USP Virtual Roundtable on Insulin Quality: Executive Summary

On June 19th, 2020, USP convened subject matter experts on insulin for a virtual roundtable discussion on insulin quality. Participants included insulin manufacturers, diabetes advocacy organizations, medical practitioners, academic researchers, regulatory agencies and other global organizations. Despite technological advances and availability of a variety of dosage forms and delivery devices, there is debate today on patient access to quality insulin products. In addition to pricing concerns, the quality of insulins has also been a topic of discussion. A recent report questioned the impact of potential lapses in the cold chain on the potency of insulins purchased at US pharmacies.[1] The potential for patients to receive poor quality or counterfeit insulin is further magnified by the increase in patients in the US that are buying insulin from other countries, through online pharmacies and from the black market. As more biosimilars receive marketing approval, patients and providers may also have additional questions about quality. There are multiple factors that may influence access to quality insulin products, including supply chain and quality of critical raw materials, manufacturing capability, regulatory status and approval, global distribution, and cold chain requirements.

Participants met to discuss potential risks to insulin quality and to provide recommendations on best practices, guidelines and standards to support patient access to harmonized and reproducible insulins from manufacturing through patient use. The goal of this first in a series of events was to identify specific topics and opportunities for collaboration among participants for future roundtables, studies, and workshops.

The roundtable included several presentations from stakeholders to provide attendees background and different perspectives on insulin quality. USP's CEO, Dr. Ronald Piervincenzi, kicked off the event and noted that Insulin is one of the world's most miraculous drugs, unique in its broad impacts on public health and health economics. Dr. Piervincenzi reviewed the history of insulin, including technological, formulation, and regulatory changes over the past 100 years. He noted that attendees comprised a distinct group, representing diverse organizations with expansive breadth, value, and advocacy capabilities, and emphasized USP's commitment to collaboration.

Insulin quality requires the right standards, applied correctly, combined with advocacy efforts that acknowledge and reward quality. To advance insulin quality, USP is committed to developing and fostering partnerships that support training and provide scientists with the tools needed to maintain and enhance global quality.

Dr. Irl Hirsch, Professor of Medicine at University of Washington, highlighted the most common issues with insulins that result in clinical problems. Temperature was cited as the biggest problem, stemming from insulin being left in the heat or patients using pumps beyond the recommended 3 days. Other common issues included improper mixing of intermediate-acting insulin (known as NPH Insulin), patients using insulin beyond the 28 day in-use period, and patients mixing up basal and bolus insulins due to the similarity of the packaging. Dr. Hirsch also identified potential issues related to excipients, which can influence the pharmacokinetics and pharmacodynamics and may cause inflammation that impacts long term insulin pump usage. Dr. Hirsch also reported on global insulin rationing rates and emphasized that insulin insecurity remains a problem in the US.

Dr. Timothy Garrett, Associate Professor at University of Florida, presented results of a study funded by JDRF, ADA, and Helmsley Trust to evaluate the impact of the cold supply chain on insulin potency. This study was initiated in response to a 2018 publication by Carter and Heinemann[1] that reported the potency of insulins from local pharmacies failed to meet the minimum standard of 95 U/ml set by USP, as well as EP, JP and other global regulatory agencies. Dr. Garrett's study evaluated a total of 200 vials of human and analog insulins and compared three different methods for assessment of insulin potency, including the USP compendial method, the mass spectrometry method utilized by Carter, and an optimized mass spectrometry method developed in the Garrett laboratory. When tested using compendial methods, all insulins tested met the USP criteria of 100 (±5 U/mL), suggesting that the cold chain is not compromised.[2] Dr. Garrett also showed that the sample preparation method used in the Carter study yielded significant

losses, but that an optimized sample preparation could produce results similar to the USP method. Additional studies are planned to assess potency throughout different seasons and to further optimize mass spectrometry methods for insulin analysis.

Dr. Sanjoy Dutta, JDRF Vice President of Research, reviewed JDRF's ongoing efforts related to insulins, which include the Garrett study as well as efforts to develop novel insulins. Efforts for development of new insulins are focused on development of 1) glucose-responsive insulins that activate/deactivate based on glucose concentration in the body 2) ultra-rapid acting insulins to lower blood glucose more quickly, and 3) insulins that are more effectively targeted to the liver. Dr. Dutta also outlined JDRF's efforts to address insulin affordability.

Dr. Guido Pante, Technical Officer at the World Health Organization (WHO), reviewed WHO's pilot prequalification program (PQ) for insulin. Prequalification is intended to increase access in low and medium-income countries to quality-assured insulin products. The pilot invites human insulin injection (soluble) and intermediate acting human insulins (as insulin zinc suspension or isophane insulin). Dr. Pante reviewed WHO's PQ invitation for insulin products, including data requirements and common application deficiencies.

Dr. Mark Atkinson, President of Insulin for Life and Director of the Diabetes Institute at the University of Florida, discussed global challenges to insulin quality and safety, with an emphasis on the developing world and disaster response. Dr. Atkinson reinforced the challenges associated with temperature, noting that three quarters of the world does not have access to refrigeration. Improper use, including dilution, rationing and overdosing, as well as challenges related to lack of education, disinformation, data gaps, and black-market insulin have a significant impact on safety. Dr. Atkinson suggested that more publicly available information on stability of insulin with respect to time, temperature, humidity, etc. would be useful. Dr. Atkinson also cited practical considerations for disaster response, including guidance for creating an emergency plan, and common issues faced in disaster situations.

Dr. Diane McCarthy, Senior Manager at USP, reviewed the evolution of USP's insulin standards since the first monograph was published 70 years ago, illustrating how analytical tests for identity, purity and potency have evolved over time as analytical techniques have improved. Dr. McCarthy also discussed how USP Biologics is expanding beyond compendial standards to develop tools that support technologies and assays that are used for raw materials, biomarkers and analytical testing of drug products and enhancing educational offerings to support researchers, manufacturers and practitioners.

Attendees discussed the following risks, opportunities, and best practices:

Insulin Stability

- Insulin stability and the impact of temperature on potency were discussed. Participants noted that thermostable insulins are needed to address lack of access to refrigeration. This is an issue not only for low and middle-income countries, but also for underserved populations like the homeless in high-income countries. Participants also noted that development of thermally stable insulins is challenging since insulins are small proteins and are therefore temperature sensitive and susceptible to the same chemical modifications as other biotherapeutics.
- The rationale behind the defined insulin shelf life and defined use period (28 days for many insulins but can be longer for some insulin analogs) was discussed. Insulins, like most biological drugs, are susceptible to degradation, which is dependent on time and temperature. Practitioners reported that their patients sometimes used insulins beyond their in-use dates, with mixed results. Unopened insulins are stable for years when refrigerated, but are stored at room temperature once opened. There are many steps in the supply chain: manufacturers, shipping, pharmacy benefit managers, pharmacies and finally the patient. Manufacturers monitor and control this process deep into the supply chain but eventually lose track. While insulin does retain activity beyond 28 days at room temperature, ambient temperature can vary widely across the globe. Manufacturers need to meet the regulatory guidelines which require insulin potency to be 95 –

105 U/mL, so shelf life and in-use time is defined based on the ability to meet those specifications. Beyond 28 days of storage at room temperature, manufacturers cannot guarantee that insulin potency will meet those specifications.

- Practitioners also reported seeing more issues with insulin pump therapy in the summer due to the heat. While patients are supposed to change out the insulin in their pumps every three days, many patients use them for longer but data is not available to illustrate the impact of extended use. Manufacturers indicated that regulators would typically ask for stability data to cover double the time of intended use. While manufacturers acknowledged the challenges that patients face, they can only recommend the product be used within the approved limits in the label and patient information leaflet.
- Participants discussed the need for new analytical tools to measure insulin potency. Compendial tests are time consuming and cannot be performed routinely at the end of the supply chain to ensure insulin quality. With emerging new technologies, there may be an opportunity to invest in development of a rapid test or a mobile laboratory that can perform a quality test within minutes at the pharmacy or eventually in patients' hands. NMR is one technology that has potential to simplify analysis and could be used by laboratories but is not amenable to a handheld device. Infrared spectroscopy is also a promising technology that can be utilized in a portable device. IR requires little or no sample preparation and could be used for vials without the need to open the vial, but would be more difficult to apply to insulin pens.

Supply Chain Disruptions

- Natural disasters, political and economic instability, climate change, homelessness, and disease outbreaks can all cause disruptions to the traditional supply chain. Participants discussed the importance of having an emergency preparedness plan and the difficulties of getting insulin to patients dealing with a crisis. Practitioners commented on the difference between what might be the "right" thing to do based on the package inserts and the answer that keeps people alive. Practitioners requested more guidance on how to help patients under extreme circumstances.

Excipients

- Excipients are added as a preservative to enhance stability and prevent microbial growth. Practitioners reported some instances where patients have proven allergies to excipients. Excipients differ between insulin products. In the US, selection of a brand of short or long-acting insulin is often dictated by the insurance companies. Excipients for a biosimilar would generally be the same as the innovator product. Recent data presented at the ADA meeting also showed potential for excipients to increase inflammation in animal models, which may have a detrimental effect on long term insulin pump use. Impurities such as trace metals in the excipients were also cited as a potential issue that needs to be monitored.

Packaging

- Participants discussed the similarity of packaging, especially with insulin pens, and practitioners noted it was easy for patients to mix up their short-acting and long-acting insulins. Participants discussed various options for preventing mix-ups. One option is for manufacturers to use different packaging for short-acting vs long-acting insulins (for example, a triangular-shaped pen vs a round pen). The packaging format would need to be consistent across all insulin manufacturers to avoid patient mix-up. A low tech option was also recommended by a practitioner who told patients to use a piece of tape to distinguish short vs long-acting insulin pens.

Practitioner and Patient Education

- Participants outlined the need for additional education for practitioners, especially those in primary care that don't readily have access to endocrinologists. Diabetes management and effective use of continuous glucose monitors (CGMs) and adjustments of insulin doses is not taught in medical schools and when practitioners go out into the community, they are not comfortable with adjusting insulin doses and interpreting CGM data, which can lead to poor diabetes management. Participants agreed there is a need to make education accessible to support primary care practitioners (PCPs) and to encourage general practitioners to look beyond hemoglobin A1c (HbA_{1c}) levels. This may require decentralizing knowledge and supporting

decision making, interpretation of data, and dose adjustments. Several practitioners indicated that this education is typically performed by nurses or diabetes educators, so they should be involved in developing a systematic approach to patient education in order to reach a larger patient population.

- Insufficient mixing of NPH insulins was also cited as a common problem by participants. Several practitioners reported this was a common problem, especially in hospital settings where NPH Insulins are used more frequently. It is difficult to know when mixing has been sufficient and improper mixing does not only impact one dose but can have downstream impacts on subsequent doses from the same vial. Best practices for proper mixing could be shared via videos.

Conclusion

This first of a series of roundtable discussions on quality of insulins brought together stakeholders throughout the diabetes community to share knowledge, challenges, and best practices related to insulin quality and laid the foundation for continuing discussions. While recent research presented by Dr. Timothy Garrett on the impact of the cold chain on insulin potency showed that insulins obtained from the pharmacy met the USP standards for potency, several opportunities to enhance the quality of insulin use were identified. Temperature excursions were the most commonly reported issue that had a clinical impact. Participant agreed that more information on stability of insulins would be useful to practitioners to help provide guidance for patients. Over the longer term, rapid tests for potency that could be performed at the pharmacy or by patients to ensure insulin potency could be developed. Additional education for primary care providers on insulin use and storage, dose adjustment, and use of continuous glucose monitors was also cited as an unmet need. USP is committed to facilitating further discussion and collaboration between stakeholders, including insulin manufacturers, practitioners, advocacy organizations and regulators, to enhance the quality and consistency of insulin treatment and provide tools and training to support manufacturers, practitioners, and patients. To further engage with the broader diabetes community, we call on all stakeholders to send their recommendations for additional insulin quality topics to Diane McCarthy at diane.mccarthy@USP.org

Insulin Roundtable Participants	
Name	**Company**
Irl Hirsch	University of Washington
Timothy Garrett	University of Florida
Sanjoy Dutta	Juvenile Diabetes Research Foundation (JDRF)
Guido Pante	World Health Organization (WHO)
Mark Atkinson	University of Florida, Insulin for Life
Archana Sadhu	American Association of Clinical Endocrinologists (AACE)
Boris Draznin	American Diabetes Association (ADA)
Sundar Ramanan	Biocon
Elizabeth Kramer	Eli Lilly
Jim Sabatowski	Eli Lilly
Anne Peters	Endocrine Society
Anjali Shukla	Food and Drug Administration (FDA)
Harold Rode	Health Canada (retired)
David Panzirer	Helmsley Charitable Trust
Morten Hach	Novo Nordisk
Wilfried Arz	Sanofi
Ronald Piervincenzi	USP
Fouad Atouf	USP
Diane McCarthy	USP

References

1. Carter AW and Heinemann l (2018) Insulin Concentration in Vials Randomly Purchased in Pharmacies in the United States: Considerable Loss in the Cold Supply Chain. *J Diabetes Sci Technol*. **12**:839–841.
2. Garrett TJ, Atkinson P, Quinlivan EP, Ang L, Hirsch IB, Laffel L, Pietropaolo M, Haller MJ and Atkinson MA (2020) Commercially Available Insulin Products Demonstrate Stability Throughout the Cold Supply Chain Across the U.S. *Diabetes Care*