Background

Diabetes is an escalating global health crisis that is expected to impact 1.3 billion people by 2050 (1). Diabetes prevalence is predicted to increase even more steeply in low- and middle-income countries (LMICs). Between 2000 and 2019, there was a 3% increase in age-standardized mortality rates from diabetes. In lower-middle-income countries, the mortality rate due to diabetes increased by 13% (2). Of those with diabetes, approximately 9 million people globally live with type 1 diabetes and thus require insulin (3). In addition, about 60 million people with type 2 diabetes need insulin to achieve optimal glycaemic control, but only about 50% of these individuals are able to access this medication (4).

Insulin was discovered in 1921, first administered to a patient in 1922, and was included on the World Health Organization’s (WHO) Model List of Essential Medicines since its inception in 1977 (5). In many countries, access to insulin and related healthcare technologies is limited, and even when available, they are often unaffordable. One of the contributing factors to this lack of affordability may be a significant shift in the insulin market's composition. This shift has been driven by the introduction and increasing use of higher-priced insulin analogues since the 2000s. Current evidence indicates that insulin analogues offer at best only marginal advantages over human insulin in terms of clinical outcomes. Moreover, in specific markets, the reduced demand for human insulin following this shift may have led to an increase in its price, making it even less affordable. Additionally, these changes may further disrupt the global supply of human insulin, thereby limiting its availability for healthcare systems and individuals with diabetes who cannot afford more expensive insulin analogues. Collectively, these factors have placed substantial constraints on the ability of healthcare systems to ensure universal access to insulin. These challenges are not limited to low-income countries, as even high-income countries have reported self-rationing of insulin among people with diabetes to reduce costs, resulting in severe health consequences (6).

WHO Global Diabetes Compact

To respond to the growing burden of diabetes around the world, WHO has launched the Global Diabetes Compact. The WHO Global Diabetes Compact has a goal to reduce the risk of diabetes and ensure that all people who are diagnosed with diabetes have access to equitable, comprehensive, affordable and quality treatment and care (7). These objectives will be achieved through six workstreams, one of which focuses on increasing access to essential diabetes medicines, including insulin, and associated health technologies. In 2021, the Seventy-fourth World Health Assembly (WHA) adopted resolution WHA74.4, “Reducing the burden of noncommunicable diseases through strengthening prevention and control of diabetes”. This resolution identified the lack of affordability of insulins as one of the main barriers to access (8).
The stability of human insulin depends on a number of environmental factors (e.g. purity, pH, humidity, changes in the primary structure of the insulin molecule and added substances for enhancing or prolonging insulin absorption). It is especially susceptible to high or low ambient temperature, sunlight and usage beyond the expiration date, as well as excess usage time once opened or in use (9-11).

Exposure to high temperatures for a prolonged time usually leads to denaturation due to irreversible conformational changes and the formation of insulin fibrils (11). In contrast, fluctuating temperatures may not cause irreversible aggregation of insulin molecules when compared to continuous heating (12).

Regulatory authorities emphasize that human insulin is temperature sensitive and should be protected from both heat and freezing conditions. As such, the manufacturers’ specifications advise that intact insulin vials and cartridges should be stored at low temperatures, i.e. between 2 °C and 8 °C, thus requiring reliable refrigeration. Once opened, an insulin vial or cartridge can be stored at ambient temperature and used for approximately four to six weeks (12). However, a growing population of people with diabetes resides in LMICs where warm or tropical climates, wars and natural disasters may result in exposure to extreme heat (13-15). In some of these settings, there is also poor or no access to refrigeration. Given this, it is critical to ascertain a nuanced understanding of the thermostability of insulin.

This paper evaluates the existing evidence regarding the thermostability of insulin and how this knowledge could be leveraged by pharmaceutical companies and health authorities. Due to the dearth of evidence for superiority of the more costly insulin analogues, human insulin is the first choice insulin recommended in WHO guidelines and thus the focus of this brief (16).

**Overview of clinical and non-clinical data regarding insulin stored at higher or lower temperatures than those recommended by the manufacturer**

A systematic Cochrane review utilized two major information sources to evaluate this question: published studies and previously unpublished data from pharmaceutical manufacturers of human insulin (17). Among all published laboratory studies, there was only one small pilot clinical trial (18). Furthermore, nine, three and four studies investigated storage conditions for insulin vials, insulin cartridges/pens and prefilled plastic syringes, respectively. Overall, publications indicated no substantial loss of insulin activity for various storage conditions and temperatures. A significant portion of these data originated from pharmaceutical companies, as they investigated the widest range of storage and temperature conditions. Four manufacturers provided previously unreleased human insulin thermostability data on short-acting and intermediate-acting insulins. Data for insulin vials and cartridges across manufacturers were comparable. According to this evidence, insulin did not show a clinically relevant loss of potency for up to six months at 25 °C and up to two months at 37 °C. Data that reported on the appearance, visible particles or macroscopy, particulate matter, zinc, pH, metacresol and phenol remained within manufacturer specifications. No data were available on bacterial endotoxins and sterility. There were also no data available for cold environmental conditions or insulin pumps (17).
Prequalification pathways available to update storage conditions

WHO prequalification of medicines is a service provided by WHO to assess the quality, safety and efficacy of medical products (19). If the products are in line with current good practice guidelines and regulations and consistent with safety, quality and efficacy standards, they are placed on WHO’s list of prequalified products. This list is then used by procurers (such as United Nations agencies, member states and nongovernmental organizations) when selecting medicines to purchase and distribute throughout LMICs.

Biotherapeutics (BTPs), including their corresponding similar biotherapeutic products (SBPs), are highly complex biological medicines and the regulatory assessment of those products according to internationally acceptable guidelines and standards can be challenging in some countries (20). Given the success of BTPs, and corresponding SBPs, in treating many life-threatening chronic diseases, WHO launched the first prequalification pilot project for Rituximab and Trastuzumab in 2018. Other BTPs and SBPs for different therapeutic areas were subsequently invited by WHO to take part in prequalification.

Manufacturers were invited to submit their human insulin dossiers to the WHO prequalification medicine programme in 2020. The purpose of the prequalification programme for human insulin is to facilitate approval of high-quality human insulin BTPs and SBPs at country level and consequently to expand the distribution of quality-assured insulin products on the global market. Another objective is to increase insulin accessibility for individuals with diabetes in LMICs.

Prequalification can typically follow either one of the following two pathways (21):

- full assessment of human insulin BTPs, or the corresponding SBPs, that have not been registered by stringent regulatory authorities (SRAs); and
- abridged assessment of human insulin BTPs, or the corresponding SBPs, that have been approved by an SRA and marketed in the country of registration.

The first human insulins were prequalified by WHO in September 2022 via the abridged assessment pathway, therefore relying on assessment and inspections performed by the SRA (22). However, WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) uniquely assessed the data package submitted to update the product’s stability. The data provided by the applicant supported the product’s storage at temperatures up to 30 °C for four weeks before opening the vial/cartridge. These updated storage conditions should facilitate the use of these prequalified essential medicines under challenging temperature conditions where there is limited access to refrigeration. This is particularly relevant to LMICs.

While the products being prequalified via the abridged assessment pathway must be identical in all characteristics to the SRA’s approved products, the submission of prequalification-specific data packages for approval of prequalification-specific storage conditions offer an additional option for manufacturers.

Alternatively, applicants can update their product’s storage conditions and shelf-life by submitting an updated version of the products that have been prequalified via the full assessment pathway. WHO PQT/MED then undertakes an evaluation of these changes according to the established WHO guidelines (23) and communicates the outcome to the applicant.
Prequalification assessment

The purpose of stability testing is to provide evidence regarding how the quality of a substance or drug product varies with time under a variety of environmental conditions, such as temperature, humidity and light, and to establish a shelf-life for the drug product as well as recommended storage conditions (24). In general, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q1A(R2) guideline - “Stability testing of new drug substances and drug products” also applies to biotherapeutic products. However, the activity of these products, in which the active ingredients are generally large proteins and polypeptides, is determined by their molecular conformation and by covalent and non-covalent forces. BTPs are, therefore, particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content and shear. Stability testing for biotherapeutic products is of paramount importance. In order to ensure the maintenance of biological activity and to avoid degradation, stringent conditions for their storage are also usually necessary. ICH Topic Q5C – “Quality of biotechnological products: stability testing of biotechnological/biological products” provides specific guidance for biotherapeutic products (25). There is no single stability assay or parameter that profiles these characteristics of a biotherapeutic product. Consequently, the stability profile should assure that changes in the identity, purity and potency of the product will be detected (26). At the time of submission, analytical methods used in the stability profile should be validated. Furthermore, because the prequalified product’s target is mainly patients in LMIC settings, the principles detailed within the ICH Topic Q1F guideline – “Stability data package for registration applications in climatic zones III and IV” should also be taken into consideration, as appropriate.

Conclusion

Optimal cold-chain management of human insulin from manufacturing to the point of delivery to people with diabetes should always be maintained. People with diabetes and access to reliable refrigeration should follow manufacturers’ recommendations.

In many fragile health systems, including many LMICs, vaccine immunization programmes often have the best - or only available - refrigerated cold chain systems (27). WHO encourages greater health commodity supply chain integration in storing, handling, and distributing vaccine and non-vaccine temperature-sensitive medicines and health products (28). The benefits of a more integrated approach include improved systems efficiency through the optimal use of existing resources, the reduced risk of spoilage, the streamlining of delivery routes, as well as the increased specialization of supply chain professionals.

Stability studies are key to determining the shelf-life and storage conditions of labile products such as biotherapeutics. The prequalification programme lists quality-assured biotherapeutics that are particularly relevant for LMICs where storage conditions and cold chain management cannot always be ensured. In this context, stability programmes that also take into consideration LMIC settings can be game-changers for the availability and affordability of life-saving essential medicines such as human insulin.

To modify the storage conditions for an approved human insulin product, the manufacturer should provide data supporting the updated guidance on storage conditions. These would include
submission to WHO PQT/MED of long-term studies conducted in real-world conditions using batches of insulin that are representative of the proposed commercial product. Manufacturers could apply for a revised temperature label that provides data in support of the new claims about storage conditions.

Indeed, research and development on insulin stability is required to increase the availability and affordability of human insulin in LMICs. Researchers and manufacturers should be encouraged to produce and/or share new and/or existing data on insulin stability and storage conditions at higher temperatures.

However, the ultimate responsibility to request approval to vary storage conditions for marketed insulins or prequalified products lies solely with marketing authorization holders.

Manufacturers of human insulin are encouraged to contact drug approval authorities and make thermostability data available to establish more pragmatic storage recommendations for human insulin.
References


Thermostability of human insulin

ISBN 978-92-4-008905-1 (print version)

© World Health Organization 2024. Some rights reserved.
This work is available under the CC BY-NC-SA 3.0 IGO licence.

WHO Global Diabetes Compact
Avenue Appia 20, 1211 Geneva, Switzerland
Email: gdc2030@who.int
Website: https://www.who.int/initiatives/the-who-global-diabetes-compact/