ACCESS TO MEDICINES
AND HEALTH PRODUCTS

# Keeping the 100-year-old promise: making insulin access universal

World Health Organization

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# Contents

# Foreword

In 1921, researchers at the University of Toronto discovered insulin, which changed the diabetes narrative forever.

In keeping with a promise that insulin "belongs to the world", the patent was sold for just one Canadian dollar. Subsequently, the private sector was engaged to improve manufacturing processes, technical know-how of insulin purification was shared, prices were reduced to improve affordability, and non-profit-making bodies were established to care for people living with type 1 diabetes.

Those were times of optimism and expectation, with a sense of urgency to give new hope and precious years of life to millions of people living with diabetes. However, despite the goodwill of the early days and collective efforts from many sectors, the promise that insulin would belong to the world has not been kept. Today, at least 30 million people who need insulin for diabetes do not have access to it.

This report presents a global picture with considerable access gaps, especially in low- and middle-income countries, where the use of insulin has not kept pace with the rising burden of diabetes. Even in some high-income countries, the price of insulin is unaffordable for many people, forcing them to ration the medicine, thereby risking their lives.

The report spotlights the main barriers to access to insulin and to medical devices for administering insulin and monitoring glucose levels, which are necessary for the appropriate use of the medicine. Many of these barriers can be overcome immediately through better policies and targeted interventions, with contributions from all stakeholders. The report describes five areas for action that will improve the availability and affordability of insulins and associated devices, as well as the capacity and research and development necessary to address future needs.

On the hundredth anniversary of insulin's discovery, we have a responsibility to take stock of current inequities and urgently seek to redress them, with the same spirit of solidarity the discoverers of insulin displayed. I hope the pages that follow will inspire new thinking, bolder policies and better collaboration across all relevant spheres, so that the millions of people who today are losing their health and precious years of life to diabetes can finally access a medicine discovered 100 years ago.

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# List of abbreviations

| | |
|---|---|
| COVID-19 | coronavirus disease 2019 |
| EML | WHO Model List of Essential Medicines |
| FDA | United States Food and Drug Administration |
| IU | international unit |
| NGO | nongovernmental organization |
| NRA | national regulatory authority |
| OECD | Organisation for Economic Co-operation and Development |
| R&D | research and development |
| WHO | World Health Organization |

# Executive summary

The year 2021 marks 100 years since the momentous discovery of insulin in 1921, which marked a turning point in care for those with diabetes mellitus (diabetes). Over the past century, better health outcomes for people living with diabetes have been incrementally achieved. However, despite the wishes of the discoverers of insulin, access to insulin and associated devices, and diabetes care more broadly, remains limited in many countries today. This report describes the current situation regarding access to insulin and associated devices. It seeks to understand the barriers to access and proposes actions to address them.

### Why do millions of people with diabetes need insulin?

Insulin is a hormone that controls the blood glucose level with effects on how the body regulates carbohydrates, proteins and fats. Absence of insulin or lacking a response to insulin are the causes of diabetes – a long-term health problem characterized by a persistently high level of blood glucose. There are two types of diabetes: in type 1 diabetes, the body does not make, or makes very little, insulin; in type 2 diabetes, the body progressively loses its ability to make sufficient insulin and to respond normally to the hormone. Left untreated or poorly managed, diabetes can lead to complications like heart attacks, strokes, blindness, kidney failure and lower limb amputation.

Diabetes is a significant cause of premature deaths and a major public health problem. It also imposes a significant financial burden on health systems and individuals. Today, more than 420 million people are living with diabetes globally; 4 in 5 of them live in low- and middle-income countries. An estimated 9 million people living with type 1 diabetes rely on life-long treatment with insulin for survival. Among people living with type 2 diabetes, an estimated 63 million people need insulin as part of their treatment, but only about half of them are treated with it.

### Why don't people with diabetes have adequate access to insulin and associated devices?

Access to essential health products like insulin and associated devices to administer it depends on having appropriate products available at affordable prices. In many countries, however, insulins and associated devices are neither available nor affordable if available. One of the reasons for this may be due to the significant market shift in the types of insulin being used. Since the introduction of higher-priced insulin analogues in the 2000s, their use is increasing in place of human insulin. While this trend has been observed initially in high- and middle-income countries, it is now being seen in low-income countries as well. This shift is concerning for several reasons.

First, evidence shows that insulin analogues confer small or no additional benefit for most clinical outcomes compared to human insulin, except possibly for people with diabetes for whom the risk of hypoglycaemia cannot be overcome by self-management. Second, in certain markets, the lower quantity demanded for human insulin following the market shift may have led to price increase for human insulin, thereby reducing its affordability. Third, the shift may disrupt the overall global supply of human insulin, which would restrict availability of human insulin for health systems and people with diabetes unable to afford higher-priced insulin analogues. Together, this shift has added considerable constraints on health systems' ability to provide universal access to insulins, including in high-income countries where there have been reports of people living with diabetes resorting to self-rationing to save money, with grave health consequences.

The market shift also reflects a suite of underlying market and health system problems. Specifically, there is a non-competitive market environment, with the global supply of insulins being dominated by three pharmaceutical companies that have considerable market power on pricing, supply and demand. Furthermore, the comparatively small market size, intellectual property protection and other market exclusivities on insulins or associated devices, and regulatory requirements have discouraged market participation of potential manufacturers of biosimilar insulins, thereby stifling competition. Suboptimal regulation and policies have also contributed to access barriers. These include suboptimal pharmaceutical pricing policies, weak procurement and supply chain management, insufficient financing to cover demand and overall weak governance.

In addition, appropriate use of insulin is hampered by a lack of access to affordable medical devices for safe administration and optimal glucose monitoring to guide insulin use. The market for diabetes medical devices is characterized by market exclusivity due to patents, excessive product differentiations and problematic marketing practices. One example is the so-called freemium practice where consumers or health systems are locked into using proprietary high-cost glucose monitoring test strips in exchange for low- or no-cost glucose meters. More broadly, insufficient health system capacity and infrastructure has also limited access to appropriate treatment. These include a lack of service integration at the primary health care level; inadequate capacity (e.g. skilled clinicians and services) for providing diabetes care and ensuring supply continuity; and infrastructure for information management, supply management and local production of insulins.

Alongside, research and development has not been geared towards the public health needs of low- and middle-income countries, where there is a significant burden of diabetes and a lack of thermostable insulins – effectively further limiting access to insulin due to the medicine's cold chain requirements.

### How should access barriers be addressed?

To address the barriers to access, this report presents five key areas for action with specific sub-items identified through discussions with stakeholders, summarized in Fig. 0.1 Recognizing that concerted efforts are needed by all stakeholders, Annex 2 presents specific areas for action illustrated in Fig. 0.1 and suggests primary and secondary actors required to realize these actions in the short, medium and long term.

### Making insulin access universal is an urgent public health priority

The great disparity in access to insulins and associated devices globally, and the associated health outcomes, is not acceptable and certainly does not align with the vision of the discoverers of insulin a century ago. Many barriers to access outlined in this report could be addressed immediately through better policies and targeted interventions. This would have an immediate effect on the disease burden associated with diabetes and improve the lives of millions of people. Implementing such actions would allow the global community to carry on the legacy and goodwill of the discoverers of insulin, and keep their promise that insulin "belongs to the world".

Fig. 0.1. Areas of action to improve access to and appropriate use of insulins and associated devices

# 1. Introduction

The year 2021 marks 100 years since the momentous event in 1921 when researchers at the University of Toronto successfully extracted insulin from a dog's pancreas. In 1922, experiments in people living with type 1 diabetes mellitus (diabetes) who were administered insulin showed reduced levels of glucose in blood and urine, and the disappearance of ketone bodies in urine – a sign of uncontrolled diabetes (*1*). In 1923, Frederick Banting and John Macleod were awarded the Nobel Prize in Physiology or Medicine "for the discovery of insulin" (*2*); they subsequently shared their joint accolade with two other co-researchers, Charles Best and James Collip. This discovery has forever transformed the lives of millions of people living with diabetes.

Indeed, the ensuing years since the discovery of insulin saw a collective quest to urgently broaden patient access to this life-saving medicine (*1*): the patent on insulin was sold to the University of Toronto for just 1 Canadian dollar under an agreement to ensure affordability for everyone who needed the medicine; the university entered a partnership with Eli Lilly to scale up production and to reduce variability of potency; August Krogh was authorized to use the protocol for insulin purification developed by the researchers, who then brought insulin production to Scandinavia through a non-profit-making body, Nordisk Insulin Laboratory; and diabetes clinics were set up in the Americas and Europe to offer specialized care and insulin for people with diabetes.

> *"Insulin does not belong to me, it belongs to the world"*
>
> *– Frederick Banting*

At the time, the commitment to save lives was also met with urgent actions to make insulin more affordable. For example, a publication in 1923 documented that within nine months of insulin becoming available in the United Kingdom, the retail price of insulin was halved to "12s. 6d. per bottle of 100 units"[1] (*3*). In the United States of America, price was reduced by an additional 37% in the same period of time, resulting in the lowest global price at the time. The price reduction was achieved alongside "enhancement in the strength of the unit, so that the total effective reduction in cost to the patient is much larger than appears from the figures of price revision" (*3*). With larger economies of scale and better efficiency in manufacturing process, price reduction continued, with the price of 100 units of regular short-acting insulin in the United States falling to "less than 20 cents in the 1940s (about $3 in 2019 U.S. dollars)" (*4*).

In the decades that followed, scientific advancements have seen the advents of a prolonged release profile with the protamine formulation in the 1930s; production based on recombinant technology in the 1980s to create exact copies of human insulin instead of relying on bovine and porcine extracts; and modification of the site of amino acids in insulin to alter its pharmacokinetic profiles, creating insulin analogues in the 1990s. In parallel, there were also improvements in the delivery devices for insulins including reusable and

[1] Estimated by Bank of England's inflation calculator to be equivalent to approximately £ 38 in 2020, assuming an average inflation of 4.3% a year (https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator).

disposable pens; technologies used for monitoring glucose control; as well as positive progresses in service delivery and self-management by people living with diabetes.

Despite all the advancements made in the past century and Banting's proclamation that "Insulin does not belong to me, it belongs to the world", universal access to insulin remains an elusive promise in many countries today. The centenary year since the discovery of insulin therefore marks not only a time for celebration, but also a time for deep reflection on how the global community could urgently narrow the gaps in access to insulins and diabetes care more broadly.

## 1.1 Aims of this report

This report aims to describe the current situation regarding global access to insulins (Chapter 2), clarify the sources of barriers to access (Chapter 3), and suggest collective actions required from all stakeholders to improve access to quality, safe, effective, affordable insulins and associated health products (Chapter 4).

# 2. Access to insulin for people living with diabetes

## 2.1 Diabetes and treatment with insulin

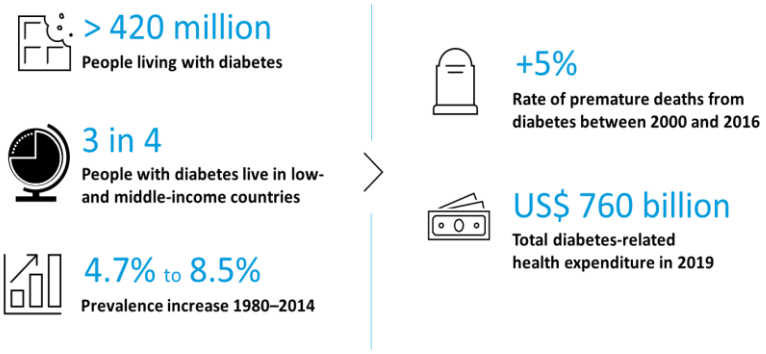
### 2.1.1 Diabetes and its disease burden worldwide

Diabetes is a chronic, progressive disease characterized by elevated blood glucose levels. There are two types of diabetes. In type 1 diabetes, the body does not make, or makes very little, insulin. In type 2 diabetes, the body progressively loses its ability to make sufficient insulin and to respond normally to insulin. Controlling diabetes requires management of glucose levels in people living with diabetes. Left untreated or poorly managed, diabetes can lead to complications such as damage to the heart and blood vessels, eyes, kidneys and nerves, causing heart attacks, strokes, blindness, kidney failure and lower limb amputation and ultimately premature death.

Diabetes is a major global public health problem due to its high and increasing prevalence and associated morbidity and mortality. It is estimated that more than 420 million people are living with diabetes globally, and that 80% of them live in low- and middle-income countries (*5*), as classified by the World Bank[2] (*6*). Among these are 9 million people estimated to be living with type 1 diabetes (*7*). The number of people with diabetes has almost quadrupled since 1980. This is due to an increasing and ageing population, and rising prevalence of major risk factors of type 2 diabetes: overweight and obesity, and physical inactivity (*8*). The age-adjusted prevalence in adults has increased from 4.7% in 1980 to 8.5% in 2014, increasing more rapidly in low- and middle-income countries where prevalence is the highest globally (*5*).

Diabetes has health and economic impacts on individuals and societies, and imposes considerable human cost due to premature deaths and health expenditure (Fig. 2.1). Between 2000 and 2016, the rate of premature death due to diabetes increased by 5%. The International Diabetes Federation estimated the total diabetes-related health expenditure in 2019 to be US$ 760 billion; continuing increases are expected as the number of people with diabetes is predicted to reach 578 million by 2030 (*9*).

Fig. 2.1. Diabetes and its worldwide burden in numbers




Source: (*5*,*9*)

[2] Country income groupings of low, lower-middle, upper-middle and high are determined by the World Bank based on gross national income per capita.

### 2.1.2 Insulins for the management of diabetes

Insulin is a hormone that controls the blood glucose level with effects on how the body regulates carbohydrates, proteins and fats. The bodies of people living with type 1 diabetes do not make or make very little insulin to regulate blood glucose levels, and they rely on lifelong treatment with insulin for survival. Treatment with insulin is also important for people living with type 2 diabetes upon disease progression, when natural insulin secretion decreases and oral medicines are insufficient to control blood glucose level.

Specifically, the 2018 World Health Organization (WHO) guidelines recommend the use of human insulin to manage blood glucose levels in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (*10*). The recommendation includes both short-acting and intermediate-acting human insulin. The guidelines recommend considering the use of long-acting insulin analogues to manage blood glucose in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin. The recommendation for long-acting insulins is considered as a weak recommendation, reflecting the lack of, or very low-quality evidence for the long-term outcomes of long-acting insulin analogues compared to short- and intermediate-acting human insulin.

For people living with diabetes who are using insulin, monitoring of blood glucose is necessary to detect hyperglycaemia and hypoglycaemia because it allows them to adjust the dose of insulin accordingly, or if low blood glucose level is detected, to consume food or drink that contains sugar or use glucagon (*11*).

### 2.1.3 Insulins and the WHO Model List of Essential Medicines

Human insulin has been listed on the WHO Model List of Essential Medicines (EML) since the first list was published in 1977. In 1985, the WHO Expert Committee on the Selection and Use of Essential Medicines approved the inclusion of the intermediate-acting insulin isophane neutral protamine Hagedorn, commonly abbreviated as NPH insulin.

In 2021, the WHO Expert Committee on the Selection and Use of Essential Medicines recommended inclusion of long-acting insulin analogues (insulin detemir, insulin degludec and insulin glargine, and their quality-assured biosimilars, as therapeutic alternatives), on the core list of the EML and EML for Children for the treatment of people with type 1 or type 2 diabetes who are at high risk of experiencing hypoglycaemia with human insulin (*12*). In recommending the listing of long-acting insulin analogues, the WHO Expert Committee on the Selection and Use of Essential Medicines noted that "the magnitude of clinical benefit of long-acting insulin analogues over human insulin for most clinical outcomes was small, making the large price differential between insulin analogues and human insulin difficult to justify", and was "unequivocal that affordable access to human insulin remains a critical priority, globally" (*12*). The inclusion of insulin analogues on the EML and EML for Children intends to facilitate participation of biosimilar insulin manufacturers in the WHO Prequalification programme[3] - a programme relied on by many countries and procurement agencies to ensure the quality standards of medicines and health products. Over time, this programme could

[3] The WHO Prequalification programme undertakes assessment of product dossiers, inspection of manufacturing and clinical sites, and organization of quality control testing before certifying a medicine and health product as being prequalified, in readiness for procurement. A prerequisite for establishing a WHO Prequalification programme for a medicine is its listing on the EML.

increase the availability of biosimilar insulins and create greater market competition, leading to price reduction and potentially improved affordability.

### 2.1.4 Treatment coverage and gaps

Diabetes and its consequences can be effectively managed with a combination of non-pharmacological lifestyle interventions (e.g. diets and exercise) and pharmacological treatments (e.g. medicines to lower blood glucose, blood pressure and cholesterol). Despite existing knowledge on how to manage diabetes effectively, treatment coverage varies among people living diabetes. For example, a recent study found that only about 1 in 20 adults with diabetes[4] living in low- and middle-income countries reported having had their needs for recommended treatments fully met (*13*). For glucose-lowering medicines (including insulin), this study found that about 1 in 2 people with diabetes reported having their treatment needs met (*13*).

Specific treatment coverage with insulin among people living with type 1 diabetes has not been estimated, but it is important to reiterate that the 9 million people living with type 1 diabetes (*7*) depend on lifelong treatment with insulin for survival. For people living with type 2 diabetes, a modelling study estimated that about 15% of them require insulin (i.e. about 63 million globally), but that only about half of them are being treated with it (*14*). It estimated that if insulin were accessible to all people living with type 2 diabetes who need it, the total volume of insulin used globally would increase from 516.1 million 1000-IU vials in 2018, to 633.7 million 1000-IU vials in 2030 (*14*).

### 2.1.5 Global mandate on the prevention and control of diabetes and access to insulin

In 2021, the Seventy-fourth World Health Assembly adopted resolution WHA74.4 *Reducing the burden of noncommunicable diseases through strengthening prevention and control of diabetes* (*15*). The resolution urges Member States to raise the priority given to the prevention, diagnosis and control of the diabetes epidemic, as well as the prevention and management of risk factors such as obesity.

The resolution recommended action in a number of areas, including improving access to insulin; promoting convergence and harmonization of regulatory requirements for diabetes medicines, including insulin, biosimilars and other related health products; and assessing the feasibility and potential value of establishing a web-based tool to share information relevant to the transparency of markets for diabetes medicines and health products (*15*).

In addition, the resolution recommended development of potential targets for the prevention and control of diabetes. In response, the Secretariat had consulted experts and proposed five voluntary global diabetes coverage targets to be established and achieved by 2030 (*16*)[5]. These are:

i. 80% of people with diabetes are diagnosed;
ii. 80% of people with diagnosed diabetes have good control of glycaemia;

[4] In this study, diabetes status was defined by self-reported use of a glucose-lowering medication (oral glucose-lowering medication or insulin) or biochemical evidence of diabetes using the WHO definition. The study did not differentiate between subjects with type 1 and type 2 diabetes.

[5] Please note that the listed targets will be presented to the 150th WHO Executive Board and the 75th World Health Assembly for consideration and approval.

iii. 80% of people with diagnosed diabetes have good control of blood pressure;
iv. 60% of people aged 40 years and older with diabetes receive statins; and
v. 100% of people with type 1 diabetes have access to affordable insulin treatment and blood glucose self-monitoring.

## 2.2 Market dynamics of insulin

### 2.2.1 Producers of insulin

At least 40 companies currently manufacture or market insulin products globally (*17*). These include three large multinational pharmaceutical companies (Eli Lilly, Novo Nordisk, Sanofi), manufacturers of biosimilar insulins in commercial partnership (Eli Lilly-Boehringer Ingelheim[6], Mylan-Biocon, Sandoz-Gan&Lee), and smaller companies serving local or regional markets. Many of these smaller companies have licensing or supply agreements with major producers, and local manufacturing is primarily limited to human insulin. After accounting for licensing and supply agreements, one study estimated "probably ten independent insulin manufacturers globally" (*17*).

The relatively low number of manufacturing firms for insulin globally is likely to be related to several factors. Unlike the manufacturing of medicines with low molecular weights (so-called small molecules), manufacturing biological medicines (including insulins) requires a higher level of engineering and facility requirements. Additional steps are also required to ensure compliance with good manufacturing practice, regulatory requirements and to minimize batch-to-batch variability. The scale and optimization of production processes are also important to reduce the overall cost of goods (*18*,*19*). These factors, together with the dominance of the large biopharmaceutical companies (see sections 2.2.2 and 2.2.3), have to date hindered smaller pharmaceutical firms from entering the market.

### 2.2.2 Market size

According to trade data (*20*), customs value[7] of insulin products in 2020 is estimated to be worth around US$ 7.2 billion in export value and US$ 10.15 billion in import value (Fig. 2.2). A significant proportion of insulin trade (including reimportation) occurred among high-income and upper-middle-income countries, and in countries located in the WHO Region of the Americas, WHO European Region, and the WHO Western Pacific Region. Revenue information from the audited financial statements of Eli Lilly (*21*), Novo Nordisk (*22*), and Sanofi (*23*) showed that insulin products generated an estimated US$ 16.64 billion of sales in 2020, with more than 60% of the revenue being generated in North America and Europe.

Epidemiological data (*24*) indicated that about 3 in 4 people with diabetes lived in countries outside of North America and Europe in 2019. The trade and revenue information presented above therefore demonstrates that there are a significant number of underserved markets in lower-income countries and in the WHO African Region, WHO South-East Asia Region and WHO Eastern Mediterranean Region. A study by Sharma & Kaplan also identified mismatches between trade data to the diabetes prevalence data from

[6] Marketing approval of insulin glargine by Eli Lilly-Boehringer Ingelheim was granted following a new drug application.
[7] Customs valuation is typically based on the actual price of the goods shown on the invoice. For further explanation, please refer to www.wto.org/english/tratop_e/cusval_e/cusval_info_e.htm.

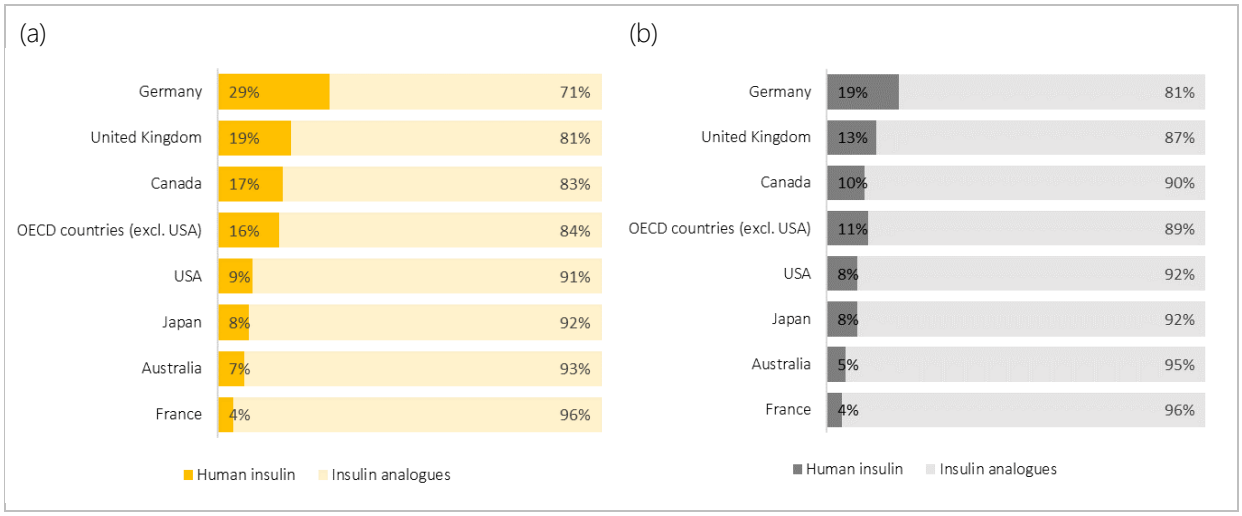
the NCD Risk Factor Collaboration (NCD-RisC) in Africa and Asia, indicating insulin imports were insufficient to meet the estimated needs in these regions (*25*).

In low- and middle-income countries, insulin produced by three companies – Eli Lilly, Novo Nordisk, and Sanofi – accounted for at least two thirds of the market, as estimated by level of consumption (WHO-Defined Daily Dose[8]) (*26*). In 60% of the low- and middle-income countries studied, products from these companies accounted for as much as 95% of the market, suggesting a moderately to highly concentrated market[9] in those countries.

### 2.2.3 Market share by insulin type

A significant market shift in the types of insulin being used has been observed in high- and middle-income countries since the introduction of insulin analogues in the 2000s. The trend is an increasing use of insulin analogues (short-acting and long-acting) in place of human insulin in those contexts. A study by Beran, Ewen & Laing (2016) found that in 2009, two thirds of insulin products used in high-income countries and one third in middle-income countries were insulin analogues (*27*). A study compared the market share of insulins in countries in the Organisation for Economic Co-operation and Development (OECD) in 2020 and found that insulin analogues had dominated the markets in many of these high-income countries in volume and sales (Fig. 2.2) (*28*). However, significant variations exist in the relative market share, with human insulin retaining 29% in volume in Germany compared to only 4% in France (*28*).

**Fig. 2.2. Market share by insulin type in select OECD countries in 2018, by (a) volume and (b) sales**




*Source*: (*28*).

Beran, Ewen & Laing (2016) observed a similar shift in demand towards insulin analogues had begun in lower-income countries since mid-2000 (*27*). A recent study found that insulin analogues accounted for 42% of the days of therapy for insulins across the 32 low- and middle-income countries studied in 2020, compared to 25% a decade ago (*26*). Eli Lilly, Novo Nordisk, and Sanofi supplied 92% of the insulin

[8] Defined Daily Dose is defined by WHO as "the assumed average maintenance dose per day for a drug used for its main indication in adults". Please refer to www.who.int/tools/atc-ddd-toolkit/about-ddd for further explanations.

[9] With a Herfindahl-Hirschman Index of at least 1500.

analogues in these countries (*26*), suggesting market dominance and influence, with implications on pricing and affordability (see section 3.4).

### 2.2.4 Biosimilar insulins

Biosimilar products, or similar biotherapeutics, contain biological substances for medical use that are made by living organisms (e.g. insulin) rather than manufactured chemicals. They produce the same therapeutic effects as the original product because they are highly similar, although not chemically identical, to the original product. Thus, biosimilar insulins approved by stringent regulatory authorities produce the same therapeutic effects to the insulin product made by the originator company, even though they may not be chemically identical.

All forms of human insulin are no longer under patent protection. However, there is a lack of biosimilar human insulin approved by stringent regulatory authorities. In November 2019, WHO initiated the prequalification programme for human insulin (*29*), with the goal of maintaining and expanding the market for human insulin. In recent years, the patents for several insulin analogues have expired, paving the first steps for market entry of biosimilar insulins. The European Medicines Agency approved the first biosimilar insulin, LY2963016 insulin glargine, in 2014. The United States Food and Drug Administration (FDA) approved the first biosimilar insulin, Semglee (insulin glargine-yfgn) in 2021 (*30*), which may be interchangeable with its reference product. Information from the audited financial statements of Eli Lilly, Novo Nordisk, and Sanofi in 2020 showed that about 20% of their total revenue for insulins was generated from insulins under market protection for patents relating to their chemical substance, formulation or delivery devices. These include insulin glargine in 300-IU/mL formulation (*23*), insulin degludec and its combinations (e.g. insulin aspart, liraglutide) and insulin aspart (*22*).

The markets for biosimilar insulins have not been substantially compared to the markets of reference products marketed by the original patent holders in some markets. For example, in Europe, since the introduction of the first biosimilar insulin in 2014, biosimilar insulins only accounted for 13% of the volume in post-exclusivity market and 4% of the total insulin market by 2020 (*31*). Compared to other therapeutic areas, the rate of growth in market share for biosimilar insulins has also been much slower. To this point, in Europe, biosimilar anti-tumour necrosis factor accounted for 41% by volume of the post-exclusivity market by 2020, while biosimilar anti-cancer medicines accounted for 45% by volume of the post-exclusivity market by 2020 (*31*).

One explanation for the low market penetration of biosimilar insulin relates to the fact that only few companies have launched biosimilar insulins. For example, in the United States, one of the two insulin lispro products is marketed by the original patent holder (Eli Lilly). Biosimilar insulins have been launched by one of the three large multinational pharmaceutical companies (e.g. Sanofi's biosimilar insulin lispro, Eli Lilly's biosimilar insulin glargine[10]), effectively extending their market dominance.

In certain markets, market penetration also relates to reimbursement policies of pharmaceutical insurance schemes and clinical recommendations. For example, in the United States, biosimilar insulin glargine was not included on the Medicare Part D formularies until January 2018, despite being launched two years earlier in

[10] Note that these products were approved by the FDA through a New Drug Application, rather than biosimilars pathway 351(k) or the 505(b)(2), although it was intended to compete as a similar biotherapeutic.

December 2016 (*32*). In Denmark, biosimilar insulin only accounted for 18% in volume of the market in 2020 (*31*). In contrast, biosimilar anti-tumour necrosis factor accounted for more than 90% in market volume in Denmark, reflecting the tendering system and treatment recommendations from the Danish Medicines Council to use adalimumab biosimilars for all indications following patent expiry (*31*,*33*).

A lack of market participation from potential biosimilar manufacturers who are not the original patent holders can be explained by other underlying factors. These include the comparatively small market for insulins, market dominance of the large biopharmaceutical companies and higher technology and cost requirements. As will be presented in Chapter 3, barriers related to intellectual property, regulatory requirements, and policy and clinical recommendations on interchangeability, can also influence the ability of smaller pharmaceutical firms to enter and compete in the market.

# 3. Barriers to access to insulin and associated devices

## 3.1 Research and development

One of the main needs in research and development (R&D) is on the clinical efficacy of insulins at ambient temperatures in different home and storage settings. The cold storage requirement of insulin is a major challenge especially in hot climates and in countries or humanitarian settings where people have limited access to refrigeration or reliable electricity. Manufacturers' specifications require unopened insulin vials to be stored at 2–8°C, while storage at room temperature (25–30°C) is usually permitted for the 4-week usage period during use. However, room temperatures in many settings often exceed these requirements. Results from a recent study by Kaufmann and colleagues (*34*) indicate that insulin remains stable and biologically active and that vials can be stored after opening, at oscillating ambient temperatures and up to 37°C over a four–week period, offering promise for easier management of diabetes in resource limited settings. However, additional research is needed to definitively determine efficacy and safety of insulins at ambient temperatures in different settings.

As noted in section 2.1.2, appropriate use of insulins requires monitoring of blood glucose level. To this end, one area of need for R&D is on standardization of blood glucose monitoring devices to avoid barriers arising from a lack of compatibility across different brands or different iterations of devices, hindering users' ability to interchange between devices or compelling them to purchase new devices. This is a known problem in the medical device sector, where extreme diversity of medical devices - types, degrees of complexity, applications, usage, users, context, and research – is often "not based on public health need" (*35*). Standardization would therefore avoid the need to regularly change to different glucose meters due to inconsistent availability of glucose test strips. It would also encourage market competition and protect consumers against marketing practices of unauthorized devices (e.g. (*36*)).

## 3.2 Intellectual property

Intellectual property can be a barrier to market entry for some insulins currently on the market as well as future products, including delivery devices. Currently, there are no patents on human insulin. Most patents on first generation insulin analogues (e.g. insulin glargine, insulin detemir) have expired since 2015, and patents in low-income countries have been infrequent (*37*). However, new patents are being filed (e.g. insulin glargine 300-IU/mL formulation) and additional forms of intellectual property protection and other strategies, including regulatory and market exclusivities, are creating barriers to competition and access.

Many new patents in the past decade were linked to delivery devices and not the insulin per se (e.g. (*38*)), which effectively extends the patent life of the underlying insulin (*39*). Excessive filing of secondary patents also occurs in addition to primary patents. For example, the primary patents of insulin glargine expired in 2015 in the United States, but Sanofi has filed 70 secondary patent applications (*40*,*41*). If granted, these additional patents would add 37 more years of market protection (*40*). Such intellectual property barriers created by patents on devices and secondary patents have implications on pricing and affordability. For

example, more than 90% of privately insured people with type 2 diabetes in the United States are prescribed the more expensive versions of insulin (*41*). With market dominance, a company could also dictate price increases. One study in the United States observed a significantly higher rate of increase in the reimbursement prices of insulins with patent protection (US$ 0.20 per quarter) compared to insulins without patent protection (US$ 0.05 per quarter) (*42*).

## 3.3 Regulatory challenges

Regulatory authorities are responsible for ensuring that medicines meet requirements for quality, safety and efficacy. As such, medicines must be registered by national regulatory authorities (NRAs), and the diversity of requirements used by different regulatory authorities for marketing authorization can add costs and complexity for manufacturers. For biological products including biosimilars, this process is more complex than for chemical entities.

WHO issued guidelines for the regulatory evaluation of biosimilars in 2009 (*43*). These guidelines have contributed to increasing regulatory convergence but challenges remain. Specifically, limited experience and a lack of expertise for the evaluation of the quality, safety and efficacy of biosimilars by NRAs in resource-limited countries are a common barrier to market entry for biosimilar manufacturers in these countries. Sharing experiences and knowledge relating to biosimilars among NRAs may reduce this challenge. This type of work and information sharing have been recognized as possible avenues for the development of expertise as a short-term measure (*44*).

Biotherapeutics that are neither originator products nor biosimilars have been approved in several countries (*44*). These products should be referred to differently than biosimilars (e.g. "noninnovator products" or "copy-version products", distinguishing them from biosimilars), since they were not approved according to the regulatory evaluation principles for biosimilars. In addition, some countries have products called "biosimilars" that were approved prior to the establishment of a regulatory framework for approving biosimilars, including insulin (*45*). Inappropriate labelling of such products as biosimilars may have a negative impact on public trust in biosimilars. Since gaining the trust of all stakeholders is essential for increasing the uptake of biosimilars, NRAs should distinguish such products from biosimilars (*46*). Some of these biotherapeutics may need to be reassessed by NRAs to establish their suitability for clinical use (*47*).

Another regulatory challenge for developing biosimilar medicines relates to the need for collecting a larger amount of nonclinical and clinical trial data to demonstrate biosimilarity, thereby increasing the time and resource requirements for their development. Developing biosimilar insulins would be subjected to such requirements, but the time and costs are expected to be lower than many other biotherapeutics. First, insulin has a relatively smaller and simpler molecular structure, which means that it can be comprehensively characterized chemically. Insulin also has well-established mechanisms of action and clinical experience. These two facts could allow for reduced clinical trial data (e.g. no efficacy trial requirements), which in turn would contribute to saving time and lowering the development costs of biosimilar insulins.

## 3.4 Pricing and affordability

A lack of affordability of insulins has been noted as one of the main barriers to access. In adopting resolution WHA74.4, the World Health Assembly noted

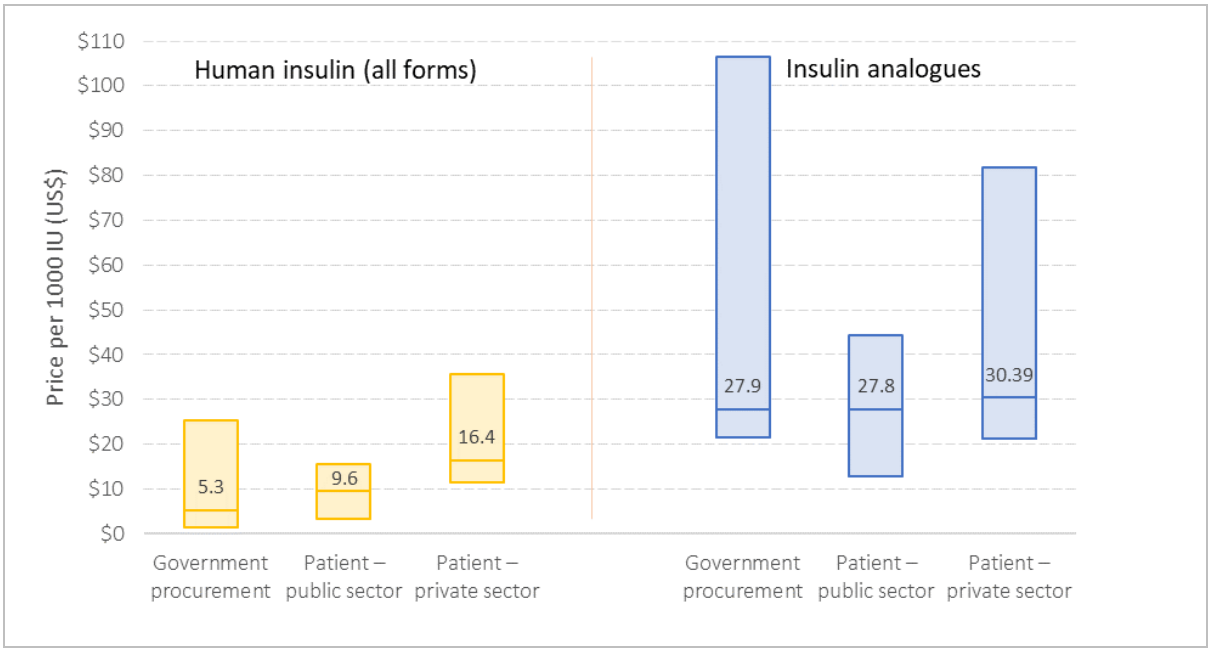
> that insulin is largely unaffordable for people paying out-of-pocket and that its high prices are a burden for national health systems, and [noted] the significant role that mark-ups along the value chain may play in pricing for patients and health systems (*15*).

This section examines the pricing of insulin products, with a view to understanding problems relating to its lack of affordability. It is important to note from the outset that comparative assessment of the pricing of insulin products has been challenging because of inconsistent and non-transparent reporting of prices. For example, due to non-transparent pricing, most studies report list prices without accounting for rebates or discounts that might have been applied. There are also methodological differences in data collection and analysis. For example, some studies expressed the price per international unit (IU) of insulin, while other studies reported price per standard unit vial. Other studies expressed the price as the cost per day based on an assumed standard dose of 40 IU per day, or the Defined Daily Dose. Furthermore, prices might have been collected at different points along the supply and distribution chain (e.g. ex-manufacturer, ex-pharmacy or reimbursement price). Readers should be mindful of these methodological differences as they read the following sections.

### 3.4.1 Pricing of insulin products in low-income and middle-income countries

Ewen and colleagues (2019) investigated the pricing of insulins in health facilities, as well as government tender prices, in 13 low- and middle-income countries in 2016 (*48*). They reported considerable variability in the prices of human insulin and insulin analogues in the countries surveyed, with prices sourced from the public and private sectors typically showing a 3- to 5-fold difference between the lowest and highest reported prices per 1000 IU (Fig. 3.1). The study found that in all sectors pricing of insulin analogues was generally much higher than that of human insulin.

**Fig. 3.1. Reported price range of human insulin and insulin analogues in 13 low- and middle-income countries, by purchasing source[a]**




[a] The boxplots show the median and maximum and minimum standardized prices for 1000 IU across product presentation; low- and middle-income countries studied were Brazil, China (Hubei and Shaanxi provinces), Ethiopia, Ghana, India (Haryana and Madhya Pradesh states), Indonesia, Jordan, Kenya, Kyrgyzstan, Mali, Pakistan, Russian Federation (Kazan province) and Uganda.

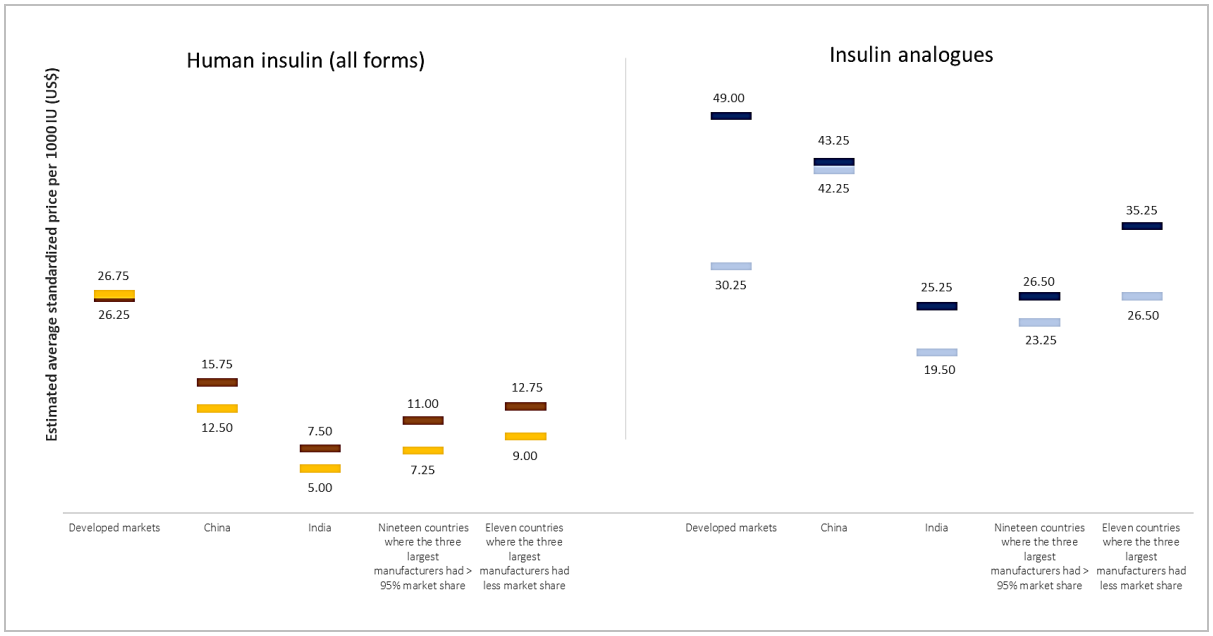
*Source*: (*48*).

Another study analysed sales and pricing data of insulins collected at varying points in the supply chain in 32 low- and middle-income countries (*26*). It reported list prices at the ex-manufacturer level after data were normalized statistically and according to margins and mark-ups allowed under the pricing legislations or regulations. In this study, human insulin (at the ex-manufacturer level) were estimated to cost about US$ 0.20–0.63 per 40 IU (i.e. the Defined Daily Dose), while insulin analogues were estimated to cost about US$ 0.78–1.73 per 40 IU. These estimates correspond to US$ 5.00–15.75 per vial (1000 IU) of human insulin and US$ 19.50–43.25 per vial of analogue insulin, which seem comparable to the government procurement (i.e. ex-manufacturer/distributor) prices reported by Ewen and colleagues (*48*) (Fig. 3.1).

*Pricing of insulin analogues was much higher than human insulin in all sectors globally*

The study also reported price comparisons with consideration of market characteristics (Fig. 3.2). The study observed higher list prices of human insulin and insulin analogues in so-called developed markets (i.e. high-income countries) than in the low- and middle-income countries under study[11] (*26*). In 13 of the 32 markets where the three largest insulin manufacturers did not have a significant presence, the study found that the estimated average standardized prices were 21–33% lower for human insulin and 2–25% lower for insulin analogues.

**Fig. 3.2. Estimated standardized prices of human insulin and insulin analogues, by market characteristics[a]**




[a] Dark-colour bars represent the average prices from Eli Lilly, Sanofi and Novo Nordisk, and light-coloured bars represent the average prices from other companies (ranging from 1 to 10 companies depending on country). For comparability, prices were standardized and expressed in 1000-IU vials (rather than 40 IU Daily Defined Dose).

*Source*: (*26*).

[11] The only exception was in China where the list prices of analogue insulins not made by the largest insulin companies were higher than the prices of analogues similarly-made in high-income countries.

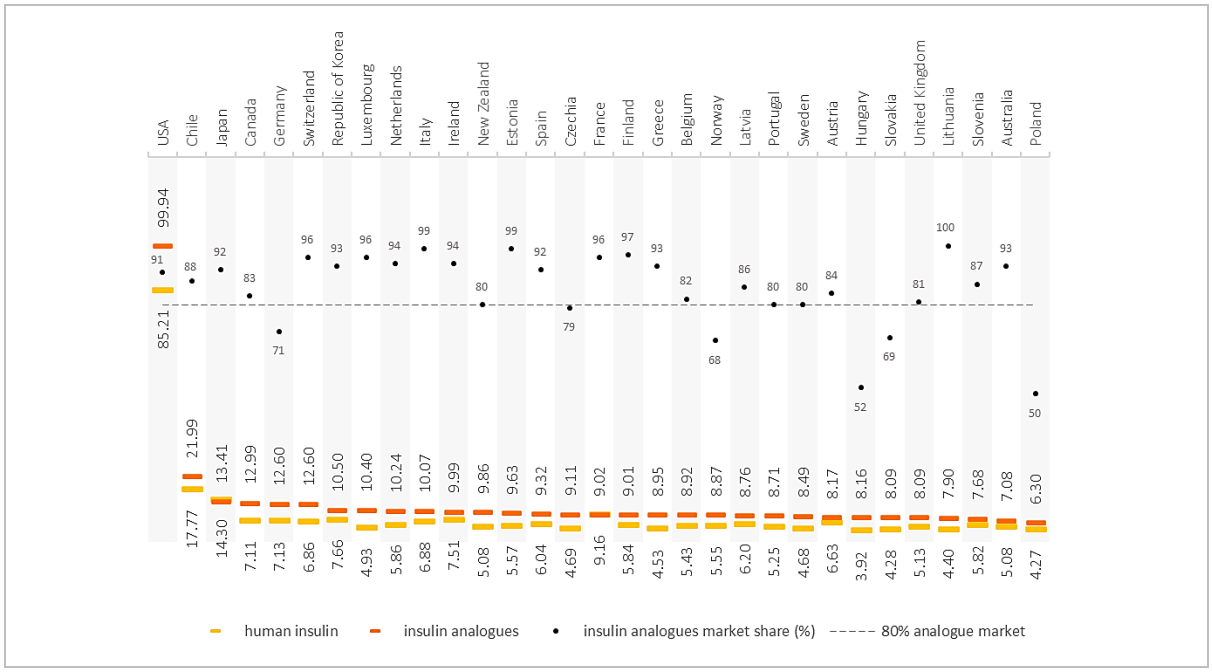
### 3.4.2 Pricing in high-income countries

A study commissioned by the U.S. Department of Health and Human Services investigated the prices of insulins in a select set of high- income countries (*28*). Based on ex-manufacturer prices in a proprietary database, this study found that list prices for human insulin and insulin analogues in 2018 were significantly higher in the United States compared to other high-income countries studied (Fig. 3.3). The study attempted to account for volume characteristics in its analysis and found that prices in the United States for all insulin types combined ranged from 5.9 to 9.4 times those in the selected high-income countries, despite having a large market by volume and sales (*28*). The market share of insulin analogues was also high in the United States. Authors acknowledged that the data used for the analysis did not reflect rebates or other discounts, but such rebates and discounts would need to have been very large to offset the large differences in price relative to other high-income countries (*28*).

*While analogue insulins account for more than 80% of the markets in many high-income countries, some countries continue to maintain the market for human insulin with significant market share*

Despite having a higher price, the market share of insulin analogues (by volume) in the high-income countries studied were generally above 80% of the total market for insulins (Fig. 3.3). Insulin analogues accounted for less than 80% market share in six of the 31 countries studied: Czechia (79%), Germany (71%), Hungary (52%), Norway (68%), Poland (50%) and Slovakia (69%) (*28*).

**Fig. 3.3. Average ex-manufacturer prices[a] of insulin per standard unit[b], by type of insulin and country**



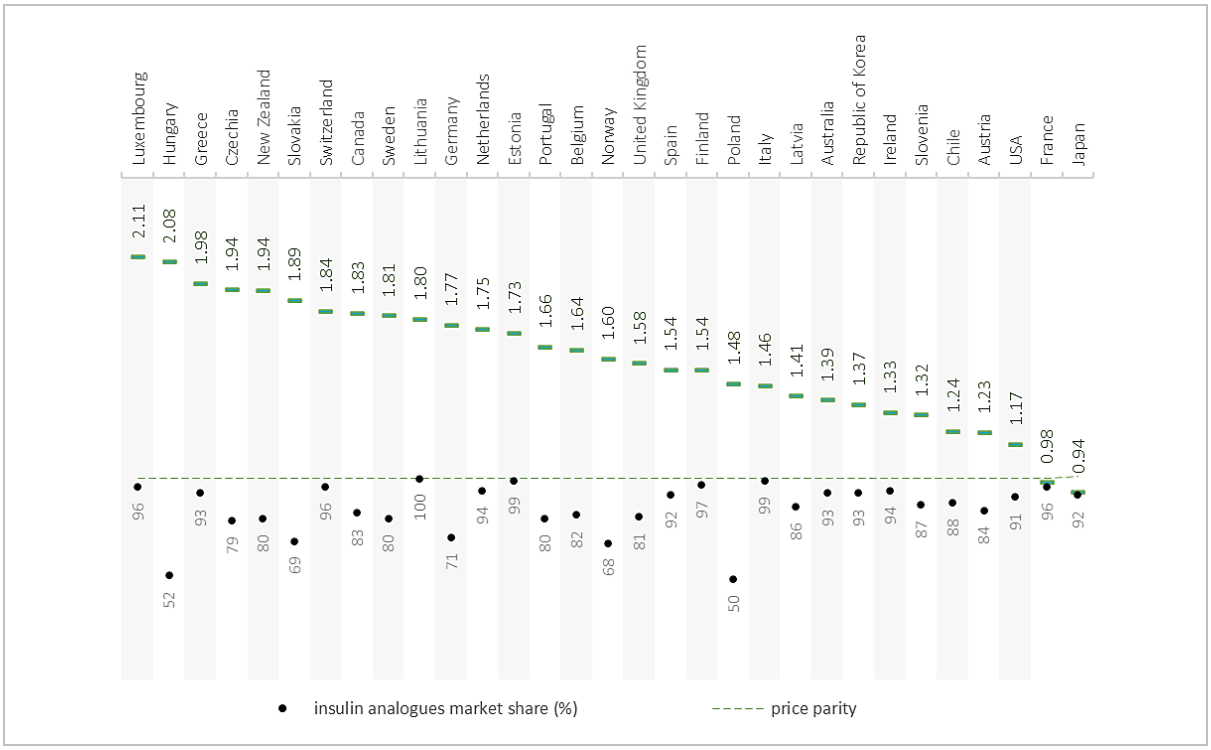

[a] In US dollars. [b] For the purposes of this table, a standard unit of insulin refers to a unit vial as per IQVIA's data provided to Mulcahy, Schwam & Edenfield (*28*).

*Source*: (*28*).

### 3.4.3 Price comparison between human insulin and insulin analogues

Price of insulin analogues were higher than human insulin in a large majority of high-income countries studied, ranging from 2.1-fold higher in Luxembourg to near price parity in France and Japan (Fig. 3.4) (*28*). The markets in some countries seemed to have responded to the significant price differences by using much lower volumes of insulin analogues (e.g. Germany, Hungary, Norway, Poland and Slovakia) (Fig. 3.4) (*28*).

**Fig. 3.4. Analogue-to-human insulin price ratio, by country**




*Source*: WHO analysis based on IQVIA data presented by Mulcahy, Schwam & Edenfield (*28*).

### 3.4.4 Price comparison between originator and biosimilar insulins

Promoting the use of quality-assured generic and biosimilar medicines has been a recommended policy option to improve access to lower-priced equivalents or near equivalents of trade-name products, and to generate savings for patients and health systems (*49*).

The study by Ewen and colleagues (2019) found that biosimilar insulins were mostly cheaper than the originator products when available in the countries studied (*48*). However, the study observed considerable variation in the difference in prices between biosimilar and originator insulins, ranging between 2% and 25% depending on insulin types and study contexts. Another study examined the price changes on insulin glargine (Lantus), following the entry of insulin glargine (Basaglar)[12] in 2015 in low- and middle-income countries (*50*). From 2010 to 2015, the net prices of Lantus were observed to have increased by 3.8% every quarter from US$ 6.90 to US$ 12.80. From 2015 to 2020, the study observed that the overall net prices of

[12] Insulin glargine (Lantus) was first marketed by Sanofi. Eli Lilly and Boehringer Ingelheim marketed insulin glargine (Basaglar) approved under the FDA's New Drug Application. For this reason, it is not strictly considered biosimilar.

insulin glargine, weighted by the respective sales volume of the two trade name products, declined at an average of 3.4% every quarter (*50*).

There is mixed evidence regarding whether biosimilar insulins lead to financial savings in practice, which is influenced by both pricing and reimbursement policies as well as policies on interchangeability and substitution. For example, prescribing biosimilar insulin glargine by general practitioners under the National Health Service in England generated savings of £ 900,000 over about three years between October 2015 and December 2018 (*51*). However, the authors noted that this only represented 3.42% of the total savings that could have been achieved had all prescriptions been biosimilar insulin glargine. Another study observed a slow decrease in price per Defined Daily Dose for insulin glargine in Bulgaria between 2000 and 2014, since the introduction of biosimilar insulin glargine – from 2.77 to 2.22 Bulgarian lev (i.e. US$ 1.6–1.3 assuming a 0.6 conversion rate of lev to dollars)(*52*). Godman et al.(2021) also noted that the small price differences between originator and biosimilar insulin glargine had limited the potential savings. The saving potential was further reduced by a concurrent increasing use of the patented (and higher-priced) 300-IU/mL formulation (Toujeo) marketed by one of the originator companies (*53*).

The mixed effects of market entrance of biosimilar insulins on price and expenditure, or the lack thereof, is likely a result of a lack of competition. The presence of dominant companies in the current market environment results in a high barrier to market entry for biosimilar insulins. A more competitive market (e.g. through increased government intervention) could lead to market entry of quality-assured biosimilar insulins. This in turn could lower price, broaden access and generate savings to health systems and patients.

*Market entry of quality-assured biosimilar insulins could lower price, broaden access and generate savings to health systems if a more competitive market exists*

### 3.4.5 Affordability

Finding an objective benchmark to indicate affordability is challenging, in part, because of the subjective nature of an affordability threshold.

To assess affordability of insulins in low- and middle-income countries, Ewen and colleagues (2019) (*48*) expressed the estimated median purchase price of a 1000 IU of insulin (approximately 30 days of insulin supply) as the number of wage-days of the lowest paid unskilled government worker. Their study showed that the lowest paid unskilled government worker in the 13 low- and middle-income countries studied needed to spend 6–8 days of wages to purchase 1000 IU insulin analogues in the public sector and 7–16 days of wages to purchase in the private sector. In contrast, human insulin were found to be more affordable, with an estimated 4 equivalent days of wages when purchased in the public sector and 2–4 days in the private sector (*48*).

In recent years, the financial burden caused by the high prices of insulins and associated products have attracted significant attention from society and policy-makers. In the United States, there have been documented cases where this financial hardship has forced people with diabetes to restrict their insulin use (*54*), causing catastrophic harms to their well-being (*55*) and even deaths. It is likely that the lack of

affordability of insulins and associated devices contributed, among other factors, to similar catastrophic harms on patients in other countries, as indicated by the reported cases of diabetic ketoacidosis due to discontinuation of insulin use (*56*,*57*).

### 3.4.6 Comparing price with production costs of insulins

The lack of affordability of medicines and ongoing discussions on fair pricing have triggered comparative research that seeks to understand the difference between production costs and price, including for insulins.

A study by Gotham and colleagues (*58*) found that the manufacturing processes for human insulin and insulin analogues are similar, but the reported prices of active pharmaceutical ingredients differed significantly; they ranged from US$ 24 750 per kilogram (kg) of human insulin, US$ 68 757 per kg of insulin glargine, to US$ 100 000 per kg for various other insulin analogues. Based on the prices of these active pharmaceutical ingredients and applying several informed assumptions (e.g. mark-ups, formulation), this study estimated that the production costs per 1000 IU ranged from US$ 2.30-3.40 for human insulin, US$ 3.70-5.10 for insulin glargine, to US$ 13.50-17.40 for insulin detemir; their respective estimated prices[13] ranged from US$ 3.30-4.90, US$ 5.30-7.40, to US$ 19.40-25.00 (*58*). The estimated prices of insulin analogues were significantly lower than the market prices. Relatedly, the estimated price differences between analogue and human insulin were much smaller than the differences in their respective reported government procurement prices in low- and middle-income countries. Based on these findings, the authors argued that a competitive biosimilar market (i.e. a concentrated market as described in section 2.2) would improve affordability of insulins and broaden access.

### 3.4.7 Industry pricing and patient access schemes

In response to growing concerns on the affordability of insulins, the manufacturers of insulins, including Novo Nordisk, Eli Lilly, Sanofi and Biocon, have implemented various pricing schemes to support patient access. These programmes support patient access to insulins through donation of goods, guaranteeing a maximum ex-manufacturer price or offering a discounted price for patients meeting certain criteria (Table 3.1). Other donation programmes have been managed through non-government organizations. One example is the Diabetes NSW's Life for a Child programme. In that programme, Eli Lilly and non-profit-making partners support the provision of human insulin[14], associated devices and a suite of capacity-building activities to improve care for children and youth with type 1 diabetes in developing countries.

A study found that the number of children and young adults with type 1 diabetes receiving insulins through programmes with donated or discounted insulins, rose from 8193 in 2009 to 35 382 in 2015 (*59*). This study also observed an increasing number of diabetes treatment centres affiliated with these programmes, citing examples from the United Republic of Tanzania, Guinea and Cameroon. Other studies were cited that reported positive impacts on:

[13] After adding estimated costs of transportation, operating margins and the costs associated with development, capital expenditure and regulatory filing.

[14] In 2021, Life for a Child launched Vision 2030, which will also start supplying analogue insulins: https://lifeforachild.org/vision2030/#1614505993814-13db46f4-5fcf (see webpage section "Improve access to essential supplies and care").

- health outcomes, such as increase in body weight of underweight beneficiaries, better glycaemic control and reduced mortality;
- non-health outcomes, such as improved school attendance and performance; and
- health system capacity, such as training of health workers and facilitating service integration (*59*).

However, the authors cautioned not to overinterpret the findings given the incomplete and inconsistent reporting (*59*). Specifically, many of these programmes did not report, or reported few beneficiaries compared to the health needs. As such, these programmes did not address the core access problems (i.e. unaffordability and system barriers).

Notwithstanding, the authors argued that "these programmes can play a 'pathfinder' role in countries where the public sector is currently unable to provide insulin and where high prices in the private sector make insulin unaffordable", while recognizing that "the only sustainable future towards universal access [for insulins] in low- and middle-income countries is inclusion of standard diabetes care and prevention in national health insurance or social security programmes" (*59*).

Other studies examined the impacts of industry-led access-to-medicines initiatives in low- and middle-income countries more generally (*60*,*61*). One of these studies showed that within the first year of an access programme, patient access did not improve even through the programme resulted in a reduced wholesale price of the medicines (*61*). The other study also observed an increasing number of programmes in low- and middle-income countries that either provide medicine donation or price reduction (*60*). While the commissioned evaluations of these programmes claimed positive impacts, the quality of evidence was rated by the authors as "low" or "very low" (*60*).

*"The only sustainable future towards universal access [for insulins] in LMIC is inclusion of standard diabetes care and prevention in national health insurance or social security programmes"*

*– Hogerzeil and Recourt (2019)*

While these programmes might be helpful in meeting the immediate health needs of some people with diabetes, it is important to recognize that these schemes are limited in scope, with eligibility criteria covering only certain jurisdictions, types of patients and products. There are also longer-term risks associated with these industry initiatives (*62*). For example, they can lead to duplication of services because of a lack of coordination with mainstream health system access pathways. These initiatives may delay the entry of generic or biosimilar medicines into the market because it might have strengthened dominance of the originator companies. They may also increase undue influence from the industry on regulatory and procurement decisions, as well as weaken public accountability. For these reasons, countries currently participating in these programmes should be mindful of the long-term impacts associated with industry pricing and access schemes.

**Table 3.1. Industry programmes with components on affordable pricing of insulins**

| Programme | Key features | Implementation scope | Reported impacts |
|---|---|---|---|
| **Base of the Pyramid programme** by Novo Nordisk (*63*) | 〉 Insulin supply<br>〉 Access to high-quality care delivered by trained health care professionals<br>〉 Improved self-management through increased awareness<br>〉 Early diagnosis of diabetes | A total of 28 counties in Kenya through gradual expansion of programme between January 2012 and December 2014 | The price of insulin for the patient was reduced from a mean price of 1000 Kenyan shillings in Dagoretti (Nairobi) and 850 shillings in Nyeri to a fixed price of 500 shillings (about US$ 5) |
| **Changing Diabetes® in Children** programme by Novo Nordisk (*64*) | 〉 Patient education and advocacy<br>〉 Training of health care professionals<br>〉 Support the establishment of national clinics<br>〉 Free insulins and medical supplies and cold chains | More than 28 000 children from 222 clinics across 14 low- and middle-income countries have participated in the programme | A total of 2.67 million vials of insulin have been donated along with blood glucose monitoring devices and associated medical supplies |
| **Access and Affordability** programme in low- and middle-income countries by Novo Nordisk (*65*) | 〉 Being the lead supplier of low-priced human insulin in the world<br>〉 Guaranteeing a ceiling price of human insulin at US$ 3 per vial<br>〉 Addressing challenges in insulin distribution and health care capacity | 〉 The United Nation's Least Developed Countries<br>〉 The World Bank's low-income countries and middle-income countries where large low-income populations lack sufficient health coverage<br>〉 "Selected humanitarian organizations with a global commitment" | None identified from targeted searches of public sources |
| **Lilly 30x30** by Eli Lilly (*66*) | 〉 Patient support programmes on reimbursement and access issues, providing information, and training<br>〉 Alternative access programmes<br>〉 Lilly 30x30 fellow | A total of 40 countries for patient support programmes | A total of 2.4 million insulin vials donated as of 2020 related to support of the Life for a Child programme since 2009 |
| **Lilly Insulin Value Program** by Eli Lilly (*67*) | 〉 Patients who use Eli Lilly insulin – regardless of their insurance status – are eligible to purchase their monthly insulin for US$ 35 | United States, as of January 2021 | Up to 20 000 people each month |
| **Insulins VALyou Savings Program** by Sanofi (*68*) | 〉 Guaranteed monthly supply of all Sanofi insulins for US$ 99 (10-mL vials) or US$ 149 for a pack of Lantus SoloStar pens. It was later amended to US$ 99 per month for up to 10 boxes of pens and/or 10-mL vials | United States | None identified from targeted searches of public sources |
| **Sanofi Temporary Access Program** (*69*) | 〉 One-time 30-day supply of your medication at no cost | Residents of the United States, Puerto Rico, Guam or the U.S. Virgin Islands | None identified from targeted searches of public sources |
| **The 10-cent answer to diabetes** by Biocon (*70*) | 〉 Human insulin available at less than 10 US cents per day in low- and middle-income countries | 〉 Low- and middle-income countries (no details presented) | None identified from targeted searches of public sources |

*Source*: (*63–70*).

## 3.5 Supply and distribution chain management

A well-managed supply and distribution chain is critical to timely access to medicines and health products, as it ensures supply efficiency and continuity, and maintains product quality and affordability.

Effective supply chain management is particularly important for insulin as its storage requires good maintenance of the cold chain. Disruption of the cold chain and inappropriate product storage may have a negative impact on insulin potency, which represents an important health risk. In many resource-limited countries, people without access to refrigeration at home may need to travel daily to the nearest health clinic for injections and monitoring. Travel may also be required if insulin prescriptions are only available from secondary or tertiary health care facilities. For all these reasons, a lack of strong network of suppliers and distributors may create access barriers for people living with diabetes. Indeed, the low number of producers of insulin as discussed in section 2.2.1 create vulnerabilities in supply, especially if countries rely on only one supplier (*71*). There have also been reported shortages of insulins in countries due to inefficiencies in supply chain management that have been aggravated during the coronavirus disease 2019 (COVID-19) pandemic and political crises (*72–75*).

Effective supply and distribution chain management can also minimize costs and avoid excessive mark-ups. Specifically, mark-ups can occur in the supply chain due to import tariffs, storage costs, transportation costs, dispensing fees, and sales taxes for example (*76*). Case studies in six low- and middle-income countries showed that cumulative mark-ups for insulin ranged from 8.7% to 565.8% depending on country and health system context (*77*). As a result, mark-ups from the supply and distribution chain accounted for 8% to 85% of the final patient price of insulin. While most countries included in this study (except Ghana) had removed import tariffs on insulin, value-added tax in the private sector was found to have added 5% to 20% to the price across the countries studied (*76*). It is worth noting that WHO guidelines on country pharmaceutical pricing policies has made recommendations on the use of mark-up regulation across the pharmaceutical supply and distribution chain (*49*). In addition, the guidelines suggest countries consider exempting essential medicines and active pharmaceutical ingredients from taxation (*49*).

*A well-managed supply and distribution chain can improve access by ensuring supply efficiency and continuity, product quality and minimizing mark-ups*

## 3.6 Barriers arising from market structure

As noted in section 2.2.3, there has been a major shift from the use of human insulin towards the use of higher-priced insulin analogues in recent years. While this trend was first seen in high- and middle-income countries, it is now beginning in low-income countries as well.

This shift is concerning for several reasons. Firstly, evidence shows that insulin analogues confer small or no additional benefit for most clinical outcomes compared to human insulin, except possibly for a subgroup of people with diabetes for whom the risk of hypoglycaemia cannot be overcome by self-management (see evidence cited in (*12*)). Second, in certain markets, the lower quantity demanded for human insulin following

the market shift may lead to a price increase for human insulin, thereby reducing affordability. Third, the shift may disrupt the overall global supply of human insulin, which would restrict availability of human insulin for health systems and people with diabetes unable to afford higher-priced insulin analogues. Together, this shift has added considerable constraints on health systems' ability to provide universal access to insulins, including in high-income countries where there have been reports of individual patients resorting to self-rationing to save money (*54*), with grave health consequences.

The market shift also reflects a suite of underlying market and health system problems. Specifically, there is a non-competitive market environment, with the global supply of insulins being dominated by three pharmaceutical companies that have considerable market power on pricing, supply and demand. Furthermore, the comparatively small market size, intellectual property protection on insulins or associated devices, and regulatory requirements all have discouraged market participation of potential manufacturers of biosimilar insulins, thereby stifling competition. Suboptimal regulation and policies have also contributed to access barriers. These include suboptimal pharmaceutical pricing policies, weak procurement and supply chain management, insufficient financing to cover demand and weak governance.

## 3.7 Interchangeability and switching of insulins

Uncertainties about the interchangeability between originator and similar biological insulins may affect uptake of biosimilars at the clinical level and create barriers to patient acceptance. Differences between definitions regarding interchangeability and regulatory approaches also exist.

In 2021, the FDA approved the first interchangeable biosimilar insulin (insulin glargine-yfgn). In communicating this approval, the FDA noted that "an interchangeable biosimilar product may be substituted for the reference product without the intervention of the prescriber" and that

> biosimilar and interchangeable biosimilar products have the potential to reduce health care costs, similar to how generic drugs have reduced costs. Biosimilars marketed in the U.S. typically have launched with initial list prices 15% to 35% lower than comparative list prices of the reference products (*30*).

Other NRAs, such as the European Medicines Agency, do not have regulatory provisions for interchangeability and the decision on interchangeability is left to national authorities (*78*).

Nonetheless, various authorities and professional bodies have issued guidance to inform clinicians and patients regarding the use of biosimilar medicines. For example, the WHO Expert Committee on Selection and Use of Essential Medicines has recommended that quality-assured biosimilars should be considered interchangeable with the biological medicines included in the EML, and eligible for selection and procurement at country level (*12*). The European Medicines Agency and the European Commission have jointly published an information guide for health care professionals (*79*). This information guide explains the key features of biological medicines, development and approval of biosimilar medicines, as well as interchangeability,

*Public trust in using biosimilar medicines is important for facilitating greater availability, appropriate clinical use and stronger market competition*

switching and substitution policies. It assures that "Prescribers can have confidence in using biological medicines (including biosimilars) for all their approved indications, as all approved indications of a medicine are granted based on scientific evidence" (*79*).

Building public trust in using biosimilar medicines is particularly important for facilitating greater availability, appropriate clinical use and stronger market competition. Studies have shown the importance of addressing potential barriers to prescribing biosimilar medicines, such as safety and efficacy concerns, patients' opinion and how any cost savings arising from the use of biosimilar medicines would be shared across the health system; one example from the United Kingdom is a study by Aladul, Fitzpatrick & Chapman (*80*). Similarly, education to build awareness and knowledge among patients on quality, safety and efficacy, and pricing of biosimilar medicines, such as biosimilar insulins (*81*), is critical to their overall acceptance.

## 3.8 Access to affordable devices to support appropriate use of insulin

Appropriate use of insulin hinges on having access to affordable medical devices for safe administration, including optimal glucose monitoring to guide insulin use. However, these devices are not always available or are unaffordable to patients, clinicians and health systems, particularly in low-resource settings (*76*,*82*).

### 3.8.1 Devices for dose administration of insulin

A study reported inadequate provision of syringes for the injection of insulins in about half of the surveyed public health systems in low- and middle-income countries. When available, prices of syringes were often high (i.e. up to US$ 0.97 per syringe) (*83*). The unaffordable cost of syringes had led to reuse of needles in almost all countries surveyed, which had compromised safe injection of insulins and exposed patients to the risk of infections.

Changes in the dose administration of insulin, from the conventional vial-and-syringe insulin delivery to that of disposable or reusable pen devices, can also create access barriers. For example, pen devices often require specific needles, which may not be available or are more costly than needles required for conventional dose administration from a vial. On the other hand, patient comforts and ease of use associated with certain devices may facilitate greater adherence. Needles also require safe disposal, and may pose environmental risks if not disposed of properly (*84*). In considering access to insulin, it is important to consider potential access barriers associated with dose administration, including the complete device requirements and the total costs of the dose administration method.

### 3.8.2 Devices for glucose monitoring

The costs of blood glucose meters and test strips for self-monitoring of blood glucose can also hamper affordability. Various studies have reported high proportions of costs for managing diabetes being

attributable to devices associated with blood glucose monitoring, with some being as high or higher than the costs of insulins. For example, a review of studies found that this was the case in Mexico – 53% of the annual household cost for managing type 1 diabetes (vs 15% for insulin); in Brazil – 52% of the total outpatient costs for type 1 diabetes (vs 26% for insulin); in Germany – 28% of the average annual per-person cost for type 1 diabetes (vs 18% for insulin); and in Canada – 41.6% of the total costs for people with type 1 and type 2 diabetes (vs 48.6% for insulin) (*82*). Studies have also noted that health insurance schemes in countries with limited resources, such as Ghana and the Plurinational State of Bolivia, sometimes provide insulin, but rarely provide the test strips for glucose monitoring (*82*).

*Costs of devices associated with blood glucose monitoring have been found to be proportionally higher than the costs of insulins in some contexts*

Access to devices and equipment for monitoring glucose levels and the complications of diabetes (e.g. retinopathy and nephropathy) can also have a negative impact on appropriate use of insulin and diabetes care. In low-, middle- and upper middle-income countries, it has been estimated that less than 50% of primary health care facilities have the needed supplies for glucose measurement and the equipment for screening diabetes complications. Considering the lack of service integration, an absence of supplies for glucose measurement and the equipment for screening diabetes complications is likely to be prevalent in low-income countries. Tests and devices for monitoring diabetes and its complications are only available in relatively few specialized institutions. This level of availability is insufficient for providing standard of care for all people living with diabetes (*85*).

In addition to problems of access, device quality and performance, such as blood glucose meters, may vary in countries, including in high-income countries (*36*,*86*). For example, a review concluded that a considerable proportion of blood glucose monitoring devices approved for sales in the market "do not perform at the level for which they were cleared or according to international standards of accuracy" (*87*). This review found that only about half to one third of the tested devices met the standards set by the International Organization for Standardization (ISO). Another recent review reached a similar conclusion and called for better quality research on monitoring the performance of medical products for diabetes management (*88*). Substandard blood glucose monitoring devices can lead to negative clinical outcomes and economic consequences. This problem therefore must be addressed through stronger regulatory measures with accompanying policies, including post-marketing surveillance.

Market factors could also play a role in limiting access to quality-assured and affordable medical devices for the safe use of insulins and monitoring of glucose and complications. For example, excessive product differentiation has caused incompatibility across different commercial brands. The customization of test strips to specific brands of meters, as well as frequent upgrades of devices for glucose monitoring, have worsened availability and affordability (*89*). The marketing practice of offering glucose monitoring devices as a so-called freemium has also caused access problems. In this business model, suppliers provide the glucose meters for free or at heavily reduced price, which can only be used with highly priced proprietary test strips (due to incompatibility with other devices). This marketing practice is driven by the fact that consumption of test strips is a main revenue source, with research showing a 90–97% share of revenue coming from test strips compared to glucose monitoring meters and lancets (*89*).

## 3.9 Other health system factors

### 3.9.1 Financing

Adequate, stable and predictable financial resources are required for the provision of essential medicines, such as insulins. The International Diabetes Federation published a commissioned study in 2020 to estimate the direct medical costs attributable to diabetes, including the costs associated with pharmaceutical products. Based on demographic data, epidemiology and health expenditure estimates, the study estimated that yearly per-person health expenditure for the management of diabetes ranged from US$ 63.9 (Bangladesh) to US$ 11 900 (Switzerland) (*90*).

A systematic review examined the costs of treatment for diabetes (mostly for type 2) in low- and middle-income countries (*91*). It found great variability in the costs of treatment[15] in the countries studied: every outpatient visit incurred a median cost of US$ 7 (range US$ 5–40); median annual inpatient cost of US$ 290 (range US$ 10–1790); median annual laboratory cost of $25 (range US$ 5–195); and median annual cost of medicines of US$ 177 (US$ 15–US$ 864), with particularly wide variation found for insulin (*91*).

> *Yearly per-person health expenditure for the management of diabetes ranged from US$ 64 to US$ 11 900*
>
> *– International Diabetes Federation Diabetes Atlas*

It is important to place the above estimates on the cost of treatment in the context of overall health expenditure. The estimated average per capita general health expenditure (weighted for population size) in 2017 was: US$ 5045 in high-income countries: US$ 433 in upper middle-income countries: US$ 80 in lower middle-income countries: and US$ 36 in low-income countries (*92*).

Comparing these two sets of estimates, it seems that the medical costs associated with diabetes care are much higher than the average medical costs for the general population. For those managing diabetes in lower-income countries, insulin costs (see Fig. 3.1) are likely to account for a significant part of their overall health expenditure, especially if insulin analogues are used. The costs of delivery devices, blood glucose meters and test strips add to this expenditure. For this reason, it is important to ensure adequate, stable and predictable financial resources are made available to health systems to ensure timely and equitable access to insulins and the associated devices needed for appropriate care.

### 3.9.2 Governance

Effective governance is a critical factor in access to insulin. Poor policy development and implementation at national level, weak or inefficient management particularly in procurement and supply chain, and poor-quality or lack of data all pose challenges to effective governance.

[15] Expressed in 2016 US dollars.

National policies are needed, particularly for regulating prices, mark-ups, and eliminating taxes and tariffs (*48*,*93*). Procurement inefficiencies have been noted as a challenge particularly when a lack of data on needs and supplies inhibit accurate forecasts (*25*). In addition, national procurement practices may hinder access in case of restrictive tender policies and poor planning practices (*93*).

Many stakeholders have highlighted the lack of transparency on pricing and patent status of insulins and associated devices, as well as supply arrangements with manufacturers (*94*,*95*). Greater transparency is important for accountability and to guide appropriate policy development. World Health Assembly resolution WHA74.4 *Reducing the burden of noncommunicable diseases through strengthening prevention and control of diabetes* calls on WHO to assess the

> potential value of establishing a web-based tool to share information relevant to the transparency of markets for diabetes medicines, including insulin, oral hypoglycaemic agents and related health products, including information on investments, incentives, and subsidies (*15*).

### 3.9.3 Service delivery capacity

Diabetes care is often initiated at the tertiary or secondary levels of the health care system, particularly care for people with type 1 diabetes and the initiation of insulin treatment. It is therefore important to ensure health care workers are well trained and there is sufficient service capacity at these levels.

Training of health care workers and expansion of service capacity at the primary health care level should be developed as well, considering the growing prevalence of type 2 diabetes worldwide. This would be vital to the delivery of people-centred, community-based and integrated diabetes care. However, various studies have noted that insulin and diabetes care is only available at secondary or tertiary hospitals at a level insufficient to meet the need (e.g. China (*96*), Trinidad and Tobago (*97*)). Where diabetes care does exist at the primary care level, knowledge and competencies of health care workers in using insulins and educating patients may not be available. A systematic review on the perceptions of insulin use in type 2 diabetes showed several barriers to optimal insulin use at the primary care level; these related to clinical skills, insulin-related beliefs, social influences, psychological factors, hypoglycaemia, and service integration (*98*). This review indicates a need for improving the knowledge and competencies of health care workers at the primary care level in using insulin; providing more effective patient education and self-management support; and introducing integrated insulin support systems (*98*).

Optimal diabetes care includes having control of blood pressure and cholesterol. For this reason, health services should also facilitate the detection and treatment of hyperlipidaemia and hypertension, including providing access to statins and antihypertensive medicines, in line with the proposed global targets mentioned in section 2.1.5.

# 4. Pathways to improve access to insulin

Pathways to improve access to insulin, and associated devices to support its appropriate use, have been put forward in the literature and in various forums by stakeholders. Fig. 4.1 summarizes various areas of action noted in WHO meetings, namely the workshop on *Insulin and associated devices: access for everybody* (*99*) and dialogue with the industry (*100*). The following sections discuss these areas of action in greater detail.

**Fig. 4.1. Areas of action to improve access to and appropriate use of insulins and associated devices**


*Source*: Various forums convened by WHO.

## 4.1 Areas of action to improve access

### 4.1.1 Improving the availability of human insulin and insulin analogues, especially biosimilar products

Human insulin, long-acting insulin analogues (insulin degludec, insulin detemir and insulin glargine), and their biosimilars are listed on the EML and EML for Children, with long-acting insulin analogues recommended for use only in patients with diabetes at high risk of experiencing hypoglycaemia with human insulin (*12*). Comparing epidemiological data of diabetes against trade and revenue information relating to insulins suggests that populations in need of insulins for the management of diabetes are underserved in many countries and particularly in the African Region, South-East Asia Region and Eastern Mediterranean Region (section 2.2.2). There have also been trends towards greater use of insulin analogues particularly in high- and middle-income countries (section 2.2.3), despite the significantly higher prices of insulin analogues than human insulin (section 3.4.3). Global inequitable and unaffordable access to insulins would worsen if these trends were to continue to expand, particularly in lower-income countries.

For all these reasons, maintenance and expansion of the market for human insulin is an important area of action. Human insulin, given its lower prices, is more affordable for many people with diabetes especially in contexts where resources are limited. This means that, at the same budget, human insulin will deliver more positive health outcomes compared to insulin analogues. That message should be conveyed to policy-makers and health care professionals; to do so it would be important to build clinical competence, correct any misperceptions on the efficacy and safety of human insulin and implement measures to halt or reverse the transition towards insulin analogues (such as their over-promotion). This would require policy and clinical leadership at country and international levels. Sharing experiences from health systems where a considerable proportion of the market consists of human insulin (e.g. Germany, Norway, Poland, the United Kingdom; section 3.4.3) would also facilitate a better understanding of factors influencing the market composition. Finally, it is important for WHO and relevant authorities to engage with manufacturers of human insulin to ensure continuity of production and supply, including formulating incentive structures to align public health goals with commercial interests where appropriate.

WHO will continue with the Prequalification programme for human insulin initiated in November 2019 (*29*), in line with the goal of maintaining and expanding the market for human insulin. In addition, WHO will initiate a new Prequalification programme for long-acting insulin analogues**,** upon receiving formal request from the WHO disease programme to invite these products for prequalification according to standard procedure. This is in view of the listing recommendation of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines. These programmes aim to provide a regulatory pathway to improve the availability of biosimilar insulins. Upon greater market participation of suppliers of biosimilar insulins, positive competitions on price, quality and supply may ensue, leading to better affordability over time. With a competitive market environment or with the application of appropriate pricing policy (e.g. internal reference pricing), prices of biosimilar analogues should align with those of human insulin in the long run.

In addition, WHO will continue to work with countries to facilitate product assessment and national registration of biosimilar insulins. Specifically, a WHO collaborative registration procedure (*101*) will be used to facilitate assessment and to improve the timeliness of national registration of biosimilar insulins. For the

long-term, NRAs should consider their capacity building measures, and where appropriate, seek WHO technical support. The WHO guidelines for evaluation of biosimilars are currently under revision. The main principle in the guidelines is that reduced data package requirements in nonclinical and clinical evaluation are acceptable if analytical techniques are able to provide a high level of confidence in the demonstration of similarity. Efforts to improve capacity of both manufacturers and regulators will be needed to understand and implement the evaluation principles described in the guidelines.

It is also important to clarify the regulatory pathways and evidence requirements for changing storage conditions of insulin in marketing authorization. This is important to address the challenges of having to store insulins at ambient temperature because of a lack of adequate infrastructure (e.g. electricity), facility (e.g. storage space) or equipment (e.g. refrigeration) to maintain cold chain in many resource-limited contexts. A better understanding of the impacts of storage in conditions inconsistent with regulatory approval on the efficacy and safety of insulins is needed. If heat stability data demonstrate greater range of storage conditions without compromising the efficacy and safety of insulins, regulatory requirements should be revised accordingly.

Finally, it is important to build confidence among clinicians and people living with diabetes when switching to biosimilar insulins. To this end, providing and adopting clear clinical guidance on interchangeability and substitutability of biosimilar human insulin and insulin analogues would be essential. It would also require investment in treatment literacy among people living with diabetes.

### 4.1.2 Enhancing the affordability of human insulin and insulin analogues

Unaffordable insulins have been identified as one of the main barriers to access. Addressing this problem could start with judicious selection and inclusion of insulins in national essential medicine lists according to health care needs and economic contexts. As noted, human insulin is suitable for use by patients with diabetes who are not at high risk of experiencing hypoglycaemia, and it is more affordable than insulin analogues for both individuals and health systems. It is also worth noting that, in many cases, the risk of hypoglycaemia can be reduced by patient education on self-management. To generate greater value for money and enhance affordability, health systems should therefore prioritize the selection and use of human insulin except for patients where the risk of hypoglycaemia could not be managed through education and self-management.

The affordability of insulins could also be enhanced by a suite of policies related to the pricing and procurement of pharmaceutical products if these policies are carefully planned, implemented, monitored, and revised according to changing market conditions. To this end, WHO's Member States (*15*,*102*) and policy guidance (*49*) have recognized the importance of promoting the transparency of pharmaceutical markets, including the market for insulins. These include avoiding so-called evergreening practices (e.g. patent based on modification of strength of insulin glargine to 300 IU/mL), and improving the transparency of patent status of insulins and associated devices, supply arrangements with manufacturers (e.g. donation) and pricing of insulins and associated products (e.g. public sector procurement in low- and middle-income countries). Disclosed information could be analysed to guide development and revision of pricing and related policies to enhance affordable access. Policy options include, but are not limited to:

- regulating mark-ups across the pharmaceutical supply and distribution chain;
- eliminating taxes and import tariffs;

- promoting the use of quality-assured biosimilar insulins using a suite of demand and supply-side measures; and
- consolidating demand through pooled procurement mechanisms, within and where appropriate, across countries (e.g. participation in UN and other international global and regional procurement schemes).

Considering the concentration of suppliers in the current market, the option to consolidate demand through pooled procurement could be particularly beneficial for insulins – if such arrangement would generate greater purchasing power and create efficiencies by streamlining procurement processes. Pooled procurement might also enhance bundling arrangements for the provision of other devices and other capacity-building activities (e.g. training). In any case, the initiation of pooled procurement must be accompanied by a clear understanding of the price and non-price benefits to be achieved from the outset. For specific guidance, policy-makers considering these policy options should consult *WHO guideline on country pharmaceutical pricing policies* (*49*) for recommendations and implementation considerations.

### 4.1.3 Addressing access problems associated with devices to support the appropriate use of insulins

The appropriate use of insulins should be guided by the principle that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (*103*). To this end, having affordable access to medical devices for the safe dose delivery of insulins and monitoring blood glucose levels is essential.

Section 3.8 describes various issues relating to availability and affordability of medical devices to support the use of insulins. Sources of inadequate access to these devices are manifold and context specific. Overall, including devices for dose administration and glucose monitoring, as well as related health services in health benefits packages will improve access and care. This package-of-care approach recognizes the importance of including all essential components required to facilitate optimal use of insulins.

There is also a need for better management of intellectual property and marketing practices of devices to curb barriers to their use. For example, patent protection on insulin pens and testing devices have allowed some companies to preserve their market position by preventing competition. Countries may consider applying stricter rules and practices in national patent laws and examination processes to prevent patenting of routine obvious improvements and broad patenting on devices. Countries should also explore the use of competition law to tackle the barriers arising from excessive patenting on insulin pens and devices. Compatible with the spirit and obligations under World Trade Organization Trade-Related Aspects of Intellectual Property Rights, appropriate use of non-restrictive and non-exclusive voluntary licences or compulsory licences for devices (e.g. diagnostics and pens) may be necessary to improve access, particularly in countries with high burden of disease. Health system managers and consumers should be made aware of the implications of marketing practices that might have negative impacts on financial and public health goals. These include curbing the so-called freemium marketing practice for glucose monitoring devices, which locks consumers into using proprietary and costly glucose monitoring test strips exclusively (section 3.8). Formal assessments on financial and public health implications should be made prior to accepting these seemingly favourable offers.

### 4.1.4 Building capacity and investing in infrastructure to support access to and appropriate use of insulins

Like other major public health problems, the complexity of diabetes and its care, including the appropriate use of insulins, demands a whole-of-system approach. The *WHO health systems framework* (*104*) specifies six core interlocking building blocks: service delivery; health workforce; health information systems; access to essential medicines; financing; and leadership/governance. Measures to improve access to insulins therefore should be accompanied by commitments to capacity building and investing in relevant infrastructure.

One area of action is to integrate diabetes care, including access to insulins, at the primary health care level. These include early detection of diabetes, as well as initiation and adequate provision of treatment and disease management. Specifically, health care workers should be trained on initiation and titration of insulin. It is recognized that the initiation of insulin for people living with type 1 diabetes may require a higher level of clinical competence than could be delivered in the primary care setting. In this case, health care workers should receive training to at least be able to maintain insulin treatment and care. Establishing formal referral mechanisms to higher level of care would be a necessary addition to this training. Furthermore, where possible, establishing remote clinical support for patients and health care workers would facilitate greater access to appropriate care, including access to insulin and associated products. Overall, such integration would require careful planning and capacity-building activities on service delivery design, workforce development, financing and appropriate governance. Such integration should also consider building capacity in the public and nongovernmental organization (NGO) sectors particularly in low- and middle-income countries for diagnosis, care and patient education. It is also important to establish information infrastructure, with a view to informing clinical care, health service planning and overall system governance. These should entail collection of epidemiological and health service data, as well as information pertaining to industry's pricing and patient access schemes.

Substandard and falsified products, including medicines and devices for the management of diabetes (*88*), are a threat to patient safety, optimal clinical care and public health goals. The responsiveness of health systems and industry in monitoring and reporting the occurrence of substandard and falsified insulins and devices is critical for implementing corrective regulatory measures and safeguarding public safety and confidence. Such information should be managed by NRAs and shared with WHO. Similarly, establishing a system for reporting shortages of insulins and devices, actual or impending, would allow system managers and clinicians to institute appropriate mitigating measures to ensure treatment continuity. Such reporting mechanisms should not only involve health-care providers, but also ensure channels are established for conveying messages to the public about quality and supply problems.

In the longer term, there is a need for investing in local production of insulins and associated devices, as part of the overall approach in building supply security to meet population needs, especially in lower-income countries. Locally produced quality-assured insulins and associated devices may also improve affordability if scale of production and operational costs are sufficient to generate lower prices and costs than those associated with imported products.

During the COVID-19 pandemic, insufficient manufacturing capacity and high prices due to supply constraints or supply chain disruption have been particularly notable. In recognition of this problem, among others, the 74th World Health Assembly adopted resolution WHA74.6 *Strengthening local production of medicines and other health technologies to improve access* (*105*). Essential medicines and devices like insulins

and associated devices should be considered in the implementation of this resolution. As part of this development, strengthening supply chain management, including capacity for securing cold chains, is essential.

### 4.1.5 Supporting R&D to improve access to insulins and associated products

A final area of action pertains to R&D to improve access to insulins and associated products. Two priorities have been identified: i) improve collection and publication of data on diagnostic, pricing and usage of insulins and associated devices; and ii) support R&D on insulins and devices responding to the needs of people living with diabetes in low- and middle-income countries. The latter includes research on stability of insulins and its impacts on efficacy and safety at ambient temperatures that exceed 30°C – temperatures that frequently occur in many countries. This research would have implications on cold chain management. Relatedly, stakeholders supported a need for developing thermostable insulins suitable for use in countries where cold chain management is suboptimal, or where patients do not have proper equipment or infrastructure (e.g. electricity) to support recommended storage conditions.

It is recognized that the formulations, product presentations and treatment regimens of insulin may not be suitable for use in resource-limited and humanitarian settings. A research agenda (e.g. pipeline horizon scanning and clinical trials) should consider the characteristics of these settings. To this end, WHO will support the development of missing products related to the appropriate use of insulin in low- and middle-income countries. In addition WHO will consider developing target product profiles, preferred product characteristics and target regimen profiles according to standard procedure (*106*). The aim of considering these settings is to ensure that future research and industry efforts address gaps in the scale up of the appropriate use of insulin for patients in low- and middle-income countries.

Another area of research need is on standardization of blood glucose monitoring devices to facilitate compatibility and interchangeability across different brands. Such standardization would also diversify and stabilize supply as well as encourage market competition.

## 4.2 Milestones and ongoing activities in working with stakeholders

WHO has a long-standing commitment to work with countries to ensure affordable access to essential medicines and devices, including insulins and associated devices. To this end, WHO core programmes of work have contributed towards improving access to insulins and associated devices, and this work will continue and include the actions described in section 4.2.1.

Furthermore, like all public health work, concerted efforts from all stakeholders are needed to improve access to insulins and associated devices. Accordingly, the primary and secondary actors required to realize the actions in the priority areas in the short, medium and long term are shown in Annex 2. Section 4.2.2 highlights the Global Diabetes Compact – a major multi-stakeholder initiative aiming to address the challenges in meeting the diabetes-related targets in the WHO *Global action plan for the prevention and control of noncommunicable diseases 2013-2020* (*107*).

### 4.2.1 Activities at WHO relating to access to insulins and associated devices

Activities at WHO can be categorized broadly in three areas: i) norms and standards; ii) convening of stakeholders; and iii) country support. Table 4.1 summarizes some of the core activities and milestones relating to access to insulins and associated devices.

**Table 4.1. Milestones and ongoing activities at WHO**

| | |
|---|---|
| **Norms and standards** | 〉 EML: listings of human insulin and long-acting insulin analogues<br>〉 Model List of Essential In Vitro Diagnostics: listing of dipsticks and glucose meters<br>〉 WHO Prequalification programme on human insulin<br>〉 WHO Prequalification programme on glucose meters and test strips<br>〉 Standardization of nomenclature, coding and classification of medical devices to facilitate better regulation, procurement, supply and post-market surveillance<br>〉 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes<br>〉 WHO guideline on country pharmaceutical pricing policies<br>〉 Revision of WHO guidelines on regulatory evaluation of biosimilars |
| **Convening stakeholders** | 〉 WHO Technical Advisory Group of Experts on Diabetes<br>〉 Global Diabetes Compact<br>〉 Informal consultations with people living with diabetes<br>〉 WHO stakeholder workshop on insulin and associated devices<br>〉 Dialogue with the private sector on medicines and technologies for diabetes care (Annex 1)<br>〉 Workshop for manufacturers on similar biotherapeutics with a special focus on insulin, covering most critical aspects of inspection, quality, non-clinical and clinical requirements for human insulin prequalification |
| **Country support** | 〉 Global strategy on diet, physical activity and health<br>〉 WHO module on diagnosis and management of type 2 diabetes<br>〉 Web-based tool to share information relevant to the transparency of markets for diabetes medicines and health products<br>〉 Ongoing support on the developing of national medicine policies, regulatory system strengthening, pharmaceutical pricing policies, and health benefit package development |

Table 4.2 lists the specific actions at WHO that will be undertaken in the coming years in response to the areas for action described in section 4.1, and in complement to the activities and milestones described in Table 4.1. These actions are aligned with WHO existing mandates from the core programmes of work and World Health Assembly resolutions on access to medicines and health products, and diabetes.

Table 4.2. Specific actions at WHO relating to the five areas of work outlined in Fig. 4.1

| Activity area | Specific actions at WHO |
|---|---|
| **a. Improving the availability of human insulin and insulin analogues, especially biosimilar products** | |
| (a.1) Maintain and expand market of human insulin | 〉 Facilitate demand assessment for human insulin, including support for technical analysis<br>〉 Host events for sharing experiences from health systems to understand factors influencing market composition of insulin (e.g. how some health systems maintain the use of human insulin in relatively high proportion) |
| (a.2) Initiate or participate in the Prequalification programme on long-acting insulin analogues alongside the prequalification of human insulin | 〉 Continue with the WHO Prequalification programme for human insulin<br>〉 Conduct prequalification of long-acting insulins listed on the EML according to standard procedure |
| (a.3) Facilitate product assessment and national registration of biosimilar insulins | 〉 Use the Collaborative Procedure for Accelerated Registration to facilitate assessment and to improve the timeliness of national registration of biosimilar insulins<br>〉 Revise and publish guidelines for the evaluation of biosimilars; and promote convergence and harmonization of regulatory requirements for diabetes medicines, including insulin and biosimilars |
| (a.4) Clarify regulatory pathways and evidence requirements for changing storage conditions | 〉 Review and publish data on insulin stability and storage conditions at ambient temperature and promote data sharing |
| (a.5) Provide and adopt clinical guidance on interchangeability and substitutability of biosimilar human insulin and insulin analogues | 〉 Work with countries to share information with health professionals and people with diabetes to promote the use of biosimilar human insulin and insulin analogues |
| **b. Enhancing the affordability of human insulin and insulin analogues** | |
| (b.1) Improve the selection and inclusion of insulins in national essential medicine lists | 〉 Support countries in using the EML and apply recommendations in guidelines, as well as to set policies according to their contexts |
| (b.2) Promote transparency of the pharmaceutical market, including insulins | 〉 Collect, analyse and report price, volume, patent and other market information of insulins and associated devices at various points along the pathway from R&D to the point of use by people with diabetes |
| (b.3) Develop pricing and procurement policies to ensure affordable prices and lower patient out-of-pocket costs | 〉 Support countries in considering and implementing pricing and procurement policy options |

| Activity area | Specific actions at WHO |
|---|---|
| **c. Addressing access problems associated with devices to support the appropriate use of insulins** | |
| (c.1) Include delivery devices, screening and blood glucose monitoring devices in health benefits packages | 〉 Support countries to perform health interventions and technology assessments to assess how to include insulins, their delivery devices and associated health services in health benefits packages |
| (c.2) Manage intellectual property of devices associated with the use of insulins | 〉 Examine the feasibility of voluntary patent pools of upstream and downstream technologies to promote innovation of and access to insulins and medical devices |
| (c.3) Implement measures to reduce the so-called freemium marketing practice for monitoring devices | 〉 Publish standards on reporting price and cost components of medical devices associated with insulin use |
| **d. Building capacity and investing in infrastructure to support access to and appropriate use of insulins** | |
| (d.1) Integrate diabetes care, including access to insulins, at the primary health care level | 〉 Support professional bodies on the training of health care professionals on initiation and titration of insulin at the primary care level<br>〉 Provide technical assistance on the planning and capacity building activities relating to service delivery design, workforce development, financing and appropriate governance |
| (d.2) Strengthen capacity of public and NGO sectors in Low- and middle-income countries, in diabetes diagnosis, care, and patient education | 〉 Raise awareness about the national public health burden caused by diabetes, through a life course perspective, and about the relationship between diabetes, poverty and social and economic development (e.g. the relationship between obesity and risk for developing type 2 diabetes)<br>〉 Share policies with public and NGO sectors on WHO guidelines and standards for early detection of diabetes, as well as initiation and adequate provision of treatment and disease management<br>〉 Develop understandable and high-quality, patient-friendly information and education |
| (d.3) Establish information infrastructure to inform care and demand assessment | 〉 Establish an information platform for the collection, analysis and publication of data on diagnostic, pricing and usage of insulins and associated devices |
| (d.4) Monitor and report shortages and occurrence of substandard and falsified insulins | 〉 Monitor shortages of insulins through the Global Notification System for Shortages and Stockouts<br>〉 Continue to monitor occurrence of substandard and falsified insulins through the Global Surveillance and Monitoring System for substandard and falsified medical products |
| (d.5) Build infrastructure and capacity in local production of insulins and supply chain management | 〉 Support technology transfers and collaboration between institutions in developing countries and the pharmaceutical industry for the production of insulins and supply chain management<br>〉 Create local and regional networks for collaboration on R&D and transfer of technology relating to the production of insulins and supply chain management |

| Activity area | Specific actions at WHO |
|---|---|
| **e. Supporting R&D relating to access to insulins and associated products** | |
| (e.1) Improve collection, analysis and publication of data on diagnostic, pricing and usage of insulins and associated devices | 〉 Establish platform for collection, analysis and publication of data on diagnostic, pricing and usage of insulins and associated devices, in conjunction with item b2 |
| (e.2) Support R&D that responds to the needs of low- and middle-income countries | 〉 Develop target product profiles, preferred product characteristics, and target regimen profiles relating to the health care needs in low- and middle-income countries, according to standard procedure |

### 4.2.2 WHO Global Diabetes Compact

Actions for improving access to insulins and associated devices will need to be placed within the broader programme of work on preventing, treatment and monitoring diabetes. At WHO, the Global Diabetes Compact (*108*) was launched in April 2020. This initiative has a vision of

> reducing the risk of diabetes, and ensuring that all people who are diagnosed with diabetes have access to equitable, comprehensive, affordable and quality treatment and care. It seeks to reduce inequity in access to diagnosis and treatment, ensuring that everyone can access care in primary health settings. It will also support the prevention of type 2 diabetes from obesity, unhealthy diet and physical inactivity (*108*).

This initiative has identified eight key points.

- **Unite**: Collaboratively unite stakeholders, including people living with diabetes, around a common agenda.
- **Integrate**: Integrate diabetes prevention and management in primary health care and universal health coverage.
- **Innovate**: Close research and normative gaps while spurring innovation.
- **Treat**: Improve access to diabetes diagnostics, medicines and health products, particularly insulin, in low- and middle- income countries.
- **Track**: Develop global coverage targets for diabetes care, accompanied by a "global price tag".
- **Fund**: Improve diabetes care for those living through humanitarian emergencies.
- **Educate**: Improve understanding of diabetes.
- **Power ahead**: Build back better based on experiences from the COVID-19 pandemic.

This initiative will engage all stakeholders, including people living with diabetes, scientific and technical experts, policy-makers, governments, civil society and the private sector. The Global Diabetes Compact works in conjunction with the Global Hearts Initiative, and plans to deliver a workplan with twelve workstreams.

## 4.3 Mobilizing community to improve access to insulins and associated devices

Strengthening community action is one of the core pillars of the Ottawa Charter for Health Promotion. As a major and complex public health problem, diabetes cannot be addressed simply through a top-down approach in the absence of community involvement. Enabling people living with diabetes, as well as the broader community affected by diabetes, to take control over and to improve their own health and well-being ought to be a core feature of any meaningful and effective response to address this major public health problem.

On this principle, actions will need to embrace and apply the principles of community participation when addressing the underlying problems of global access to insulins and associated devices. Communities will need to be equipped with the necessary knowledge and resources to take action, with a view to encouraging self-reliance and promoting enduring solutions to improve access. One of the first steps to this end is to ensure that governments, authorities, industry and the community understand the public health imperative and duty for providing universal access to insulins and devices. People living with diabetes are an essential component to raising this awareness.

Examples of well-coordinated community mobilization for improving diabetes care have been documented. In Lilongwe, Malawi, a network of trained peer supporters was established under the leadership of nurse-educators and trained peer-leaders to act as advocates and coaches for their groups in the community through problem solving, listening and facilitation (*109*). The network contributed towards better knowledge and tools for daily diabetes management (e.g. dietary planning, insulin injection techniques, etc.), social and emotional support, as well as linkage to clinical care. In the United Kingdom, having a support network has also been found to be important for people initiating insulin pump therapy, not only on topics relating to diabetes, but also for practical and emotional support (*110*). Various engagement methods have been used to mobilize communities in different countries. In Bangladesh, semi-weekly mobile phone messaging with mini-dramas, dialogues and songs raise awareness about the importance of healthy behaviour among people living with diabetes in 96 villages (*111*). In Indonesia, traditional theatre performing arts are used to improve blood glucose control behaviours among people living with diabetes in Yogyakarta (*112*).

## 4.4 Conclusions

This report has described the growing need for insulins, associated devices and diabetes care more broadly. It has documented a range of known barriers to access, arising from market and health system factors. Many of these barriers can and should be addressed immediately through better policy and targeted interventions.

A century has passed since the discovery of insulins, offering a time to reflect on how much medical innovations have improved the lives and well-being of people living with diabetes in need of insulins. It is also a sobering time for the global health community to realize how much more needs to be done to address the great disparity in access to insulins and associated devices.

Concerted efforts by all stakeholders are needed now to narrow the gaps in access to insulins and associated devices, and diabetes care more broadly. To this end, WHO has taken steps as part of its core

programme of work as well as new initiatives (Table 4.1 and Table 4.2). Annex 2 presents specific areas for action discussed in section 4.1 and suggests primary and secondary actors required to realize these actions in the short, medium and long term.

All these actions must be driven through social mobilization, so that people and the communities affected by diabetes can take control over and improve their own health and well-being. This includes enabling people living with diabetes with knowledge to advocate for universal access to affordable insulins and associated devices.

Making insulin access universal is an urgent public health priority. Let us act now and carry on the legacy and goodwill of the discoverers of insulin, and keep their promise that insulin "belongs to the world".

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## Annex 1. WHO requests of the private sector[16]

**Immediate: Commitments from pharmaceutical and associated health technology industry**

1. Guaranteed ongoing production and uninterrupted supply of human insulin for low- and middle-income countries
2. Participation in the WHO/UN prequalification programme for insulin and associated health technologies
3. Agreement to participate in UN or international procurement mechanisms, when these are established
4. Public disclosure of patent status of all diabetes products, including technologies
5. Rapid filing for registration of all essential diabetes products in low- and middle-income countries, with public disclosure of registration status of all products, by country
6. Rapid reporting on product shortages by country and industry, substandard, and falsified products to NRAs and WHO
7. Developing and publicly sharing access strategies in low- and middle-income countries for diabetes products, with specific components such as: intellectual property strategy and licensing, ethical marketing and supply strategy, equitable access strategies (including pricing), humanitarian emergencies, and company incentives for access-to-medicines initiatives
8. Report and participate in the reporting mechanism that WHO will use to register and publish contributions of the private sector

**Short-term: Commitments from pharmaceutical and associated health technology industry**

1. Submission of first file to WHO/United Nations prequalification; or request review
2. Development of first product-specific access plans for low- and middle-income countries
3. Data on heat stability of human insulin products shared with WHO
4. Full transparency and public disclosure of all company commitments, actions, and outcomes in support of universal access to essential diabetes products with public reporting and to WHO on company progress in relation to these commitments
5. Filing of regulatory submissions in low- and middle-income countries
6. Company commitment not to file or enforce patents in low- and middle-income countries and some upper middle-income countries with high burden of disease (diagnostics and pens)
7. Transparency about prices for public sector procurement in low- and middle-income countries
8. Transparency on all long-term product donations (geographic range, targets, actual volumes donated, and transition plans)
9. Diagnostics trade association: prepare a report on company access initiatives on diagnostics, differential pricing, licensing, and donations
10. Biosimilar trade association: prepare a report on company access initiatives including differential pricing, licensing, and donations

[16] www.who.int/news-room/events/detail/2021/09/01/default-calendar/dialogue-with-the-private-sector-on-medicines-and-technologies-for-diabetes-care

11. Capacity strengthening in low- and middle-income countries public and NGO sector, in diabetes diagnosis, care and patient education, in collaboration with WHO Member States and other actors, and adhering to WHO guidance

**Medium-term: Commitments from pharmaceutical and associated health technology industry**

1. A company-wide Access to Medicines and Devices Strategy, integrated into the global corporate strategy
2. Intra-country differential pricing started in several low- and middle-income countries, based on ability to pay by economic quintile
3. Participation in UN and other international global and regional procurement schemes
4. R&D responding to the needs of low- and middle-income countries (e.g. heat-stable insulin, self-monitoring tools)
5. Responsible sales and business practices (e.g. no sales-related salary incentives, no direct-to-consumer advertising of insulin analogues, no marketing of analogues in the public sector of low- and middle-income countries, public disclosure of all value transfers to health professionals and relevant NGOs, and compliance controls)
6. No so-called evergreening of patents (i.e. where small modifications lead to new patents for items such as insulin pens and testing devices)
7. Corporate intellectual property strategy that is conducive to access to medicines and in line with the company's public position on the Doha Declaration on TRIPS and Public Health, as well as including transparent nonexclusive voluntary licensing with wide geographic coverage through the Medicines Patent Pool or other mechanisms

**Long-term: Commitments from pharmaceutical and associated health technology industry**

1. Corporate access to medicine strategy, with details on management oversight with board-level representation, measurable targets, incentives, headquarters accountability for actions by national offices, and a routine monitoring system that can be independently assessed, with public disclosure of targets and outcomes of access-related activities
2. Public disclosure of company resources dedicated to R&D
3. Routinely-developed access plan for low- and middle-income countries and vulnerable populations for all new diabetes products from Phase-2 onwards, with details on registration, supply, intellectual property strategy, licensing and affordability
4. Support to increasing national capacity in clinical trials in low- and middle-income countries, following good practice standards
5. Capacity building in domestic manufacturing and supply chain management (including cold storage), following good practice standards

## Annex 2. Areas of action to improve access to insulins

| Option | Time frame for action* | | | Proposed actions taken by: | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Short | Medium | Long | WHO and other UN agencies | Government^ | Payer^ | Industry | Health care professional | People with diabetes | NGO§ |
| **a. Improving the availability of human insulin and insulin analogues, especially biosimilar products** | | | | | | | | | | |
| (a.1) Maintain and expand market of human insulin | ▭ | ▭ | ▭ | ✱ | ✱ | ✱ | ✱ | ✱ | ✶ | ✶ |
| (a.2) Initiate or participate in the prequalification programme on long-acting insulin analogues alongside the existing prequalification of human insulin | ▭ | ▭ | | ✱ | ✶ | | ✱ | | | |
| (a.3) Facilitate product assessment and national registration of biosimilar insulins | ▭ | ▭ | | ✶ | ✱ | | ✶ | | | |
| (a.4) Clarify regulatory pathways and evidence requirements for changing storage conditions | ▭ | | | ✶ | ✱ | | ✶ | | | |
| (a.5) Provide and adopt clinical guidance on interchangeability and substitutability of biosimilar human insulin and insulin analogues | ▭ | | | ✱ | ✱ | | | ✶ | ✶ | |
| **b. Enhancing the affordability of human insulin and insulin analogues** | | | | | | | | | | |
| (b.1) Improve the selection and inclusion of insulins in national essential medicine lists according to health care needs and economic contexts | ▭ | | | ✶ | ✱ | ✶ | | ✶ | ✶ | ✶ |
| (b.2) Promote transparency of the pharmaceutical market, including insulins | ▭ | ▭ | | ✱ | ✱ | ✶ | ✱ | | | ✶ |

| Option | Time frame for action* | | | Proposed actions taken by: | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Short | Medium | Long | WHO and other UN agencies | Government^ | Payer^ | Industry | Health care professional | People with diabetes | NGO§ |
| (b.3) Develop pricing and procurement policies to ensure affordable prices and lower patient out-of-pocket costs | | | | ✱ | ✱ | ✶ | ✶ | | | |
| **c. Addressing access problems associated with devices to support the appropriate use of insulins** | | | | | | | | | | |
| (c.1) Include delivery devices, screening, and blood glucose monitoring devices in health benefits packages | | | | ✶ | ✱ | ✶ | | | | |
| (c.2) Manage intellectual property of devices associated with the use of insulins | | | | ✱ | ✱ | ✶ | ✶ | | | |
| (c.3) Implement measures to reduce the so-called freemium marketing practice for monitoring devices | | | | | ✱ | ✶ | ✶ | ✶ | | |
| **d. Building capacity and investing in infrastructure to support access to and appropriate use of insulins** | | | | | | | | | | |
| (d.1) Integrate diabetes care, including access to insulins, at the primary health care level | | | | | ✱ | ✶ | | ✶ | ✶ | ✶ |
| (d.2) Strengthen capacity of public and NGO sectors in low- and middle-income countries, in diabetes diagnosis, care, and patient education | | | | ✶ | ✱ | ✶ | ✶ | ✶ | ✶ | ✶ |
| (d.3) Establish information infrastructure to inform care and demand assessment | | | | ✶ | ✱ | ✶ | | ✶ | ✶ | ✶ |
| (d.4) Monitor and report shortages and occurrence of substandard and falsified insulins | | | | ✱ | ✱ | ✶ | ✱ | ✶ | ✶ | ✶ |
| (d.5) Build infrastructure and capacity in local production of insulins and supply chain management | | | | ✶ | ✱ | | ✱ | | | |
| **e. Supporting R&D relating to access to insulins and associated products** | | | | | | | | | | |

| Option | Time frame for action* | | | Proposed actions taken by: | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Short | Medium | Long | WHO and other UN agencies | Government^ | Payer^ | Industry | Health care professional | People with diabetes | NGO§ |
| (e.1) Improve collection, analysis and publication of data on diagnostic, pricing and usage of insulins and associated devices | | ▭ | | ✶ | ✱ | ✶ | ✶ | ✱ | ✱ | ✱ |
| (e.2) Support R&D that responds to the needs of low- and middle-income countries, including cold chain management, thermostable insulins, and standardization of interchangeable blood glucose monitoring devices | | ▭ | | ✱ | ✱ | | ✱ | ✶ | ✶ | ✱ |

**Key:**

* Short term: within 1 year; medium term: 1–3 years; long term: more than 3 years

^ Government and payer may be the same

§ NGO, nongovernmental organizations including international NGOs, academia and civil society

✱: Primary actor; ✶: Complementary actors


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