# Insulins are critical medicines - USP standards help ensure quality

**Insulin is life sustaining and lifesaving for many patients with diabetes.** Diabetes is the seventh leading cause of death in the US.[i] It is increasing in incidence with estimated costs in the US of approximately $327 billion per year.[ii] Approximately 30.3 million people have diabetes (9.4% of the US population).[iii] Of these, about 1.25 million children and adults have Type 1 insulin-dependent diabetes.[iv]

People with diabetes must control their blood sugar with external assistance, and for many this requires insulin.[v] These patients—particularly those being treated with insulin—must monitor their blood sugar, often multiple times a day. Adjusting their doses of insulin must be done carefully to avoid life-threatening episodes. The cost of care can be high and is often lifelong.[vi]

Multiple manufacturers make insulin,[vii] and often sell the same product across multiple jurisdictions worldwide. Insulin is available in several short-acting and long-acting forms and in combination with various syringes and pumps and is generally self-administered by patients.[viii]

**Insulin quality standards help ensure quality and regulatory predictability for all stakeholders.** Insulin therapy has been used since the early 20th century, progressing from naturally-sourced, animal-derived material used initially to the very sophisticated and modified recombinant protein analog materials used today. USP's standards and international standards have accompanied insulin development from the beginning, and today, there are USP standards for the majority of insulins currently marketed in the US. These standards help ensure the quality of the medicine and play an important role in ensuring accurate patient dosing, which is extremely important for patient safety and good therapeutic outcomes.

**USP has worked closely with FDA, industry, and other stakeholders to develop useful standards that help ensure product quality and support regulatory predictability as science evolves**, regardless of the source of insulin (i.e., sourced naturally from animals, made recombinantly). Since the introduction of the first official USP insulin standard in 1941, USP's standards have been continuously revised and updated to accommodate subsequent technological advances and regulatory changes associated with insulin and its many forms. Additionally, USP has effective mechanisms to accelerate its public revision process for standards when specific issues arise and to promptly address new products that enter the marketplace, as has occurred with insulins in the past.[ix] USP also coordinates with other standards-setting organizations worldwide and important public health groups such as the World Health Organization (WHO).

**USP standards serve as measurement calibrators during development of drug substances and drug products, and as broad standards across product classes or families** (e.g., to facilitate process development). Standards help ensure quality of active ingredients and final products. These USP standards are available to anyone to use in their

development of insulin products, providing manufacturers with efficiency and cost-savings. They also facilitate calibration when transitioning from one quality testing regime to another. This was especially important as recombinant products became available to replace animal-sourced products as the purity of the product could be calibrated in terms of both insulin content and activity.

USP's insulin standard is aligned with the WHO International Standard for potency—which is essential for ensuring patient safety. Insulin is dosed in units, and a unit is the most basic measure of insulin activity in the body. In order for patients to be confident that they have access to and are taking the right amount of insulin regardless of geography, there has to be a way of aligning units throughout the world. Take the example of an American patient who moves to another country, establishes new long-term care with a local physician and needs insulin of the same therapeutic activity to continue uninterrupted treatment. Such alignment applies around the world and is being strongly encouraged by WHO to assure quality and reliability for insulin around the globe.

**The regulatory status of insulin may transition, but the need for quality medicine continues.** Insulin has historically been regulated by FDA as a drug, under section 505 of the Federal Food Drug and Cosmetic Act (FFDCA). As part of the Affordable Care Act (ACA) and Title VII, the Biologics Price Competition and Innovation Act (BPCIA), insulin will be deemed to be a biologic, and after March 23, 2020, all insulins will be licensed as biologics under the Public Health Service Act (PHS Act).[x, xi]

The implications of the transition are important to consider carefully, as any confusion among patients and their providers as a result of the regulatory shift could lead to interruptions in care. This could easily have significant negative public health consequences. Standards help assure continuity. For example, consider that after the insulins are deemed to be biologics by FDA in 2020, the products themselves will not change, even though the regulatory provisions applied by FDA will have changed. Thus, the benefit of quality standards to help ensure the quality of the medicine and accurate patient dosing applies regardless of whether the insulin is regulated as a drug under the FFDCA or a biologic under the PHS Act.

**Conclusion**

Standards in general—and insulin standards from USP in particular—help efficient development of products, help maintain the quality of currently approved products, and facilitate access to safe and reliable insulins for the many US patients who need them. USP drug substances and drug products standards ultimately relate to products that FDA has approved or licensed. This symbiosis between FDA and USP helps foster public health worldwide—and the benefit of USP quality standards to help ensure the quality of the medicine and accurate patient dosing applies, regardless of how insulin is regulated.

[i] https://www.cdc.gov/diabetes/data/statistics-report/deaths-cost.html
[ii] http://care.diabetesjournals.org/content/early/2018/03/20/dci18-0007
[iii] https://www.cdc.gov/diabetes/data/statistics/statistics-report.html
[iv] Diabetes comes in two forms: Type 1 - formally called juvenile onset, affects ~200,000 American under age 20 (0.24%) and is lifelong. Patients with Type 1 diabetes depend on external insulin to manage their disease. Type 2 – formerly called adult-onset and the more common form of diabetes. Patients with Type 2 diabetes still produce their own insulin but are unable to use it properly. These patients are managed through lifestyle changes, oral medicines and insulin.
[v] National Diabetes Statistics Report, 2017 Estimates of Diabetes and Its Burden in the United States https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf; National Diabetes Statistics Report, 2017, https://www.cdc.gov/diabetes/data/statistics-report/index.html
[vi] https://www.cdc.gov/diabetes/data/statistics-report/deaths-cost.html
[vii] Three leading manufacturers in the US are Eli Lilly, Novo Nordisk and Sanofi
[viii] FDA – information for consumers – Insulin https://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm216233.htm
[ix] Accelerated revision: https://www.uspnf.com/sites/default/files/usp_pdf/EN/fcc/guideline-on-use-of-accelerated-processes.pdf; Pending monographs: https://www.uspnf.com/pending-monographs
[x] Statement from FDA Commissioner Scott Gottlieb, M.D., on new actions advancing the agency's biosimilars policy framework https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-actions-advancing-agencys-biosimilars-policy; FDA Final Guidance Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009 – Federal Register Notice https://s3.amazonaws.com/public-inspection.federalregister.gov/2018-26854.pdf.
[xi] FDA Draft Guidance The "Deemed to be a License" Provision of the BPCI Act Questions and Answers Draft Guidance for Industry – Federal Register Notice https://s3.amazonaws.com/public-inspection.federalregister.gov/2018-26855.pdf, Draft Guidance https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM628115.pdf