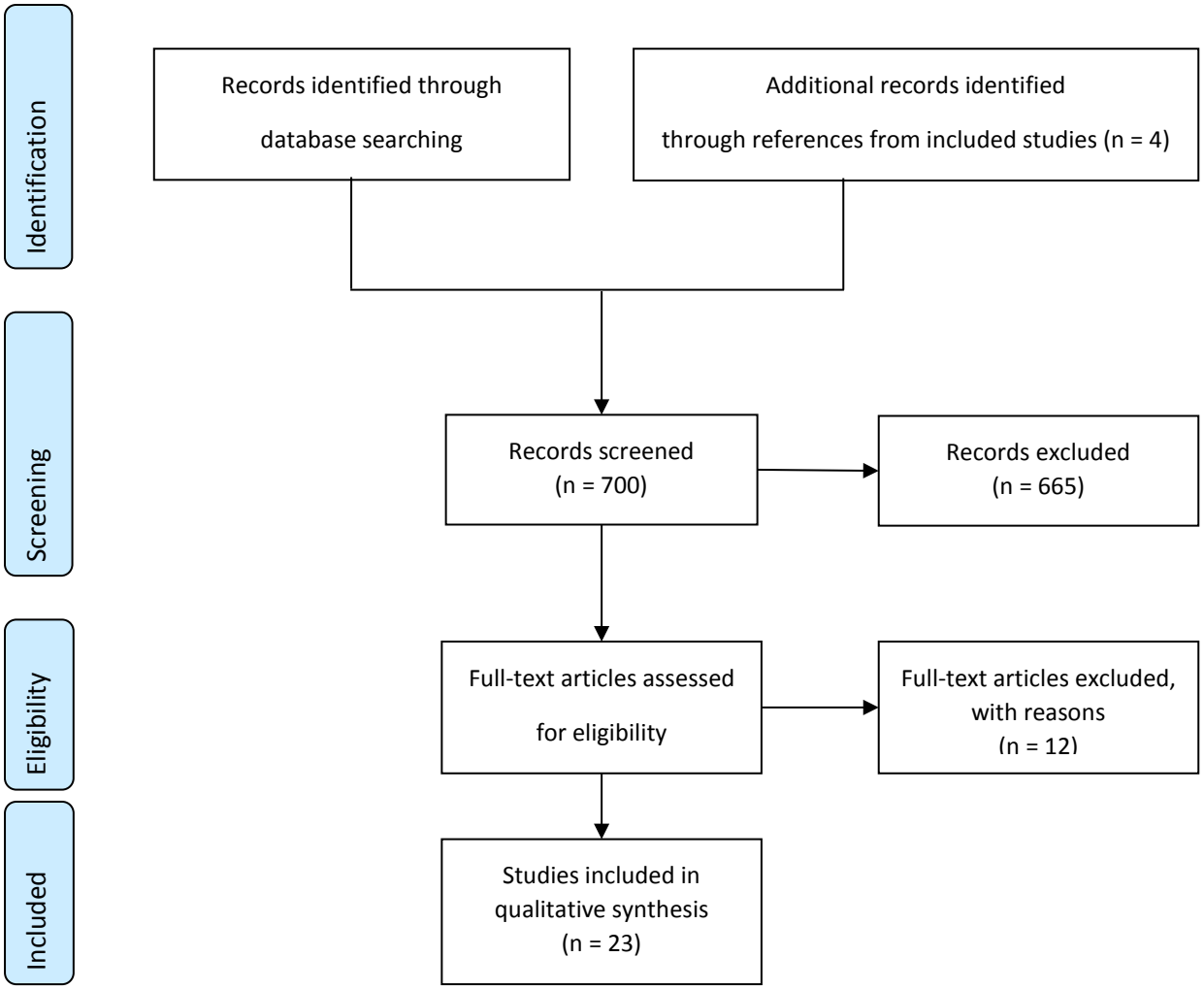
8.3 Results

8.3.1 Description of studies

Results of the search

The initial search identified 9,021 publications (Figure 9). After evaluating the first 700 titles and abstracts, 35 were selected for analysis. Twenty-three articles met our inclusion criteria and were included in our data synthesis. Four of the included papers were found by through references from included studies. The other 12 articles were excluded because they failed to meet our inclusion criteria.

Figure 9. PRISMA flow diagram of study selection.



Participants

In total, the 17 studies that used patient data had 28,745,631 diabetes participants (range 218 to 18,810,311). The three studies that used prescription data contributed 70,012,187 prescriptions for analysis. Alexander et al 2008 reported 36,000,000 type 2 diabetes patient treatment visits (57), Holden et al 2014 reported 42,518 insulin users (58), and Sarayani et al reported DDDs per 1,000 inhabitants per day for A10 medicines (59), all of which were also used in our analyses.

Heymann et al 2013 did not report the number of total diabetes participants in the study (60). Twelve of the studies reported the mean age of their patients, which ranged from 51.5 to 66.7 years. In six of the studies, gender distribution was not reported; in ten studies female participation constituted less than 50 percent and in the remaining seven studies male participation was less than 50 percent.

8.3.2 Outcomes

Primary outcomes

Type 2 Diabetes–Specific Insulin Consumption Studies

Our primary interest concerned insulin consumption amongst the type 2 diabetes populations at the national level. Twelve included data that either directly or indirectly reported prevalence of insulin consumption amongst type 2 diabetes patients. The findings from these studies are summarised in Table 24. To qualify for this category, >99 percent of the study population needed to contain patients diagnosed with type 2 diabetes.

Insulin consumption rates ranged from 2.4 percent of the type 2 diabetes population in Taiwan (61) to 23.5 percent of the type 2 population in the US (62). This large range suggests that prescribing trends vary widely by country, though determinants of this variation could not be identified through this review. In addition, study methods contributed to consumption measurement, as illustrated by the range of values for the US (15.1 percent to 23.5 percent).
As discussed previously, the included articles used one of three study populations when assessing insulin consumption rates. Among the eight articles that measured insulin consumption among all patients with diabetes (both those with and without antidiabetic medication prescriptions), the lowest rate was in Thailand at 2.8 percent of the type 2 diabetes population (63). The highest rate was 23.5 percent of the type 2 diabetes population as reported in Sargen et al 2012 (62), which was also the highest rate of all type 2 diabetes data. The median rate was 14.95 percent.

Two of our included studies only measured insulin consumption rates amongst the type 2 diabetes population that were currently using some form of diabetes medication, due to the nature of their prescription-driven data sources. Because of this measurement method, we would expect these studies to have slightly higher insulin consumption rates, since those diabetic patients without any antidiabetic medication would be excluded from the sample population. However, these measures were actually quite similar to those calculated in the more inclusive studies; Cohen et al 2003 reported 18.1 percent of US diabetes medication users were prescribed insulin (64), and Sultana 2010 reported that 11.5 percent of diabetes medication users at Majeedia Hospital in New Delhi, India were prescribed insulin (65). The mean of these two data points, 14.8 percent, is very similar to the median 14.95 percent reported amongst studies whose study population included all diabetes patients.

Unlike most of the studies included in our review, two of the type 2 diabetes-specific studies used prescription data rather than patient data when measuring insulin consumption. We would expect this type of measure to be similar to that which used medication users, which was true for the US. Alexander et al 2008 found that 19.0 percent of US diabetes medication prescriptions were for insulin (57), which is similar to the 18.1 percent of diabetes medication users receiving insulin found in Cohen et al 2003 (64). However, the lowest consumption rate for insulin was also found in this category—2.4 percent of diabetes medication prescriptions in Taiwan were for insulin, as reported in Chiang et al 2006 (61).

Nonspecific (Both Type 1 and Type 2 Diabetes) Insulin Consumption Studies

Eight of the studies analysed in our review reported insulin consumption rates cumulatively, with no segregation of patients (or prescriptions) into type 1 or type 2 diabetes.

Because these studies include patients with type 1 diabetes, insulin consumption rates are expected to be slightly higher because all type 1 patients require insulin. This was found to be true for both US and UK rates. In the US, the highest measured rate in the type 2-specific

publications was 23.5 percent, while the rate measured in the nonspecific publication for the United States was 27.1 percent. In the UK, Holden et al 2014 reported that 15 percent of type 2 diabetes patients use insulin (58), while Patel et al 2007 reported that 22.9 percent of all diabetes prescriptions, serving both type 1 and type 2 diabetes patients, were for insulin (69).
Like the type 2 diabetes-specific data, the nonspecific insulin consumption studies also fell into one of the three measurement categories. For those studies which used all patients with diabetes as their measure, the lowest rate was 13.3 percent, as reported in Heymann et al 2013 for Israel (60). The highest rate was 36.8 percent of diabetic patients in Indonesia (66), and the median rate was 23.4 percent.

The two papers that used diabetes medication user data had similar results as the four papers that used all diabetes patients for their measure. Baviera et al 2011, the highest measure across all categories, reported that 40.5 percent of diabetes medication users in the Lombardy region of Italy used insulin (67), while Hampp et al 2014 reported that 27.1 percent of diabetes medication users in the US used insulin (68). Prescription data was slightly lower, with a mean 19.6 percent of diabetes prescriptions being for insulin (69,59).

Combination Therapy Studies

Several of our reviewed publications focused on consumption rates of oral antidiabetic agents (OADs) and therefore only reported insulin consumption in dual, triple, or quadruple combination therapies. Because OADs are only typically prescribed to patients with type 2 diabetes, these studies can provide additional insight into type 2 diabetes insulin consumption. Two of these three publications evaluated countries for which no other data was available and so provided additional geographic coverage for our analysis.

Insulin consumption was much lower among these OAD users than when measured as both monotherapy and combination therapy in the previous categories. Amongst other possibilities, this could be due to dominance of insulin monotherapy over insulin combination therapy or to insufficient insulin availability in these countries; further research is necessary for such determination.

Table 24. Insulin consumption levels by measurement type.

Primary Outcome	Data Subgroup	Study	% Insulin
Type 2	All patients with diabetes	Aekplakorn et al 2003	2.8
		Boyc et al 2007	6.9†
		Holden et al 2014	15.*
		Li et al 2012	22.8
		Lipska et al 2014	15.1
		Mazzaglia et al 2008	13.3
		Yurgin et al 2007	14.9
		Sargen et al 2012	23.5
	Medication users	Cohen et al 2003	18.1
		Sultana et al 2010	11.5
	Prescription	Alexander et al 2008	19.0†
		Chiang et al 2006	2.4
Nonspecific	All patients with diabetes	Heymann et al 2013	13.3
		Kamrai et al 2010	35.*
		Ludwig et al 2006	13.6

		Soewondo et al 2010	36.8
	Medication users	Baviera et al 2011	40.5†‡
		Hampp et al 2014	27.1
	Prescription	Patel et al 2007	22.9
		Sarayani et al 2014	17.*
Combination only	All patients with diabetes	Hassan et al 2009	6.5
		Vengurlekar et al 2008	4.5
		Wabe et al 2011	8.6

Note: To qualify for this category, >99 percent of the study population needed to contain patients diagnosed with type 2 diabetes. * Holden et al 2014, Kamrai et al 2010, and Sarayani et al 2014 reported consumption levels to the nearest integer. † These percentages were calculated by author JM based on numerical data provided in the respective publications. ‡ Baviera et al 2011 reported human insulin and analogue insulin consumption levels separately, which we combined for this measurement. This may overestimate consumption level due to those patients who use both analogue and human insulin.

8.3.3 Secondary Outcomes

Geographic trends

As illustrated in Table 25, Europe and the US were well represented in scientific literature; however, publications for other countries in the Americas region and all other regions (Africa, Eastern Mediterranean, South-East Asia and Western Pacific) were scarce.

There were no clear trends in insulin consumption levels across the six WHO regions; while the two publications from the Western Pacific both have low consumption levels, all other regions with more than one publication have significant variety between findings. In the US alone, values range from 15.1 percent to 27.1 percent, and European values range from 6.9 percent to 40.5 percent. South-East Asia also exhibits a significant range of values, with a low of 2.8 percent in Thailand and a high of 36.8 percent in Indonesia.

Table 25. Summary of publications by geographic region.

Region	Country	Number of Publications	percent Insulin Value(s)
Africa	Ethiopia	1	8.6
Americas	Canada	1	13.6
	United States	6	15.1, 18.1, 19.0, 22.8, 23.5, 27.1
Eastern Mediterranean	Iran	1	17.*
Europe	France	1	6.9
	Germany	1	14.9
	Israel	1	13.3
	Italy	2	13.3, 40.5
	United Kingdom	2	15.*, 22.9
South-East Asia	India	3	4.5, 11.5, 35.*
	Indonesia	1	36.8
	Thailand	1	2.8
Western Pacific	Malaysia	1	6.5
	Taiwan	1	2.4

*Holden 2014, Kamrai 2010, and Sarayani 2014 reported consumption levels to the nearest integer.

Longitudinal trends

Thirteen of the publications, listed in Table 26, reported insulin consumption levels for multiple years. While we only analysed publications with data from year 2000 or later, earlier years of these publications have been included in this figure to demonstrate consumption trends.

Our analysis of the longitudinal studies found that while some publications reported a decreasing trend in insulin use, the majority of the data since 2000 showed a steady trend. Only three show an increasing trend. In addition, most of the longitudinal data fell within the 10-30 percent range identified in our initial report of the primary outcome.

Table 26. Longitudinal trends in insulin consumption levels.

Publication	Final Year of Study	Duration of Study (years)	Δ*	Δ per year**
Cohen 2003	2000	4	-3.5	-1.17
Ludwig 2006	2001	6	-1.1	NA
Boyc 2007	2003	3	0.9	0.47
Chiang 2006	2003	7	0.5	0.08
Mazzaglia 2008	2003	4	-0.4	-0.13
Patel 2007	2004	14	-2.7	NA
Alexander 2008	2007	14	-10	NA
Li 2012	2007	13	-11.8	-0.98
Baviera 2011	2008	5	12.8	NA
Hampp 2014	2009	10	0	0.00
Heymann 2013	2009	5	3.1	0.78
Sargen 2012	2009	4	-0.9	-0.30
Lipska 2014	2010	11	**5.4**	**NA**

*Total change in insulin consumption level (ICL) from first year to last year of study. $\Delta = ICL_{final} - ICL_{initial}$; **Average change in insulin consumption level per year. "NA" is listed for studies that did not measure ICLs consecutively.

Trends in human insulin versus analogue insulin consumption

In the five publications identified in Table 27, authors reported human insulin and analogue insulin consumption separately. As demonstrated in this table, there is no clear preference between analogue and human insulin; three of the papers reported that human insulins dominated the insulin market and two of the papers reported that analogue insulins were more common. Alexander et al 2008 and Lipska et al 2014, which both reported higher levels of analogue insulin consumption, covered the years 2007 and 2010 (57, 70) respectively, while the range of years for the three papers that reported higher human insulin consumption was 2008 to 2012. These are not far enough apart to suggest temporality affected the dominance of one type of insulin over another, and we therefore conclude that the global diabetes community has not yet reached a consensus concerning the superiority of either insulin type.

Table 27. Insulin consumption levels by type.

Publication	% Human*	% Analogue*
Alexander 2008	5.5	13.5
Baviera 2011	23.4	17.1
Lipska 2014	3.3	13.7
Sarayani 2014	16.2	0.8
Soewondo 2010	26.9	9.2

*Percentages are out of the appropriate data subgroup for each publication.

Trends in insulin monotherapy versus combination therapy

Nine of our included publications reported insulin monotherapy and OAD–insulin combination therapy separately (Table 28). There was no overall trend in preference over monotherapy or combination therapy for diabetes patients; five of the publications had higher levels of monotherapy, while four of the publications had higher combination therapy levels. Six of these publications were for type 2 diabetic patients specifically, which we would expect to increase their combination therapy levels somewhat since standard treatment for type 2 diabetes is an OAD before attempting more expensive and less convenient insulin injections. The other three publications, Baviera et al 2011, Ludwig et al 2006, and Soewondo et al 2010, did not separate type 1 diabetes patients from those with type 2 diabetes (67,71,68), and we can therefore expect these articles to have higher insulin monotherapy levels, since insulin injections are the only appropriate treatment for type 1 patients. Baviera et al 2011 and Ludwig et al 2006 did have higher monotherapy levels than combination levels (67,71), but Soewondo et al did not (66) in addition, three other type 2 diabetes–specific studies also had higher monotherapy levels. This leaves our analysis of this aspect of insulin consumption characterisation inconclusive.

Table 28. Insulin monotherapy and OAD-insulin combination therapy.

Publication	% Monotherapy*	% Combination Therapy*
Baviera 2011	13.2	10.2
Boyc 2007	1.7	5.2
Cohen 2003	13.0	5.9
Holden 2014	5.6	9.5
Ludwig 2006	8.9	4.7
Mazzaglia 2008	7.8	5.5
Soewondo 2010	17.3	19.4
Sultana 2010	11.5	13.8
Yurgin 2007	10.5	4.4

*Percentages are out of the appropriate data subgroup for each publication.

8.4 Discussion

Summary of main results

Type 2-specific insulin consumption rates ranged from 2.4 percent in Taiwan to 23.5 percent in the United States. Most type 2-specific rates fell within the 10-25 percent range, with no particular trend across the six geographic regions outlined in Table 2. Cumulative rates were slightly more varied, falling between 13.3 percent in Israel and 40.5 percent in Italy.

Studies that excluded insulin monotherapy measurements (combination only) had very low insulin consumption rates, ranging from 4.5 percent to 8.6 percent of patients with diabetes.
The availability of data was not equally distributed across the six geographic regions; Western Europe and the US were well represented by the publications, but all other geographic regions lacked research in both number of publications, international distribution of publications, and quality of data (most were performed at local or regional rather than national levels). This could be due to lack of interest in the research topic or lack of surveillance systems in these regions.
Further national cross-sectional database studies should be performed for these regions; in addition, aggregate information should be collected for countries lacking national diabetes surveillance systems so that we might more accurately characterise worldwide insulin consumption.

Few trends were found in our other secondary outcomes. Analysis of longitudinal studies showed that since 2000, most insulin consumption levels have remained steady or increased, possibly to compensate for an aging diabetes population. No clear trend was demonstrated between analogue and human insulins, nor was a trend found between insulin monotherapy and OAD–insulin combination therapy. The discrepancies found across publications may be due to geographic preferences, both at the local and national level.

As our secondary outcomes demonstrate, the diabetes community has not come to a consensus concerning best practices for insulin treatment with type 2 diabetes patients. Guidelines should be made available for physicians regarding how to initiate insulin monotherapy or OAD–insulin combination therapy, along with analogue insulin or human insulin.

Our literature review found that while data is available for many high-income countries, insulin consumption measures in low- and middle-income countries is not widely available at the national level. We recommend that further national cross-sectional database studies be performed for these countries and that aggregate information be collected for countries lacking national diabetes surveillance systems.

9. Discussion of Report Findings

This report brings together different studies on the global insulin market including manufacturing, registration, inclusion in the NEML, and promotion. It also features an analysis of demand in terms of consumption of insulin in patients with type 2diabetes and summarises evidence on the clinical efficacy of human versus analogue insulin. The aim of the report is to describe the insulin market and contribute to the knowledge on supply and demand of insulin.

The first part of the report describes the number of manufacturers. Prior to the study it was known that three manufacturers of insulin dominate the global market: NovoNordisk, Eli Lilly and Sanofi. However, this study adds to existing knowledge in presenting a list of smaller manufacturers with largely local markets and their geographical location. Southeast Asia and Latin America are regions with a higher number of smaller manufacturers than other regions. Little is known about these smaller manufacturers in terms of their product portfolio including prices, their supply channels (largely public or private sector), and main clients. Given the scarcity of publically available information on licence agreements it is difficult to ensure that these smaller manufacturers are in fact independent from the large three global producers of insulin. More research is needed to obtain a comprehensive picture of global supply.

The findings with respect to the type of insulin products registered worldwide sheds light on the market for specific products. One major finding is the difference between the product types registered between high-and-middle income country markets: a larger number of analogue products are licensed in high-income markets compared to middle-income countries. The variation between countries may be partially explained by the differences in purchasing power and in the prevalence of diabetes. Other factors are likely to be related to the regulatory framework in each country (e.g. fees to register a product, time until registration, process to register), which may present barriers to manufacturers that attempt to register their products.

Both sections highlight the identification of large information gaps about insulin manufacturers and products registered in each country. This gap is particularly apparent for low-income countries where the study was unable to identify any functioning NMRA website with information on registered insulin products. However, for other countries the data extraction from NMRA websites is cumbersome and has many limitations. Hence, it is important to take these data limitations into consideration when discussing the results. At the same time the identification of these limitations can be used to develop recommendations to improve data transparency and ultimately governance of the pharmaceuticals sector as other authors have done (25). When data on registered insulin products is doubtful or unavailable this can result in patient harm and/or increase healthcare costs. Clear product description is necessary to identify the active substance. International agreements and effective implementation on product information displayed by NMRA in all their communications including website could increase transparency. For instance, the description “insulin” is insufficient to clearly identify the type of product (e.g. regular insulin, premixed insulin). The requirement to add the ATC classification system (72) would increase clarity. The classification of insulin products compared to many other pharmaceutical products seems particularly complex given the premix of different types of insulin.

The study of national essential medicines lists shows that the large majority of countries list both short-acting and intermediate-acting insulin, which are recommended by the WHO Model List. Only a few countries do not list one or both insulin types (e.g. Democratic People’s Republic of Korea). More research is needed to identify the reasons for not listing insulin,

particularly in countries with a significant burden. It is likely that not listing insulin in the essential medicines list results in barriers to insulin access.
The fact that the countries in the Middle East are overall more likely to list analogue insulins may have to do with a combination of factors such as high prevalence of diabetes and higher healthcare spending than countries in other regions. The results on the inclusion of medicines in the national EML need to be discussed in conjunction with the analysis of the reimbursement list of countries to see whether the absence or listing of medicines on that list is associated with reimbursement.

On one hand, it is surprising to see that lower-middle income countries such as Ghana list all types of analogue insulin given their limited healthcare resources. On the other, countries such as Germany with larger resources have purposefully rejected the general reimbursement of analogue insulins and allow it only in specific circumstances; general reimbursement is only allowed if their price is equal or lower than their human insulin counterparts (73) Quality of information about the type of insulin listed was also a problem in the analysis of national EML, which is in line with other studies which found similar difficulties (26). Several EMLs had to be excluded because the information presented did not allow classification based on which type of insulin was included.

Supply of insulin is closely linked to marketing. One of the studies in this report analyses breaches of the national codes of medicines promotion. The analysis was hampered by the scarcity of information except for countries such as the UK, US, and Australia. There were no reports that met our inclusion criteria from middle income countries, except for China. Since the UK (74) and Australia have created specific databases it is much more likely to identify cases for these countries. Only cases for recently launched products from the three main manufacturers of insulin were identified. An exception was Pfizer, with breaches related to its inhalable insulin. More analysis of promotion of insulin in middle-income countries is warranted; the authors of this report are currently studying insulin promotion published in general and specialized medical journals from 16 countries.

Two systematic literature reviews have been conducted to complement the analysis of supply and demand of insulin: (a) a systematic review comparing the clinical efficacy and safety of types of analogue insulin with regular human insulin in patients with type 1 and 2 diabetes; (b) systematic literature review of published population data in order to characterise the prevalence of insulin consumption in type 2 diabetes in the last 15 years. The first review was done to gather the most recent evidence on comparative efficacy and safety of analogue insulin versus human insulin. It is noteworthy that none of the studies that we identified examine the long-term clinical effects of diabetes or diabetes mortality rates. Analogue insulins protect from nocturnal hypoglycaemic events but the studies do not demonstrate that this reduction is clinically significant (i.e. protection from severe hypoglycaemic events reducing morbidity and mortality).

The second review was carried out to get a better understanding of the demand for insulin in diabetes type 2 cases. According to the literature found, only three out of 11 studies show an increase in prevalence of consumption of insulin, indicating that there is no clear evidence of an overall increasing prevalence of insulin consumption in type 2 diabetes. Comparing studies is difficult due to variation in patient population (different age groups) and healthcare settings (primary care versus hospital data).

The studies presented in this report increase our current knowledge of global supply and demand of insulin. They also highlight the need for better data in order to analyse pharmaceutical markets in low- and middle-income markets. More research in this area can

contribute to identifying factors that influence access to insulin, and possibly other pharmaceutical products as well.

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Annex 1. Identifying Insulin Manufacturers

Annex 1.1. Log of general market review database searches

Database	Search Terms	Inclusion Criteria	Number of Search Results	Date
LexisNexis® Academic				
	global insulin market	1/1/2005-2/25/2014	26	2/25/2014
	international insulin market	1/1/2005-2/25/2014	1	2/25/2014
	global OR international w/5 market AND insulin AND OR % w/10 market OR sales OR revenue OR global AND diabet! AND manufactur! w/5 insulin	1/1/2005-2/25/2014	8	2/25/2014
	international OR global AND insulin AND manufactur! w/10 insulin AND distribut! w/10 insulin AND market w/10 insulin	1/1/2005-2/25/2014	22	2/25/2014
ProQuest®				
	ti(insulin) AND (global OR international) AND ti(market) AND ti(report) AND la.exact("English")	Published after 1/1/2005; English Language; Topic: Insulin	78	5/13/2014
Frost& Sullivan				
	global or international and insulin market report	industry(healthcare) 2005-present, industry insight or economic research	124	3/23/2014

The most successful searches, with search terms, inclusion criteria, hits, and the date of search are included in the table. These searches were used in the literature review of the global insulin market to find information about market shares, growth rate, values, manufacturers involved in the market, diabetes prevalence, and important countries.

Annex 1.2. List of 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)
Novo Nordisk	Denmark	111	91.74%	http://www.novonordisk.com/default.asp
Sanofi	France	101	83.47%	http://www.sanofi.us/l/us/en/index.jsp
Eli Lilly	United States	94	77.69%	http://www.lilly.com/Pages/Home.aspx

Bioton	Poland	26	21.49%	http://www.bioton.pl/en
Wockhardt	India	17	14.05%	http://www.wockhardt.com/
Biocon	India	17	14.05%	http://www.biocon.com/
Julphar	United Arab Emirates	13	10.74%	http://www.julphar.net/
Tonghua Dongbao	China	7	5.79%	http://www.dongbao.com/index.htm
Pisa	Mexico	5	4.13%	http://en.pisa.com.mx/
Berlin Chemie*	Germany	3	2.48%	http://www.berlin-chemie.com/
Polfa Tarchomin	Poland	3	2.48%	http://www.polfa-tarchomin.com.pl/
Popular	Bangladesh	2	1.65%	http://www.popular-pharma.com/
Soperquimia	El Salvador	2	1.65%	http://www.soperquimia.com/
SEDICO	Egypt	2	1.65%	http://www.sedico.net/English/Default_e.htm
CJSC Brinsalov	Russia	2	1.65%	http://ferain.com/company/about/
Probiomed	Mexico	2	1.65%	http://www.probiomed.com.mx/
Aspen	South Africa	2	1.65%	http://www.aspenpharma.com/
Shanghai Fosun	China	2	1.65%	http://www.fosunpharma.com/
ACI Limited	Bangladesh	1	0.83%	http://www.aci-bd.com/pharmaceuticals.php
Aristopharma	Bangladesh	1	0.83%	http://www.aristopharma.com/index.php
Hongye Biochem	China	1	0.83%	http://www.hongyechem.com/en/
Beier	China	1	0.83%	
Shanghai Biochem and Pharma	China	1	0.83%	
BCN Medical	Colombia	1	0.83%	http://bcnmedical.com
Nanjing Xinbai	China	1	0.83%	http://www.njxbyy.com/english/about/gsjj.asp
Vacsera	Egypt	1	0.83%	http://www.vacsera.com/
USV	India	1	0.83%	http://www.usvindia.com/
Laboratorios Antibioticos	Mexico	1	0.83%	http://www.amsamexico.com.mx/
Denver	Argentina	1	0.83%	http://www.denverfarma.com.ar/productos.asp?buscar=c0
Institute Bioorganic Chemical*	Russia	1	0.83%	http://www.ibch.ru/en/about
Medsyntez	Russia	1	0.83%	http://www.medsintez.com/en/
National Biotechnology*	Russia	1	0.83%	http://nbiotech.ru/history2.html
Pharmstandard	Russia	1	0.83%	http://pharmstd.com/
Sanbe	Indonesia	1	0.83%	http://www.sanbe-farma.com/
Exir	Iran	1	0.83%	http://www.exir.co.ir/
Laboratorios Cryopharma	Mexico	1	0.83%	http://www.grupoifaco.com/laboratorios-cryopharma.php
Amoun Pharmaceuticals	Egypt	1	0.83%	http://www.amoun.com/
United Laboratories	China	1	0.83%	http://www.tul.com.cn/en/
Union Pharmaceuticals	China	1	0.83%	
Shanghai Biochemical Research	China	1	0.83%	

Jinhua	China	1	0.83%	
Asia Pharma*	Syria	0	0.00%	http://www.asiapharma-syria.com/

*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 1.3. List of insulin distributors, licensed manufacturers, and subsidiary companies

Company Name	Company Headquarters Country	Associated Independent Insulin Manufacturer (if available)	Website (if available)
Abbott	United States	Novo Nordisk	http://www.abbott.com/index.htm
Al-Jishi Corporation	Bahrain		http://www.aljishi.com/index.asp
Alliance Boots	United Kingdom	Novo Nordisk	http://www.allianceboots.com/
B Braun-Melsungen	Germany		http://www.bbraun.com/
Bader Sultan and Bros	Kuwait		http://www.badersultan.com/index.html
Bayer Schering	Germany	Bioton	http://pharma.bayer.com/en/index.php
BBFarma	Italy		http://www.bbfarma.it/
Belmedpreparaty	Belarus	Novo Nordisk	http://www.belmedpreparaty.com/eng/product.php
Beta	Argentina	Denver	http://www.betapharma.com/
Cadila	India	Polfa Tarchomin	http://cadilapharma.com/
CC Pharma	Germany		http://www.cc-pharma.de/
CiplaMedpro	India	Bioton	http://www.ciplamedpro.co.za/
D.C.I.	France		
Darou Pakhsh	Iran		http://www.dppcco.com/?lang=en
Delphi	Netherlands		http://www.delphiphar.com/
Empresa Productora de Insulina y Carpules Laboratotrios LIORAD	Cuba	Novo Nordisk	
EMRA-Med	Netherlands		
Eskayef Bangladesh	Bangladesh	Novo Nordisk	http://www.skfbd.com/
EU-Pharma	Netherlands		
Eureco Pharm	Netherlands		http://www.eureco-pharma.nl/en/
Euripharm	Germany		http://www.eurim.de/en/eurimpharm-iups
Farmak	Ukraine	Eli Lilly	http://www.farmak.ua/en/
Fisher Farma	Netherlands		http://www.fisherfarma.com/content/home.asp?lang=EN
Fragua/ Farmacia Guadelajara	Mexico		https://www.farmaciasguadalajara.com.mx/PaginaWebFragua/empresa/
Galenika	Serbia	Eli Lilly	http://www.galenika.rs/index.php
Gan & Lee*	China	Tonghua Dongbao	http://www.ganlee.com/en/

Getz	Pakistan	Biocon	http://www.getzpharma.com/default.php
High Chem East Africa	Kenya	Sanofi	http://www.highchem.co.ke/
Incepta	Bangladesh	Biocon	http://www.inceptapharma.com/index.php
Indar	Ukraine	Bioton	http://indar.com.ua/en
Kharazmi*	Iran	Exir	http://www.kharazmipharm.com/english/about_en.html
Kohl Medical AG	Germany		http://www.kohlmedical.de/en/index
Kyowa Hakko Kirin	Japan		
Laboratorios Andromaco	Chile		http://www.laboratoriosandromaco.cl/
Laprophan	Morocco	Novo Nordisk	http://www.laprophan.ma/master.html
Libra	Uruguay	Biocon	http://www.laboratoriolibra.com/
Loghman	Iran		http://www.loghman-med.com/
Lupin Laboratories	India	Eli Lilly	http://www.lupinpharmaceuticals.com/
M.J. Biopharm	India	Bioton	http://www.mjbiopharm.com/
Medartuum	Sweden	Sanofi	http://medartuum.se/
Medcor	Netherlands		http://www.medcor.nl/
Medley	India		http://www.medleylab.com/#
Mega Lifesciences	Thailand	Biocon	http://www.megawecare.com/
Neoquimica	Brazil		http://www.neoquimica.com.br/
Orifarm	Denmark		http://www.orifarm.com/consumers.aspx
Paranova	Denmark		http://paranova.dk/
Pharmatech	Dominican Republic	Biocon	http://www.pharmatech.do/7o188f29d8aqc8g0012ge8yf4nb5yn
Pharmevo	Pakistan	Bioton	http://pharmevo.biz/
Phoenix Pharmahandel	Germany		http://www.phoenixgroup.eu/EN/Pages/default.aspx
Praxis	Colombia		
Ronak Darou	Iran		
Saidal Group	Algeria	Novo Nordisk	https://www.saidalgroup.dz/
SciGen	Singapore	Bioton	http://scigenltd.com/
Shreya Group	Russia	Bioton	http://www.shreya.co.in/?q=node/11
Soriana	Mexico		http://www.soriana.com/
Sothema	Morocco	Eli Lilly	http://www.sothema.com/en/
SPIMACO	Saudi Arabia		http://www.spimaco.com.sa/home.aspx
Square	Bangladesh	Biocon	http://www.squarepharma.com.bd/index.php
Veron Pharma	Germany		http://www.veronpharma.de/
Wanbang Biopharmaceuticals*	China	Shanghai Fosun	http://www.chinawanbang.com/en/about/Default.aspx
Yousuf Mahmood Husain Company	Bahrain		http://www.ymh.com.bh/
Zafa	Pakistan	Bioton	http://www.zafa.com.pk/aboutus.html

*Since compiling this list, we have received information from industry representatives and other sources that Gan & Lee is an independent insulin manufacturer and no longer associated with Tonghua Dongbao; Kharazmi was an independent insulin manufacturer not associated with Exir but has recently ceased manufacturing insulin; and that Wanbang Biopharmaceuticals is an independent insulin manufacturer.

Annex 1.4. Total number of independent insulin manufacturers with products registered and/or sold in countries by range

Range	Percentage of World's Population with Diabetes in 2013[12]	Countries
No Data	3.69%	Afghanistan, Andorra, Angola, Antigua and Barbuda, Azerbaijan, Bahamas, Barbados, Belize, Bermuda, Botswana, British Virgin Islands, Cape Verde, Cook Islands, Costa Rica, Dominica, El Salvador, Equatorial Guinea, Eritrea, Fiji, French Polynesia, Gambia, Georgia, Greenland, Grenada, Guinea-Bissau, Guyana, Haiti, Honduras, Iraq, Jamaica, Kiribati, Kyrgyzstan, Laos, Lesotho, Liberia, Libya, Macedonia, Malawi, Marshall Islands, Mauritania, Mauritius, Micronesia, Monaco, Mongolia, Montenegro, Mozambique, Myanmar, Nauru, Netherland Antilles, Nicaragua, Niger, Niue, North Korea, Palau, Palestine, Panama, Papua New Guinea, Paraguay, Rwanda, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Samoa, San Marino, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, Suriname, Swaziland, Syria, Tajikistan, Timor-Leste, Tonga, Turkmenistan, Tuvalu, Vanuatu, Yemen, Zambia
0	0.02%	Benin
1-2	3.47%	Belarus, Bhutan, Bolivia, Brunei Darussalam, Burkina Faso, Burundi, Cambodia, Cameroon, Central African Republic, Chad, Comoros, Congo, Cote D'Ivoire, Cuba, Democratic Republic of the Congo, Djibouti, Ecuador, Ethiopia, Gabon, Ghana, Guinea, Madagascar, Maldives, Mali, Moldova, Nigeria, Togo, Uruguay
3	18.77%	Albania, Armenia, Austria, Bahrain, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kuwait, Latvia, Lithuania, Luxembourg, Malta, Morocco, New Zealand, Netherlands, Portugal, Puerto Rico, Romania, Serbia, Slovakia, Slovenia, South Korea, Spain, Sudan, Sweden, Switzerland, Taiwan, Trinidad and Tobago, Tunisia, Turkey, United States, Venezuela
4	8.56%	Algeria, Argentina, Australia, Canada, Chile, Germany, Hong Kong, Kazakhstan, Lebanon, Malaysia, Namibia, Nepal, Norway, Oman, Qatar, Saudi Arabia, Singapore, South Africa, Uganda, Ukraine, United Kingdom
5-7	16.17%	Bangladesh, Brazil, Dominican Republic, Egypt, Indonesia, Iran, Jordan, Pakistan, Peru, Philippines, Poland, Sri Lanka, Tanzania, Thailand, United Arab Emirates, Vietnam, Zimbabwe
8+	49.12%	China, Colombia, Guatemala, India, Kenya, Mexico, Russia, Uzbekistan

Annex 1.5. List of insulin manufacturers with products registered and/or sold by country

Country	Big 3 Manufacturers	Additional Manufacturers
Albania	Novo Nordisk, Sanofi, Eli Lilly	
Algeria	Novo Nordisk, Sanofi, Eli Lilly	Julphar
Argentina	Novo Nordisk, Sanofi, Eli Lilly	Denver
Armenia	Novo Nordisk, Sanofi, Eli Lilly	
Australia	Novo Nordisk, Sanofi, Eli Lilly	Aspen
Austria	Novo Nordisk, Sanofi, Eli Lilly	
Bahrain	Novo Nordisk, Sanofi, Eli Lilly	
Bangladesh	Novo Nordisk, Sanofi, Eli Lilly	ACI Limited, Aristopharma, Biocon, Popular
Belarus	Novo Nordisk, Sanofi	
Belgium	Novo Nordisk, Sanofi, Eli Lilly	
Benin		
Bhutan	Novo Nordisk	Biocon
Bolivia	Novo Nordisk, Sanofi	
Bosnia and Herzegovina	Novo Nordisk, Sanofi, Eli Lilly	
Brazil	Novo Nordisk, Sanofi, Eli Lilly	Aspen, Wockhardt
Brunei Darussalam	Novo Nordisk, Sanofi	
Bulgaria	Novo Nordisk, Sanofi, Eli Lilly	
Burkina Faso	Eli Lilly	
Burundi	Novo Nordisk	Biocon
Cambodia	Sanofi	
Cameroon	Novo Nordisk	
Canada	Novo Nordisk, Sanofi, Eli Lilly	Wockhardt
Central African Republic	Novo Nordisk	
Chad	Eli Lilly	
Chile	Novo Nordisk, Sanofi, Eli Lilly	Wockhardt
China	Novo Nordisk, Sanofi, Eli Lilly	Beier, Bioton, Hongye Biochem, Jinhua, Nanjing Xinbai, Shanghai Biochemical Research, Shanghai Biomedical, Shanghai Fosun, Tonghua Dongbao, Union, United Laboratories
Colombia	Novo Nordisk, Sanofi, Eli Lilly	BCN Medical, Biocon, Bioton, Pisa, Tonghua Dongbao
Comoros	Novo Nordisk	
Croatia	Novo Nordisk, Sanofi, Eli Lilly	
Cuba	Novo Nordisk	
Cyprus	Novo Nordisk, Sanofi, Eli Lilly	
Czech Republic	Novo Nordisk, Sanofi, Eli Lilly	
Denmark	Novo Nordisk, Sanofi, Eli Lilly	
Democratic Republic of the Congo	Novo Nordisk	
Djibouti	Novo Nordisk, Sanofi	
Dominican Republic	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Pisa

Ecuador	Sanofi	Pisa
Egypt	Novo Nordisk, Sanofi, Eli Lilly	Amoun Pharmaceuticals, SEDICO, Vacsera
Estonia	Novo Nordisk, Sanofi, Eli Lilly	
Ethiopia		Julphar
Finland	Novo Nordisk, Sanofi, Eli Lilly	
France	Novo Nordisk, Sanofi, Eli Lilly	
Gabon	Novo Nordisk	
Germany	Novo Nordisk, Sanofi, Eli Lilly	Berlin Chemie
Ghana	Sanofi, Eli Lilly	
Greece	Novo Nordisk, Sanofi, Eli Lilly	
Guatemala	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Bioton, Pisa, Probiomed, Soperquimia
Guinea	Novo Nordisk	
Hong Kong	Novo Nordisk, Sanofi, Eli Lilly	Bioton
Hungary	Novo Nordisk, Sanofi, Eli Lilly	
Iceland	Novo Nordisk, Sanofi, Eli Lilly	
India	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Bioton, Polfa Tarchomin, USV, Wockhardt
Indonesia	Novo Nordisk, Sanofi, Eli Lilly	Bioton, Sanbe
Ireland	Novo Nordisk, Sanofi, Eli Lilly	
Israel	Novo Nordisk, Sanofi, Eli Lilly	
Iran	Novo Nordisk, Sanofi	Bioton, Exir, Wockhardt
Italy	Novo Nordisk, Sanofi, Eli Lilly	
Ivory Coast	Novo Nordisk, Eli Lilly	
Japan	Novo Nordisk, Sanofi, Eli Lilly	
Jordan	Novo Nordisk, Sanofi, Eli Lilly	Bioton, Julphar
Kazakhstan	Novo Nordisk, Sanofi, Eli Lilly	Wockhardt
Kenya	Novo Nordisk, Sanofi, Eli Lilly	Bioton, CJSC Brinsalov, Julphar, Tonghua Dongbao, Wockhardt
Kuwait	Novo Nordisk, Sanofi, Eli Lilly	
Latvia	Novo Nordisk, Sanofi, Eli Lilly	
Lebanon	Novo Nordisk, Sanofi, Eli Lilly	Julphar
Lithuania	Novo Nordisk, Sanofi, Eli Lilly	
Luxembourg	Novo Nordisk, Sanofi, Eli Lilly	
Madagascar	Novo Nordisk, Sanofi	
Malaysia	Novo Nordisk, Sanofi, Eli Lilly	Biocon
Maldives	Novo Nordisk, Eli Lilly	
Mali	Novo Nordisk	
Malta	Novo Nordisk, Sanofi, Eli Lilly	
Mexico	Novo Nordisk, Sanofi, Eli Lilly	Laboratorios Antibioticos, Laboratorios Cryopharma, Pisa, Probiomed, Wockhardt
Moldova	Novo Nordisk, Sanofi	
Morocco	Novo Nordisk, Sanofi, Eli Lilly	
Namibia	Novo Nordisk, Sanofi, Eli Lilly	Bioton
Nepal	Novo Nordisk, Sanofi, Eli Lilly	Bioton
New Zealand	Novo Nordisk, Sanofi, Eli Lilly	
Netherlands	Novo Nordisk, Sanofi, Eli Lilly	
Nigeria	Sanofi	Popular
Norway	Novo Nordisk, Sanofi, Eli Lilly	Wockhardt
Oman	Novo Nordisk, Sanofi, Eli Lilly	Julphar
Pakistan	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Bioton

Peru	Novo Nordisk, Sanofi, Eli Lilly	Shanghai Fosun, Soperquimia, Tonghua Dongbao, Wockhardt
The Philippines	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Bioton, Tonghua Dongbao, Wockhardt
Poland	Novo Nordisk, Sanofi, Eli Lilly	Bioton, Polfa Tarchomin
Portugal	Novo Nordisk, Sanofi, Eli Lilly	
Puerto Rico	Novo Nordisk, Sanofi, Eli Lilly	
Qatar	Novo Nordisk, Sanofi, Eli Lilly	Julphar
Republic of the Congo		Biocon, Bioton
Romania	Novo Nordisk, Sanofi, Eli Lilly	
Russia	Novo Nordisk, Sanofi, Eli Lilly	Berlin Chemie, Bioton, CJSC Brinsalov, Institute Bioorganic Chemical, National Biotechnology, Medsyntez, Pharmstandard
Saudi Arabia	Novo Nordisk, Sanofi, Eli Lilly	Julphar
Serbia	Novo Nordisk, Sanofi, Eli Lilly	
Singapore	Novo Nordisk, Sanofi, Eli Lilly	Bioton
Slovakia	Novo Nordisk, Sanofi, Eli Lilly	
Slovenia	Novo Nordisk, Sanofi, Eli Lilly	
South Africa	Novo Nordisk, Sanofi, Eli Lilly	Bioton
South Korea	Novo Nordisk, Sanofi, Eli Lilly	
Spain	Novo Nordisk, Sanofi, Eli Lilly	
Sri Lanka	Novo Nordisk, Sanofi, Eli Lilly	Bioton, Wockhardt
Sudan	Novo Nordisk, Sanofi, Eli Lilly	
Sweden	Novo Nordisk, Sanofi, Eli Lilly	
Switzerland	Novo Nordisk, Sanofi, Eli Lilly	
Taiwan	Novo Nordisk, Sanofi, Eli Lilly	
Tanzania	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Bioton, Julphar, Wockhardt
Thailand	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Bioton, Tonghua Dongbao
Togo	Novo Nordisk	
Trinidad and Tobago	Novo Nordisk, Sanofi, Eli Lilly	
Tunisia	Novo Nordisk, Sanofi	Julphar
Turkey	Novo Nordisk, Sanofi, Eli Lilly	
Uganda	Novo Nordisk	Biocon, Bioton, Wockhardt
Ukraine	Novo Nordisk, Sanofi, Eli Lilly	Bioton
United Arab Emirates	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Julphar, SEDICO
United Kingdom	Novo Nordisk, Sanofi, Eli Lilly	Wockhardt
United States of America	Novo Nordisk, Sanofi, Eli Lilly	
Uruguay	Sanofi	
Uzbekistan	Novo Nordisk, Sanofi, Eli Lilly	Berlin Chemie, Bioton, Julphar, Tonghua Dongbao, Wockhardt
Venezuela	Novo Nordisk, Sanofi, Eli Lilly	
Vietnam	Novo Nordisk, Sanofi, Eli Lilly	Biocon, Bioton, Polfa Tarchomin, Wockhardt
Zimbabwe	Novo Nordisk, Eli Lilly	Biocon, Bioton, Julphar

Annex 2. Registration of insulin products

Annex 2.1 Classification of insulin products

Type of Insulin	Generic name	Brand name (examples)	Onset	Peak	Duration	Source regarding specific insulin
Rapid acting insulins						
Analogue	Insulin Lispro	Humalog	15-30 min	30-90min	3-5 hours	http://www.rxlist.com/humalog-drug.htm
Analogue	Insulin Aspart	NovoLog or Novorapid	10-20min	40-50min	3-5hours	http://www.novonordisk.com.au/media/PIs/NovoRapid_NovoMix_PI3a.pdf
Analogue	Insulin Glulisine	Apidra	20-30min	30-90min	1-2.5 hours	http://www.medscape.com/viewarticle/426921_2
Regular or short acting insulins						
Human	Insulin Regular or Neutral	Actrapid	30 min-1 hour	2-5 hours	5-8 hours	http://www.novonordisk.com.au/media/PIs/Inshpi12a.pdf http://www.diabetesvic.org.au/type-2-diabetes/medication-and-insulin/types-of-insulin http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000424/WC500021655.pdf
Human	Insulin Regular or Neutral	Humulin R or Novolin R	30 min-1 hour	2-5 hours	5-8 hours	http://www.diabetesvic.org.au/type-2-diabetes/medication-and-insulin/types-of-insulin
Human	Insulin Regular or Neutral	Velosulin	30 min-1 hour	2-3 hours	2-3 hours	http://www.diabetesvic.org.au/type-2-diabetes/medication-and-insulin/types-of-insulin
Intermediate Acting- Basal Insulins						

Human	Insulin Lente (30 percent Semilente insulin and 70 percent Ultralente insulin)	Humulin L or Novolin L	1.5 hours	4-8 hours	Up to 24 hours	http://healthcare.utah.edu/healthlibrary/related/doc.php?type=26&id=3350
Human	Neutral Protamine Hagedorn (NPH-mixture of regular and protamine zinc insulin) or Isophane	Humulin NPH or Humulin N or Novolin N	1-2 hours	4-12 hours	18-24 hours	http://web.archive.org/web/20041229085219/http://www.merck.com/mrkshared/mmanual/section2/chapter13/13a.jsp
Premixed						
Analogue	Insulin Biphasic Aspart (70% intermediate Aspart Protamine/ 30% rapid acting Aspart)	Novomix or Novolog 70/30	10-20min	1-4 hours	Up to 24 hours	http://www.novonordisk.co.in/documents/article_page/document/insulin_analogue_brands.asp http://www.diabetesincontrol.com/articles/practicum/16641-novolog-mix-7030-confusion

Human	Biphasic Isophane Insulin Injection 70/30[Neutral Protamine Hagedorn Injection (30%) and Isophane Insulin Injection (70%)]	Mixtard 70/30 or Novolin 70/30 or Humulin 70/30 or Humulin M3				http://www.novonordisk.com.au/media/PIs/Inshpi12a.pdf http://www.drugs.com/mtm/novolin-70-30.html http://americandiabetes.com/difference-between-types-insulin/
Human	Biphasic Isophane Insulin 50/50 [Neutral Protamine Hagedorn Injection (50%) and Isophane Insulin Injection (50%)]	Mixtard 50/50 or Novolin 50/50 or Humulin 50/50				http://www.novonordisk.com.au/media/PIs/Inshpi12a.pdf http://www.drugs.com/mtm/humulin-50-50.html
Analogue	Biphasic Lispro Insulin Neutral Protamine Lispro (70%) and Lispro Insulin Injection (30%)	Humalog 70/30				http://www.netdoctor.co.uk/diabetes/medicines/humalog-mix50.html

Analogue	Biphasic Lispro Insulin Neutral Protamine Lispro (50%) and Lispro Insulin Injection (50%)	Humalog 70/30				http://www.netdoctor.co.uk/diabetes/medicines/humalog-mix50.html
Long- Acting- Basal Insulins						
Analogue	Insulin Glargine	Lantus	1-1.5 hours	No peak	20-24 hours	http://www.webmd.com/diabetes/guide/diabetes-types-insulin?page=2
Analogue	Insulin Detemir	Levemir	1-2 hours	6-8 hours	Up to 24 hours	http://www.webmd.com/diabetes/guide/diabetes-types-insulin?page=2
Human	Insulin Ultra-Lente	Humulin U	4-8 hours.	10-30 hours	>36 hours	http://www.medscape.com/viewarticle/426921_2
Human	Insulin Long-acting Isophane	Insulatard				http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000441/WC500033305.pdf

Annex 2.2: List of Countries Reviewed

Region	Country	MRA Product List	MRA Insulin Products
AFRO	Algeria	Yes	Yes
AFRO	Ethiopia	No	No
AFRO	Mali	No	No
AFRO	Ghana	Yes	Yes
AFRO	Mauritius	No	No
AFRO	Zimbabwe	No	No
AFRO	South Africa	Yes	Yes
AFRO	Botswana	No	No
AFRO	Rwanda	No	No
AFRO	Nigeria	Yes	Yes
AFRO	Uganda	No	No
AFRO	Namibia	No	No
AFRO	Kenya	Yes	Yes
AFRO	Senegal	No	No
AFRO	Burkina Faso	No	No

AFRO	Angola	No	No
AFRO	Benin	No	No
AFRO	Burundi	No	No
AFRO	Cameroon	No	No
AFRO	Cape Verde	No	No
AFRO	CAR	No	No
AFRO	Chad	No	No
AFRO	Comoros	No	No
AFRO	Congo	No	No
AFRO	Cote d'Ivoire	No	No
AFRO	Democratic Republic of Congo	No	No
AFRO	Equatorial Guinea	No	No
AFRO	Eritrea	No	No
AFRO	Gabon	No	No
AFRO	Gambia	No	No
AFRO	Guinea	No	No
AFRO	Guinea-Bissau	No	No
AFRO	Lesotho	No	No
AFRO	Liberia	No	No
AFRO	Madagascar	No	No
AFRO	Malawi	No	No
AFRO	Mauritania	No	No
AFRO	Mozambique	No	No
AFRO	Niger	No	No
AFRO	Sao Tome + Principe	No	No
AFRO	Seychelles	No	No
AFRO	Sierra Leone	No	No
AFRO	Swaziland	No	No
AFRO	Tanzania	No	No
AFRO	Togo	No	No
AFRO	Zambia	No	No
AMRO	Guatemala	Yes	Yes
AMRO	Argentina	No	No
AMRO	Brazil	Yes	Yes
AMRO	Cuba	Yes	Yes
AMRO	Mexico	Yes	Yes
AMRO	Honduras	No	No
AMRO	Peru	Yes	Yes
AMRO	Dominica Republic	Yes	Yes
AMRO	USA	Yes	Yes
AMRO	Canada	Yes	Yes
AMRO	Guyana	No	No
AMRO	Trinidad and Tobago	Yes	Yes
AMRO	Venezuela	No	No
AMRO	Colombia	Yes	Yes
AMRO	Chile	Yes	Yes
AMRO	Costa Rica	Yes	Yes
AMRO	Panama	No	No
AMRO	Uruguay	No	No
AMRO	Paraguay	No	No
AMRO	Jamaica	No	No
AMRO	Bahamas	No	No
AMRO	Bolivia	No	No

AMRO	Antigua and Barbuda	No	No
AMRO	Barbados	No	No
AMRO	Belize	No	No
AMRO	Dominica	No	No
AMRO	Ecuador	No	No
AMRO	El Salvador	No	No
AMRO	Grenada	No	No
AMRO	Haiti	No	No
AMRO	Nicaragua	No	No
AMRO	Saint Kitts and Nevis	No	No
AMRO	Saint Lucia	No	No
AMRO	Saint Vincent and the Grenadines	No	No
AMRO	Suriname	No	No
EMRO	Lebanon	Yes	Yes
EMRO	Morocco	Yes	Yes
EMRO	Pakistan	No	No
EMRO	Tunisia	No	No
EMRO	Egypt	Yes	Yes
EMRO	Jordan	No	No
EMRO	United Arab Emirates	No	No
EMRO	Oman	Yes	Yes
EMRO	Qatar	No	No
EMRO	Sudan	Yes	Yes
EMRO	Yemen	No	No
EMRO	Saudi Arabia	Yes	Yes
EMRO	Afghanistan	No	No
EMRO	Bahrain	No	No
EMRO	Djibouti	No	No
EMRO	Iran	No	No
EMRO	Iraq	No	No
EMRO	Kuwait	No	No
EMRO	Libya	No	No
EMRO	Somalia	No	No
EMRO	South Sudan	No	No
EMRO	Syria	No	No
EMRO	Palestine	No	No
EURO	Georgia	No	No
EURO	Tajikistan	No	No
EURO	Kyrgyzstan	Yes	Yes
EURO	Montenegro	Yes	Yes
EURO	France	Yes	Yes
EURO	Spain	Yes	Yes
EURO	Austria	Yes	Yes
EURO	Italy	Yes	Yes
EURO	Bosnia and Herzegovina	No	No
EURO	Serbia	Yes	Yes
EURO	Croatia	Yes	Yes
EURO	Republic of Moldova	Yes	Yes
EURO	Romania	Yes	Yes
EURO	Bulgaria	No	No
EURO	Germany	Yes	Yes
EURO	Poland	Yes	Yes
EURO	Netherlands	Yes	Yes

EURO	Kazakhstan	Yes	Yes
EURO	Denmark	Yes	Yes
EURO	EMEA	Yes	Yes
EURO	Greece	Yes	Yes
EURO	Belgium	Yes	Yes
EURO	Israel	Yes	Yes
EURO	Turkey	No	No
EURO	Ireland	Yes	Yes
EURO	Iceland	Yes	Yes
EURO	Portugal	Yes	Yes
EURO	Slovenia	Yes	Yes
EURO	Sweden	Yes	Yes
EURO	Norway	Yes	Yes
EURO	Malta	Yes	Yes
EURO	United Kingdom	Yes	Yes
EURO	Cyprus	Yes	Yes
EURO	Luxembourg	Yes	Yes
EURO	Finland	Yes	Yes
EURO	Hungary	Yes	Yes
EURO	Armenia	Yes	Yes
EURO	Azerbaijan	Yes	Yes
EURO	Ukraine	No	No
EURO	Albania	No	No
EURO	Belarus	Yes	Yes
EURO	Russian Federation	No	No
EURO	Andorra	No	No
EURO	Estonia	Yes	Yes
EURO	Czech Republic	Yes	Yes
EURO	Slovakia	Yes	Yes
EURO	Switzerland	Yes	Yes
EURO	Lithuania	Yes	Yes
EURO	Latvia	Yes	Yes
EURO	Former Yugoslav Republic of Macedonia	No	No
EURO	Monaco	No	No
EURO	San Marino	No	No
EURO	Turkmenistan	No	No
EURO	Uzbekistan	No	No
SEARO	Sri Lanka	No	No
SEARO	India	Yes	Yes
SEARO	Nepal	No	No
SEARO	Bangladesh	Yes	Yes
SEARO	Bhutan	Yes	No
SEARO	Thailand	No	No
SEARO	Maldives	No	No
SEARO	Indonesia	Yes	Yes
SEARO	Democratic Republic of Timor Leste	No	No
SEARO	DPR Korea	No	No
SEARO	Myanmar	No	No
WPRO	China	Yes	Yes
WPRO	Vietnam	No	No
WPRO	Philippines	Yes	Yes
WPRO	Fiji	No	No
WPRO	Singapore	Yes	Yes

WPRO	Republic of Korea	No	No
WPRO	New Zealand	Yes	Yes
WPRO	Brunei	Yes	Yes
WPRO	Mongolia	No	No
WPRO	Malaysia	Yes	Yes
WPRO	Japan	Yes	Yes
WPRO	Australia	Yes	Yes
WPRO	Cambodia	No	No
WPRO	Cook Islands	No	No
WPRO	Kiribati	No	No
WPRO	Lao's	No	No
WPRO	Marshall Islands	No	No
WPRO	Micronesia	No	No
WPRO	Nauru	No	No
WPRO	Niue	No	No
WPRO	Palau	No	No
WPRO	Papua New Guinea	No	No
WPRO	Samoa	No	No
WPRO	Solomon Islands	No	No
WPRO	Tonga	No	No
WPRO	Tuvalu	No	No
WPRO	Vanuatu	No	No

Annex 3. Comparison between NEMLs

Comparison of insulin on Reimbursement Lists versus NEMLs

As seen from Annex 3.1, the total number of products for the 2 pilot countries, Ghana and Morocco, are illustrated. Ghana has more products on its NEML (n=7) than its RL (n=3) in comparison with Morocco that has more products on its RL (n=42) in contrast to its NEML (n=1).

Annex 3.1. Total number of products on the NEMLs versus RLs

	No. of insulin products on the various lists	
Countries	Reimbursement List (RL)	National Essential Medicine List (NEML)
Ghana	3	7
Morocco	42	1

Annex 3.2 illustrates the different types of insulin on the NEML and RL of Ghana and Morocco. Morocco's RL lists all rapid and long acting analogue and human insulin; whereas its NEML only list human insulin. In contrast, Ghana's RL only lists human insulin whereas its NEML lists all long acting analogue insulin, 2 types of rapid acting analogue insulin and both types of human insulin.

Annex 3.2. Comparison between the Ghana and Morocco NEML and RL

Types of Insulin		Ghana		Morocco	
		RL	NEML	RL	NEML
Insulin Analogue Rapid-Acting	Insulin Lispro	0	*	*	0
	Insulin Aspart	0	*	*	0
	Insulin Glulisine	0	0	*	0
Insulin Analogue Long- Acting	Insulin Glargine	0	*	*	0
	Insulin Detemir	0	*	*	0
Insulin Human	Insulin Intermediate Acting	*	*	*	*
	Insulin Short Acting	*	*	*	*

*: Listed on National RL
0: Not Listed on National RL

Annex 4. Example Search Terms for a Single Country

Basic List
[country name] insulin marketing

[country name] insulin breach

[country name] insulin lawsuit

[country name] insulin bribe

[country name] insulin illegal

[country name] insulin corruption

Basic List with Insulin Names (used aspart, glulisine, lispro, NPH, regular human, detemir and glargine)
[country name] [insulin name] marketing

[country name] [insulin name] breach

[country name] [insulin name] lawsuit

[country name] [insulin name] bribe

[country name] [insulin name] illegal

[country name] [insulin name] corruption

Basic List with Company Names (used Novo Nordisk, Eli Lilly and Sanofi-Aventis)
[country name] insulin marketing [company name]

[country name] insulin breach [company name]

[country name] insulin lawsuit [company name]

[country name] insulin bribe [company name]

[country name] insulin illegal [company name]

[country name] insulin corruption [company name]