FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Biosimilar and Interchangeable Insulin Products

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I N D E X

MS. TEMKIN: Good morning. My name is Eva Temkin. I am the acting director for policy in the Office of Therapeutic Biologics and Biosimilars at CDER here at FDA, and I'm going to be the presiding officer for the hearing today.

It is my pleasure to introduce our Acting FDA Commissioner, Dr. Sharpless. Dr. Sharpless joined the FDA in April, after serving as the director of the National Cancer Institute at NIH, and the director of the University of North Carolina Lineberger Comprehensive Cancer Center. In his time at FDA so far, we have already seen Dr. Sharpless advocate for increased competition in and access to markets for lifesaving therapies, like insulin. Dr. Sharpless will be providing opening remarks to set the tone for the public hearing today, the future of biosimilars, increasing access, and facilitating the efficient development of biosimilar and interchangeable insulin products. Dr. Sharpless?

DR. SHARPLESS: Good morning, and thank you for having me today. I think it's a very important public meeting. The world of public health has really

never been more promising or exciting as it is now. Biomedical research is really changing the way we approach public health and has enormous opportunity. But with these advances, I think it's important to mention comes with new challenges. And one of the biggest challenges of the modern medicine era is the cost of many of these new, and in some cases not so new, treatments and devices.

The subject of today's public hearing, facilitating the efficient development of biosimilar and interchangeable insulin products tackles this challenge in part. Insulin is a life-saving medicine. The essential role in treating diabetes mellitus has been known since the time of Banting and Best in the 1920s, and as an internist I can say that no condition is more satisfying to treat than diabetic ketoacidosis. You would have these patients come in so profoundly sick and we give them 10 or 20 units of regular insulin, and these patients would rise like Lazarus and then tell you they wanted to go home so quickly. So, it was a great -- it makes it evident how important that drug is for patients in that

condition. And if that doesn't make you feel like a real doctor, then kind of nothing will.

But although insulin is an old medicine, the recent advances in science and technology has been improved in many ways in terms of formulation, monitoring and delivery, making diabetic care much simpler for patients and families in reducing the risks of long-term diabetic complications.

Earlier this year, for instance, the FDA approved the first interoperable insulin pump intended to allow patients to customize treatment through their individual diabetes management devices. And last year we expanded the approval of an automated insulin delivery and monitoring system for use in younger pediatric patients.

FDA has approved three follow-on insulin products -- Basaglar, Lusduna and Admelog since 2015. For those of you who may wonder how I can pronounce those, my wife is an endocrinologist, so I got some coaching. But against this backdrop, ongoing and hopeful medical progress is a continuing increase in the prices of insulin products.

One study from the Schaefer Center documented the average list price of four insulin categories increased on the order of 16% per year from 2001 to 2015, and a report released late last year by the Congressional Research Service noted a list price of one type of insulin had increased nearly 600% from 2012 to 2016. It hardly needs to be said that these kinds of whopping and steady price increases make it increasingly difficult for many insulin-dependent patients to afford basic medicines they need to survive. As a physician, I find this intolerable. No patient should have to choose between paying for their medicine and paying for their rent.

I know this audience is well aware of the recent news reports of people who have felt the need to stockpile insulin, or reports of patients who couldn't get the insulin they needed and have died from lack of access.

As a regulatory agency focused on science and evidence-based care, the FDA is working to support the advancement of new treatments and to build a system of public health that strengthens access to needed

medical care. At the same time, we're also very focused on making sure that the drugs patients need are affordable and accessible. One of the best ways to achieve this is to increase market competition through the introduction and expansion of safe and effective generic drugs. We've seen great success in this area with record levels of generic drug approvals in recent years. Generic drugs account for 90% or more of the prescriptions in the United States, and the generic drug supply in America is highly regulated and safer than ever. Unfortunately, however, not all pharmaceutical products are amenable to competition through the generic pathway.

That has been the case for insulin products, because insulin is regulated as a biologic presently, meaning a complex molecule generally manufactured in living cells. Biologics increasingly are a mainstay of modern medicine playing a critical role in the treatment of serious illnesses and often presenting the only effective treatment for some patients. In fact, biologics today account for about a third of new therapies approved by the FDA. Unfortunately, because

of their complexity, it's been difficult to increase competition in the market for biologic products.

One could think of it this way: Biosimilars are to biologics as generics are to small molecule drugs. Until recently, there was no pathway for FDA to approve products that are biosimilar to or interchangeable with brand-name products, as there is for small molecules. Thanks to several important legislative, regulatory and policy changes, however, the FDA expects that this is going to change, and the opportunity for companies to develop new, less expensive biosimilar interchangeable insulins will be possible.

In 2010, Congress created a Biologics Price Competition Innovation Act, which created a pathway for approval of biosimilar and interchangeable products. What this means is that biologics are now open to competition, providing more treatment options to patients at potentially lower prices. We've taken important steps to implement this pathway and promote this type of competition pursuant to Congress's direction. Our Biosimilars Action Plan released last

year is designed to improve the efficiency of the biosimilar and interchangeable product development and approval process by providing increased scientific and regulatory clarity for the biosimilar development community, and we're seeing results. The FDA has already approved 19 biosimilar products with many more biosimilar development programs underway.

And last week the FDA issued a final guidance on interchangeability of biosimilar products, describing the regulatory path whereby biosimilars can be substituted without the involvement of a prescriber for branded biologics. This is important and it's a key step to controlling the prices of biologic drugs in general, but today we're here to specifically talk about insulin.

At Congress's discretion, we are transitioning, effective next March, certain applications for biologic products currently approved under the Food, Drug & Cosmetics Act of the FD&C to be biologics under the Public Health Service Act of the PHS. That's a mouthful, but make no mistake, it's important, and let me try and explain. It offers a

promise for insulin products.

While insulin products are proteins in more biologics presently, they historically have been regulated under the FD&C, which governs the approval of drugs and generics, rather than PHS, which governs the approval of most biologics. By moving insulin and other applicable products to be under the PHS, Congress has promoted a pathway for follow-on insulin products to become available. So, this means that insulin and insulin analogs will now be open to biosimilar competition, which in turn can lead to the development of more affordable biosimilar insulin products, including products that are interchangeable with branded insulins without any compromise in safety and efficacy. We're hopeful that this approval of interchangeable products will translate into increased competition, meaning lower cost and increased access for patients.

According to the timetable in the statute, insulins and other biological products historically regulated under the FD&C will not transition to the PHS until March of 2020. And while this is slower

than many of us would like, it's clear that there is already a great deal of interest among potential sponsors. We're not where we need to be yet, but we're getting closer, and we've taken important steps.

Today's public hearing is another key step. The opportunity to hear from you, stakeholders directly affected by the price of insulin and who would benefit by the impact of additional competition from biosimilar and interchangeable products. We want to hear from you about what factors we should consider in evaluating information submitted by applicants for new biosimilar products. What scientific standards should we use for evaluating within the bounds set by the statutory requirements whether an insulin product is biosimilar or interchangeable to a reference product? Do certain products, like insulin pumps or continuous subcutaneous infusions, raise unique scientific considerations that we should be considering when evaluating biosimilar or interchangeable insulin products? And we want to know what aspects of the patient experience with insulin products should FDA consider when making this

evaluation?

Finally, what kinds of information and resources do we need to develop and foster effective communication and promote awareness among patients, clinicians, pharmacists, and other stakeholders about biosimilar and interchangeable insulin products? Your voices are what will help spur and shape the development of our policy in this area to meet public health needs. Working together, I believe we can advance the development of biosimilar insulin products that are more affordable, effective and accessible.

Thank you, and I look forward to your comments, and have a great meeting.

MS. TEMKIN: Good morning again to "The Future of Insulin Biosimilars," this public hearing. As the presiding officer, it is my pleasure to now make an enormous slew of remarks on logistics of today's hearing.

The purpose of the hearing is to provide an opportunity for broad public input as the Agency prepares for the submission and review of applications for biosimilar and interchangeable insulin products.

Before we begin, here come the administrative announcements.

First, please silence any cell phones or other mobile devices, as they may interfere with the audio in the room today. Second, we ask that all attendees sign in at the registration tables outside the meeting room. Restrooms are located in the lobby past the coffee area to the right and down the hallway. Finally, copies of today's presentations will be available upon request. Contact information is also available at the registration table.

I would now like to ask the FDA panelists to please introduce themselves.

MR. UNLU: I'm Mustafa Unlu. I'm with the Office of Chief Counsel.

MR. SCHILLER: Good morning. I'm Lowell Schiller, the principal associate commissioner for policy.

MS. YIM: Sarah Yim, Acting Director of the Office of Therapeutic Biologics and Biosimilars.

MS. LIAS: I'm Courtney Lias. I'm with the Center for Devices and Radiological Health.

MS. YANOFF: Good morning. Lisa Yanoff, Acting Director of the Division of Metabolism and Endocrinology Products in CDER.

MR. STEIN: Good morning. Peter Stein, Director of the Office of New Drugs, CDER.

MR. KOSLOWSKI: Steven Koslowski, Director of the Office of Biotechnology Products, OPQ CDER.

MS. TEMKIN: Thank you. For media inquiries, our press officer today is Lindsay Meyer. If any members -- there she is. If any members of the media are here today, please sign in, and if you have questions or interest in speaking with the FDA about this public hearing, please reach out to Lindsay Meyer. The hearing is intended to give FDA the opportunity to listen to the comments from the presenters, so panelists and other FDA employees will not be available to make statements to the media.

Although there are no rules of evidence for this public hearing, there are some general procedural rules. No participant can interrupt the presentation of any other participant, and only FDA panel members will be allowed to question the presenters. There

will be an open public comment period at the end of the day, once all the presenters have finished.

Public hearings are public administrative proceedings and are subject to FDA policies and procedures for electronic media coverage. Representatives of the electronic media are permitted, subject to certain limitations, to videotape, film or otherwise record FDA's public proceedings, including the presentations of today's speakers. This hearing will also be transcribed, and copies of the transcript can be ordered through the docket or accessed on our website approximately 30 days after today's hearing.

Today we have 12 speakers registered. Each of them will have 10 minutes to present, and after each presentation, five minutes are scheduled for panel members to ask questions. If a speaker finishes early or if the questions from the panel do not take the fully allotted five minutes, we intend to move on to the next speaker. This means that speakers may find themselves being called upon to give their presentations before the time that is listed on the agenda. Although we may be adjusting the schedule as

needed, we will keep our scheduled breaks at the time listed on the agenda.

For the speakers, we have timer lights to guide you. You'll see them when you get up here. The light will indicate when you begin speaking and when to stop. The timer will give you a two-minute warning before the red light goes on. If you have not concluded your remarks by the end of your allotted time, I will have to ask you to do so.

Please remember that the hearing is being transcribed, so please be sure to use the microphone when speaking. If you didn't register to make an oral presentation but you would like to do so at the end of the hearing, you may be able to speak during the open public comment period, which is scheduled to begin at 1:45 p.m. If you're interested, please sign up at the registration table outside the meeting room no later than 10 a.m. for one of the available three-minute speaker slots. We also strongly encourage you to submit to the docket. The Federal Register notice has details on how to submit comments to the docket. Extra copies of that notice are also available at the

registration table. As you can see from the slide, electronic or written comments can be submitted to the public docket until May 31. This hearing is being webcast live. However, the webcast is not interactive, so webcast viewers cannot comment or ask questions.

In closing, I want to thank everyone, including our panelists and speakers, for participating today. I look forward to a very productive hearing. And with that, I will ask our first speaker, Alexander Oshmyansky.

DR. OSHMYANSKY: All right. I would first like to very much thank the FDA and all the members of the panel for allowing me to speak here today. My name is Dr. Alexander Oshmyansky, and I am the CEO of Osh's Affordable Pharmaceuticals. I am here today to speak about our spinoff company, The Insulin Club.

The Insulin Club is dedicated to producing new, low-cost biosimilar versions of analog insulins. Our mission is that every American who needs insulin should be able to easily afford it. We want to dramatically decrease the cost of insulin.

We will be structured as a membership club, similar to Costco. In exchange for a small annual fee, we will supply insulin at a low fixed net margin. One of our core tenets is complete radical price transparency. We intend to tell our members exactly what it costs us to manufacture, market and develop our products so that they may be able to make informed, rational decisions about their healthcare.

Our initial goal is to have biosimilar glargine insulin available at a price of $20 a vial within the next three years.

Right now, the high cost of analog insulins has devastating consequences. The average list price of insulin has tripled between 2002 and 2013, and has continued to rise since. This has resulted in rationing of insulin for both type 1 and type 1 diabetics -- or, I'm sorry, type 2 diabetics. This practice can result in undue blindness, amputation, renal failure, and premature death. For a sense of scale, approximately 30 million Americans live with diabetes. Diabetes and its complications cost the US healthcare system an estimated $327 billion a year.

As it stands, three manufacturers control 99% of the US insulin market, resulting in a severe lack of competition and the potential for continued increased price hikes.

At the moment, the regulatory structure around insulin makes it difficult for new companies to develop insulin. Fortunately, a new regulatory framework for bringing insulin products to market is on the horizon and which has the potential to increase competition in the insulin marketplace and facilitate new entrants such as ourselves. Starting in 2020, insulin will be regulated as a biologic product under the 351(k) pathway. However, development times for biologic or biosimilar drugs remain lengthy and costly.

Today I would like to present the case that it may be appropriate to expedite the path to market for insulin biosimilars based on the inherent characteristics of insulin as a biologic. This would allow us to increase competition in the insulin market, decrease cost to patients, and get lifesaving medicines to patients faster.

In particular, we would like to propose a potential Phase 3 clinical trial waiver for insulin products. Phase 3 trials are lengthy and extremely costly. In addition, they do not provide scientific evidence in assessing biosimilarity, specifically, of a biologic drug, which is the core aim of the 351(k) pathway. They are not powered sufficiently to detect meaningful differences in safety or immunogenicity to detect adverse events or detect differences in efficacy.

It can actually be argued that the primary purpose of Phase 3 trials is to create marketing data for physicians in an effort to be able to increase claims in market share rather than truly to detect the inherent safety of a biosimilar drug. A robust CMC package in Phase 1 clinical trial should leave little uncertainty as to biosimilarity. Insulin, which is a small, extensively studied protein discovered almost 100 years ago, is particularly amenable to this approach.

At the moment, EU regulatory authorities accept manufacturing changes without clinical trials

and focus instead on the physiochemical, analytic and functional assessments to ensure comparability. So far, studies have not shown any meaningful differences in clinical or safety profiles of the drugs regulated in this fashion. We would ask the FDA consider a similar regulatory approach towards insulin specifically, given the well-studied nature of this small protein.

In the alternative, we would propose the following: (1) A more robust Phase 1 trial with more subjects taking place over a longer period of time with questions to immunogenicity addressed as endpoints; (2) we would propose rigorous post-market surveillance; and (3) we would recommend educating physicians about the basis of biosimilarity rather than creating trials for specific marketing claims.

In conclusion, insulin is a small protein with a long history of data to support its efficacy, safety and immunogenicity. Phase 3 trials are lengthy, costly and redundant. Other regulatory authorities already accept manufacturing changes without full clinical trials and without reported

adverse events. A robust CMC and Phase 1 package should be sufficient to demonstrate biosimilarity, and post-market surveillance can be performed.

I thank you very much for your time here today and would be delighted to answer any questions you may have.

MS. YANOFF: Thank you very much. Can you tell us a little more about your alternative consideration for the Phase 3 study?

DR. OSHMYANSKY: Oh, sure.

MS. YANOFF: Enrolling more subjects, can you explain your reasoning for that, what that would provide? And then in the subset that you want to expose up to one year, what are you thinking there? What would be the different angles of the larger group versus that subset? Just a little bit more detail would be helpful.

DR. OSHMYANSKY: Oh, sure. So, you know, I would say first, you know, we would like to have the large bulk of the evidence we provide for biosimilarity to come from orthogonal experiments for the actual CMC package we would produce. But in terms

of a Phase 1 trial, specifically, I think we can address some -- by making it a more robust Phase 1 trial, we might be able to add additional endpoints to the trial, which could address some of the concerns that might otherwise be raised in a Phase 3 trial. For example, we could add additional endpoints related to immunogenicity, let's say, by making that Phase 1 trial more robust.

MR. KOSLOWSKI: So, you had mentioned post-market surveillance. So, are you envisioning post-market surveillance that is different in nature than the post-market surveillance expected for all biological products?

DR. OSHMYANSKY: I think that's a topic for conversation, but I think we could, in fact, provide more robust post-market surveillance than is currently done in lieu of a full Phase 3 trial. What exactly that might entail I think is a topic for further conversation, sort of outside the scope of the present meeting.

MS. YANOFF: Has your group thought about interchangeability and what the requirements would be

for that?

DR. OSHMYANSKY: We have. For our particular business model as a membership club that we envision, we don't see interchangeability as being particularly critical for what we're doing. We think physicians will refer direct -- or hope, at least, physicians will refer directly to us. So, we're not going to be seeking interchangeability, specifically, as part of our sponsor package.

MS. TEMKIN: I think if there are no additional questions, thank you very much.

DR. OSHMYANSKY: Thank you, guys.

MS. TEMKIN: And we'll ask Dr. Steven Lucio to come up, please. Thank you.

DR. LUCIO: Good morning. My name is Steven Lucio, and I'm the vice president for the Center of Pharmacy Practice Excellence at Vizient. I am speaking today on behalf of Vizient, the largest member group and healthcare performance improvement company in the United States. Vizient provides innovative data-driven solutions, expertise and collaborative opportunities that lead to improved

patient outcomes and lower costs. Vizient would like to express our deepest appreciation of the Food and Drug Administration not only for this open forum and the others that have preceded it, but also for its continued efforts to establish, implement and enhance the biosimilar approval process.

Vizient fully endorses the scientific principles of biosimilarity, and the biosimilar pathway is critical mechanisms to mitigate accelerating growth of pharmaceutical expenditures through the development and marketing of competing biologics of comparable safety, purity and potency.

We also believe that we have reached a critical juncture in the maturation process of the biosimilars market such that any inability or unwillingness to address the residual barriers to biosimilar adoption could permanently impair the extended value we hope to achieve. As a result, we thank FDA for this opportunity to convey the perspectives of the member organizations we serve and to identify additional interventions to support and sustain competition in the insulin market, and for

other biologic molecules.

Part of Vizient's many core capabilities is our sourcing services, which represents over $100 billion in annual healthcare expenditures. Much of it is associated with pharmaceuticals. Our membership is comprised of thousands of healthcare organizations who provide care to most at risk and vulnerable patient populations. The treatment intervention to licensed practices are frequently high cost biologics; therefore, the relevance of the biosimilar product class to our membership is of the utmost importance.

Based upon our experiences, and more importantly that of the diverse membership of leading academic medical centers, pediatric facilities, community hospitals, integrated health delivery networks, critical access providers, and nonacute healthcare practitioners, who have accumulated a wealth of insight we would like to share and support FDA's efforts in facilitating and expediting the introduction of biosimilar and interchangeable and insulin products.

Since 2010, Vizient has provided ongoing

training and education on the biosimilar paradigm to its membership and other audiences in the form of over 200 in-person presentations and web conferences, has developed evidence-based clinical resources to support members in their formulary evaluations of approved and pending biosimilars, and has worked with existing and future biosimilar manufacturers on contractual relationships to maximize the value and cost-savings opportunities for our membership.

At present, Vizient has over 60 pharmacists and other subject matter experts working to facilitate the appropriate use of biosimilars and document the financial value and sustained high quality of care associated with these agents.

We are continuing to see progress in terms of improved acceptance from clinicians; however, based upon forecast and budget projections, including our own, much work still remains.

One of the most important services we provide for our members is projecting and predicting the anticipated trends in the base pricing for pharmaceuticals and the extended impact on pharmacy

department budgets. Twice a year, Vizient publishes its drug price forecast, a document that estimates the direction and degree of price changes for the pharmaceuticals most commonly used by our membership.

Our most recent version of the forecast from January of this year illustrates the challenge presented by agents used in the treatment of diabetes. Several prominent categories of diabetes medications, including the DPP-4 inhibitors and the incretin mimetics are expected to realize significant price increases based upon ongoing pricing behavior and expectations of continued market dynamics.

These trends, while not necessarily desirable from a provider or patient standpoint, are neither surprising. The drugs in these classes are newer agents and still within their period of marketing exclusivity and patent protection. As a result, we are some years away from competing versions of these molecules.

In contrast, numerous insulin produces, which in some cases have enjoyed two decades of market exclusivity, lack direct molecular level competition

and are anticipated to have similar increases in drug pricing as these new therapeutic categories.

Given this prolonged period of exclusivity, the negative impact on drug budgets and the access barriers for patients, the introduction of biosimilar insulins is required. As a result, we must do everything to ensure that the transition of insulin products from regulation drugs to biologics and enable the development of biosimilar proceeds as efficiently as possible. To that end, we recommend the following steps.

Vizient encourages FDA to apply the same scientifically justified approach the approval of insulin biosimilars as it has to the products that have already been approved. The approval methodology of maximizing analytical characterization data demonstrates sameness, the efficiencies of bridging and extrapolation in the use of PK and PT studies to demonstrate comparability have repeatedly and reliably function as intended. Therefore, we believe the approval process has already been established appropriate for the evaluation and licensing of

biosimilar insulin products.

One way that could function differently for insulins as compared to already approved biosimilars involves the concept of interchangeability and in contrast to what was here on the slide, the recent publication by FDA of the final interchangeability designation is very much applauded, and we appreciate it in terms of helping us address lingering uncertainty about the requirements for this status. We also hope that this step will enable the increased understanding of this designation.

Of the clinical topics pertaining to biosimilars' interchangeability remains one of the most difficult for clinicians to grasp. Two areas of worry include concern about physicians being disintermediated from substitution considerations and the perception that noninterchangeable biosimilars are somehow inferior to interchangeable biologics. Vizient has been working to address both concerns and would request FDA's assistance in alleviating those fears.

First, Vizient is working with its members

and their prescribers to highlight the fact that biosimilars approved to date have primarily been for products either directly administered by a healthcare provider and/or managed for a specialty pharmacy mechanism due to their associated costs. As a result, considerations about the use of a biosimilar in place of an originator has had and continues to include substantial prescriber interaction by a P&T committee oversight, formulary management processes and prior authorization requirements. There are few circumstances where a dispensing pharmacist is delivered a prescription with limited access to the prescriber and/or access to detailed patient information. Vizient has encouraged its pharmacy members to engage and educate its physician colleagues on these facts as well as their essential role in ensuring the safe use of biosimilars, and to address other concerns that could limit acceptance.

In contrast, while insulin management occurs within a health system environment, it also takes place to a great extent in the retail dispensing setting, where clarity regarding both the

interchangeability status of a biologic as well as the prescriber's intent toward product substitutability must be as effective and efficient as possible. As a result, the publication of finer interchangeability guidance is of considerable importance.

In its final guidance, FDA provides two processes by which an interchangeable biologic could be approved. One approach necessitates licensing versus biosimilar without an interchangeability designation. The other allows for a direct pursuit of interchangeability status. Vizient requests that FDA specifically characterize the insulin agents as products that could directly pursue interchangeability without first being licensed as a noninterchangeable biosimilar. The attributes of insulins relatively low structural complexity molecules from which highly similar analytical comparability can be established would seem to lend this category to licensing via a single switching study. Enabling direct pursuit of interchangeability should limit the expense and time investment needed to introduce competition.

In addition to these recommendations, Vizient

would also like to identify three other areas for requested change for biosimilars beyond just the insulin products. First, Vizient applauds FDA's approach to exclude transitional biological products from the requirement to add a devoid of meaning suffix to nonproprietary product name. Vizient asks FDA to extend this approach to all biologics and biosimilars.

Since the release of the first draft guidance on biosimilar naming, we have yet to encounter a member representative that has endorsed the devoid of meaning suffix approach. Members have continually communicated their concern regarding this methodology and have even stated they ignore this attribute to avoid additional clinician confusion. Rather than relying on the devoid of meaning suffix, members are utilizing other product identifiers to track and differentiate originator biologics or biosimilars.

We do recognize that there are even larger hurdles to biosimilar adoption than nonproprietary name requirements; however, even though this issue might be of smaller magnitude as compared to challenges such as biosimilar reimbursement, we should

refrain from introducing additional barriers.

Second, Vizient asks that FDA develop the process to disclose information on biologic manufacturing changes including those of originator referenced products similar to disclosures that take place in Europe. Vizient also requests that FDA make available for approval the summary review documents for all biosimilars and interchangeable biologics, even those that do not undergo an advisory committee discussion. Those sources of information would increase the understanding and acceptance of biosimilar approval process and improve clinicians' perception of the requirements to manufacture and license biological pharmaceuticals.

Again, we thank FDA for this forum, for its commitment to providing the US with an avenue for safe and effective medications that improve outcomes. Our ability to sustain access to critical innovative therapies will be substantially jeopardized if we are unable to foster a stable environment for biosimilars. Vizient remains committed to supporting this product category and identifying additional strategies to

improve medication use across the patient population to which we all belong. I look forward to addressing your questions about these comments.

MR. KOSLOWSKI: So, a question about your last point about publication of summary review documents. So, at Drugs@FDA documents are posted, is your concern about the timing and what's redacted, or both?

DR. LUCIO: It is about the timing. The ideal circumstance or the better circumstances would be if that information were immediately available, because people are wanting to make formulary judgments about these products, even in certain times in advance of when they come to market. So, in the attempt to be ready to introduce the products, take advantage of the reimbursement circumstances that CMS has articulated for biosimilars, it's helpful if that information can be available, so that way clinicians, physicians, pharmacists can begin discussing it even in advance. Because the clinical trials might be published in literature that are associated with those approvals, but they might not be. And so it's been a great help

to have that information, and also to walk through pharmacists and especially physicians on analytical characterization. That information has been quite helpful in terms of helping people overcome the reticence to use biosimilars.

MR. KOSLOWSKI: Thank you.

MR. SCHILLER: Could you say a bit more about the proposal to disclose manufacturing changes, which categories of changes you envision that would apply to and what benefit you think that information would provide to prescribers and consumers?

DR. LUCIO: Particularly to the prescribers, especially to physicians, it's been a very difficult circumstance to help them understand that the considerations that are taking into account for biosimilars are not inherently novel to those products, and that that sort of transitional perspective takes place for all biologics. It's managed for the originators through comparability. And so the information, in fact, that was shared -- one of the publications that was shared in the preceding presentation, as well as others, that

information from Europe has been helpful in helping to erode some of that reluctance that physicians have to understand that the originators are neither exactly the same as they were when they were first brought into the market. And so additional information would be available.

And I know there's restrictions on the extent to which certain content can be disclosed, but any information regarding the number of changes that happen, what percentage of those changes are a higher consideration, whether it's the source bacteria or, you know, cell environment that is used to produce those products, that would be helpful in setting the context that, again, biosimilars are novel from the standpoint of variability and the impact of manufacturing changes that occurs all the time. And that's part of this overall increased awareness of manufacturing that really even transcends biosimilars but is becoming increasingly important for compounded medications for generic medications. So, it's really that transparency to help all clinicians understand the workings that take place to ensure the highest

quality pharmaceutical supply chain that we have in the US.

MR. SCHILLER: So, following up on that a little bit. So, manufacturing changes are often classified by risk, preapproval supplements and other classifications. Are you interested in the number of those, or are you interested in further detail, because there's the different level of information?

DR. LUCIO: Well, both. Again, to help people understand what is going on, and particularly the highest risk, because to your point, there are certain changes that are not the magnitude of where you're changing an active ingredient, you're changing the cell culture. But that's what you're doing in biosimilars, usually, in different cell culture, and so now people are somewhat sensitized to the fact that, well, again, the biosimilar is different, it's using a different expression system, potentially. And so knowing when those changes occur over the last cycle of the originator, again, puts it in context that we're not attempting to stick something in that the, you know, that the public or clinicians are not

going to understand. We're just adopting a similar process for the separate category of agents.

MR. UNLU: Can you say a little more about what status of this disclosure is in other jurisdictions? I think you mentioned Europe?

DR. LUCIO: Yes. Again, the information that we have seen available in the public discourse is based upon European medication administration data that is made available.

MR. UNLU: What kind of information, do you know?

DR. LUCIO: Information has been -- there are a number of changes, and to the extent they are either of low, moderate or high impact in terms of the underlying molecule.

MR. KOSLOWSKI: So, this is changing the topic a little bit.

DR. LUCIO: Sure.

MR. KOSLOWSKI: You mentioned that, you know, your company is involved in educating clinicians about biosimilarity, so do you have any thoughts about what are some of the key hurdles and challenges in terms of

being able to, you know, talk to clinicians about use of biosimilars?

DR. LUCIO: Again, that's for this, and I really appreciate this narrative about how biologic manufacturing takes place and the variability associated with it, and the fact that biosimilarity is intended for either mechanism comparable to -- the comparability to process.

The other one that I mentioned, I think, there is a lot of uncertainty what interchangeability means. You mentioned the fact that, you know, I think there is starting to be a perception as potentially being closer to interchangeable biologics, that they're somehow -- noninterchangeable biosimilars are not as good. And if we have circumstances where we first have to have a certain biosimilar approved that is noninterchangeable, then go to interchangeability, it's going to be hard to get adequate uptake of the nonbiosimilar -- or, yeah, the noninterchangeable biosimilar to generate enough of marketing surveillance than to substantiate interchangeability.

So, again, for the -- especially for the less

complex molecules, like the insulins, if we're going to continue with the interchangeability need, it would be great to just be able to say these are the molecules that would go down the interchangeability direct pathway as compared to these that have to be substantiated by a noninterchangeable biosimilar approval first.

MS. TEMKIN: I'm just going to -- I know we're out of time, but I'm going to ask you one last question.

DR. LUCIO: Yes.

MS. TEMKIN: You mentioned some price, some projected trends in pricing, and I was wondering if you could speak a little bit about how you get to the numbers of what you're projecting the price increases to be for the upcoming period that's on your slide?

DR. LUCIO: Absolutely. A lot of it relies on, first of all, the historical pricing trends that we've seen across, you know, the member organizations that we support. And then looking, obviously, at what we think is going to happen in the market based upon new product approvals that come into the market, as

well as the exclusivity loss that will take place. So, that is what we as Vizient do in order to, again, estimate six to 18 months down the road what's likely to be happening from a pricing behavior standpoint.

MS. TEMKIN: Thank you very much.

DR. LUCIO: Sure. Thank you.

MS. TEMKIN: Dr. Barve?

DR. BARVE: Good morning. My name is Abhijit Barve. I head global clinical research at Mylan. I have been involved in biosimilar development for the past 10 years and have seen rapid advances both from a scientific and regulatory perspective. Thank you for this opportunity to present Mylan's thoughts on this important topic of increasing access and facilitating efficient development of biosimilar insulins.

Today's topic of increasing access is near and dear to our hearts. Mylan was established in 1961 in West Virginia with a commitment to increase access to medicines. Last year we sold close to 59 billion doses across 7,500 products in 165 countries. Our R&D efforts for the past decade have specifically focused on complex generics and biosimilars. We have started

seeing the results of these efforts with many firsts.

We were the first 40 mg twice-weekly glatiramer acetate approved by FDA in 2017. In 2017, we also received FDA approval for the first biosimilar to Herceptin. This was followed in 2018 with the approval of first biosimilar from Neulasta. And, finally, a couple of months ago we received approval for first generic respiratory drug Advair.

Coming to insulins, our biosimilar insulin glargine is available in Europe since 2018, and is also approved in 40 other countries. We have one of the largest and most diverse biosimilar portfolio in the industry.

Our portfolio includes simple biologics that include four insulin analogs, larger biologics that includes two products, and 14 complex biologics that include 12 monoclonal antibodies and two fusion proteins.

Insulins, as we all know, was discovered nearly 100 year ago. It is a relatively simple molecule with two chains of 21 and 30 amino acids, and a molecule weight of 5.8 kDa. From a regulatory

perspective, proteins less than 40 amino acids are considered nonbiologic. Similarly, chemically synthesized polypeptides up to 100 amino acids are also considered nonbiologics. The scientific requirements for approval of these small molecules is limited and straightforward. When one looks at insulin from that lens, it is more closer to a small molecule than a biologic. Insulin and analogs are very well characterized, and we have strong understanding of their PK, BD safety and immunogenicity.

This slide compares the complexity of different biologics. On the left-hand side we have got the simple biologic that includes insulin and analogs. On the right side we have got larger and complex biologics which have 3 to 30 times the number of amino acids, and 3 to 30 times higher molecular weight than simple biologics. These products, as you can see, are structurally much more complex. Since the inception of biosimilar pathway, we have 19 biosimilars approved by FDA in this category, and there is a small typo there on the left-hand side.

We know that insulins will transition to biologics next year. In this context, we would like to make three -- a couple of points. Firstly, the scientific conservation under the current 505(b)(2) route are not very different compared to the proposed biosimilar route.

Secondly, in Europe, insulins are considered as biologics but with a significantly lower data requirement. Most sponsors have global programs and are already following the biosimilar approach.

This slide supports the argument that at structural and functional level, it is much easier to characterize insulin and we exactly know what is needed to demonstrate sameness. Here we compare the characteristics of insulin versus trastuzumab, a complex biologic. Insulin's mechanism of action is linked to its binding to the insulin receptor. Like the monoclonal antibodies, we have multiple mechanisms of action. Structurally, there are limited phosphorylation of modifications for insulin versus multiple posttranslational modifications for monoclonal antibodies that can impact efficacy.

For insulin, the PK is largely structure independent and can be accurately measured using sensitive LC/MS method, which are traditionally used for small molecules. So, monoclonal's PK is impacted by glycosylation and FcR in binding.

With regards to PD, we have robust and sensitive glucose plans that are highly discriminatory for efficacy. No such correlative PD markers are available for complex biologics. So, when one takes a look at what residual uncertainty remains after expensive characterization of insulins and a PK/PD study, it really comes down to immunogenicity.

Talking about immunogenecity of insulins, we know the following. Firstly, extensive immunogenecity information is available for both insulins and analogs. Secondly, anti-insulin antibodies are not uncommon, but it has been consistently shown that they do not impact PK/PD or safety. Thirdly, because of the benign nature of these anti-insulin antibodies, FDA until recently did not require assessment of the neutralizing potential. Thus, the immunogenecity considerations are no different than complex

biologics. Perhaps the risk is lower for insulins and hence the sample size requirements for assessing immunogenecity should be consistent with well-established biosimilar principles.

We believe that any additional requirements not based on risk or clinical relevance will only be a barrier to development. In fact, we have an opportunity to streamline development by having an integrated design that addresses both biosimilarity and interchangeability in a single study as indicated in the final interchangeability guidance. Mylan believes that despite immunogenecity being of limited clinical relevance for insulins, it should be evaluated in a realistic number of patients and that innovative study designs are feasible to demonstrate interchangeability, saving time and cost.

Moving on to the second question. With regard to the requirements for insulin pumps and for substitution, the fundamental biosimilarity principle should hold good. We all know the biosimilarity principle, so for pumps, the only additional requirement should be in vitro compatibility testing

with typical materials used in pumps. If the biosimilar product is compatible and is no different compared to the reference, then no additional scientific data should be required.

With regards to substitution from a scientific perspective, once a product is approved as interchangeable, it is presumed to have the same PK/PD safety, efficacy and immunogenecity as the reference, and hence substitution should be allowed at a pharmacy level.

Coming to the question on patient experience. Drug delivery devices are important components of patient experience. For any device, the intent is to enable safe and effective way to deliver the right dose with no adverse change in safety or risk profile compared to the reference. It is well known that from an external user interface perspective, there would be limitations to exactly match the reference device due to IP considerations. However, we believe that these differences should not be a barrier for interchangeable insulins as long as we can demonstrate no negative impact over the reference product. In

this regard, special analysis should form the fundamental evaluation to assess the device and only when other differences are identified should a comparator use study be justified.

Finally, to information resources and communication. Today there are multiple insulins, multiple short- and long-acting brands that are available, and specific patient training on the selection of right device is important. However, this is irrespective of biosimilar or interchangeable insulins. Also in this dynamic space, patients, physicians and pharmacists are already exposed to switching between insulin and analogs based on insurance coverage and formulary preferences. Furthermore, most patients are experienced with self-administration, use of one or more drug delivery device, regular monitoring of blood glucose, and recognition of adverse events. So, the risk for using a biosimilar is no different.

At a broader level, education needs to continue on emphasizing the scientific vigor of biosimilar approval process including approval of drug

delivery devices.

In summary, from an operability perspective, the scientific considerations should be no different for insulins versus complex biologics. Most elements of current interchangeability guidance apply to insulin and efficient study designs are possible to address safety and efficacy after switching. Potential differences in device interface are expected; however, as long as it does not impact the risk profile, it should not be a barrier.

To conclude, insulins and insulin analogs are relatively simple molecules and pragmatic and scientifically valid approaches would increase the access to these lifesavings products. Thank you for your time.

MR. STEIN: Can I just ask, you mentioned a single study assessing immunogenecity with interchangeability design in a limited number of patients versus the two-study approach. Can you just expand on your comments and thoughts about what that might look like?

DR. BARVE: Sure. You know, I know there are

multiple discussions that are ongoing both at our level as sponsors and at FDA's level. I mean, clearly, one of the things that is very apparent is that once you do extensive characterization and you do a PK/PD study, what remains, you know, the residual uncertainty really is immunogenicity, and that applies to both biosimilarity and interchangeability.

So, right now the expectation is to do a two-step process: get the biologic approved as a biosimilar first, and then get the interchangeability designation. But here, because it is very different from complex biologics, where we don't have access to PD markers, we can actually do it in a single study, where we can have a first spot which looks at biosimilarity, because that might have separate endpoints. And then look at interchangeability in a single design, because that becomes much more efficient. And then one can actually apply for both interchangeability -- or biosimilarity and interchangeability designation.

MR. KOSLOWSKI: So, you had mentioned doing the right number of patients to address immunogenecity

as done for other biosimilar products. I'm kind of curious what you think that number is and what your endpoint would be?

DR. BARVE: I mean, today, if you really look at it, most of the products we have got -- we haven't got approved -- we have got approval from multiple biosimilars and we have had this discussion with multiple divisions. The expectation right now is that none of these studies are designed for showing differences for immunogenicity, because, you know, the data is not there for many of these products. You know, the immunogenecity assessment has dramatically changed over -- since when the innovator got the product approved. So, to design a study with the typical thought process in terms of how we design an efficacy study with regards to meta-analysis, etc., etc., we can't do that for it.

So, if this is going to be a little bit of a soft sign, so it has to be a totality of evidence as we have been all talking about, but it just doesn't focus on immunogenicity; it focuses on multiple things in case of insulin. It depends on the dose that has

been used in the study; it depends on the efficacy endpoints, although they might not be very sensitive. So, it's a host of things that need to be evaluated as part of the process versus saying that we need a power study based on immunogenicity, which is not easy to do, because we just don't have historical data for most of these things.

MR. KOSLOWSKI: One quick follow-up, because you stated that the only residual uncertainty is immunogenicity. So, you know, the answer is really that you look at all these other things, but yet, you know, your own presentation states that's the only thing you really have concern left about.

DR. BARVE: Correct. So, when you have -- when you know it's a relatively simple molecule, which is extensively -- and if you look at how it is approved in Europe today and what is the expectations from a clinical study standpoint, it is limited. And the reason it is limited is because we have got a robust PD marker, which we not necessarily have for the other products that we talk about, like the monoclonals. And in that particular case, if you show

that you have, you know, extensive analytical characterization binding data, as well as you show that the PK is similar. And here we have got LC/MS method now, which earlier we had to do some kind of subtraction to actually get the PK. Now you can actually measure the exact molecule that we are looking at, like we do for small molecules, and then you have a robust plan, which is extremely sensitive, the uncertainty that remains after that is relatively limited. And if you really look at that, you don't need that much information other than assessing immunogenicity, which you can do it in a single dose study or in a euglycemic clamp in a realistic way.

MS. YANOFF: So, in one of your slides you say immunogenecity considerations should be no different between insulins and other complex biologics, but yet you also make important points that these are sort of smaller and less complex proteins, which are almost closer to small molecules. So, can you help me understand why the immunogenecity considerations are no different?

DR. BARVE: I mean as a qualified, you know,

they're probably lower in our mind, if you really look at it from a risk perspective. You have got a complex molecule which has got probably 30 times the number of amino acids that we are talking about here with multiple chains, which can have multiple epitopes for developing immunogenicity. Here you have a relatively simple molecule, so the likelihood of having complex immunogenecity -- so, what we are saying is that it should be no -- at least not higher than what is required currently for complex biologics. If at all, it should be on the lower side given that the molecule is relatively simple.

MR. STEIN: And just to be clear, you mentioned that -- you're suggesting endpoints, you said clinically relevant impact of immunogenecity would be assessed by SMBG in changes to insulin dose. Is that what you're proposing, you'd use those as the endpoints --

DR. BARVE: I think we have to look at it as totality of evidence. We can't really look at it either just based on PK, because we know that there are challenges in, you know, evaluating PK. We can't

give a fixed dose and take a PK and say that, look, it is similar, because we treat patients to target. There are designs even in that that we can think about, where we can use a certain period where patients can receive a fixed dose of the product. We'll have to see whether this is consistent with the standard of care. But we look at immunogenicity, we look at the dose, we look at the fasting blood glucose, as well as we look at A1c. So, we can't just say that these points are -- if everything is moving in a different direction, then we have a problem. But if everything moves in the same direction, then we know the answer. And the likelihood of it, after doing extensive characterization and a PK/PD study, as well as knowing the immunogenic potential of these products, in our mind is going to be limited.

MR. KOSLOWSKI: So, you had mentioned the only thing necessary for the pump would be compatibility. So, could you elaborate a little bit about that?

DR. BARVE: So, our thoughts are that, you know, if you really followed the biosimilarity

principle, and that's really the fundamental principle that we're talking about, that if the product is approved as a biosimilar or interchangeable, then it should behave exactly the same way.

So, if you do the in vitro capability and show that there is no blockage or there is no leaching or whatever the factors are, then you don't have to do anything beyond that, because we can really use this product along with, you know, replace it to the reference product. That's our thought process in terms of how we approach either problems, because the fundamental bedrock to all of this is the biosimilarity principle, right? You want to -- I know it's kind of cliché and it's kind of oversold to some extent, but that's the reality. We are approving a product which is similar based on all these testings. Now, why do we need another layer of complexity if we show that there are no differences between the compatibility?

MS. TEMKIN: And just to clarify, are you talking, when you say that about biosimilarity, interchangeability, or both, do you see a difference?

DR. BARVE: I don't see any difference, because at the end it really should not. I mean, as long as you show that there is no difference, because we feel biosimilarity and interchangeability is just one more step in terms of how these products are used. Today we have insulins which are substituted without any interchangeability. People are switching insulins, you know, for multiple reasons including formulary preferences, you know, insurance coverage, etc. So, I don't think that should be an issue, whether it's a biosimilar or interchangeable.

MS. YANOFF: I'm also going to follow up on the same issue. So, for the biosimilarity, the criteria -- there's a caveat notwithstanding minor differences in nonactive ingredients. So, what is your view on formulations that have same excipient versus a different excipient, how that could affect use in devices?

DR. BARVE: If you -- I mean, we are not saying that they should not do anything. We are saying that there has to be some degree of testing, which includes in vitro compatibility, to make sure

that they are compatible. And if there is no difference in terms of that, or in that particular case, it should not matter, to an extent, in terms of how they are used.

MS. YANOFF: Is there a possibility that the excipient could interact with the patient interface, you know, with the tubing inserts, and how would you suggest that be assessed?

DR. BARVE: I mean, there are things that can happen, but, again, it comes down to the fundamental things that if it has been tested and shown, in our minds, it should not be an issue.

MS. LIAS: I have a related question. So, many times pump incompatibility may relate to leachables and extractables.

DR. BARVE: Correct.

MS. LIAS: It also may relate to changes in the PK/PD profile due to instability as the insulin travels through the fluid path of different pumps. So, how does a drug company might you suggest testing across different pumps, pump designs and food paths?

DR. BARVE: I think some of these will

address as part of our comments to the docket. We have got certain thoughts on this.

MS. LIAS: Thank you.

MS. TEMKIN: Thank you very much. Dr. Martin?

DR. MARTIN: Thank you for holding this hearing and inviting the views of patients, manufacturers and other stakeholders. I'm Dr. Sherry Martin, Vice President, Diabetes Global Medical Affairs, Eli Lilly and Company, and I'm very pleased to provide Lilly's views from the clinician perspective. I will be focusing on the future of biosimilars, as well as interchangeability of insulin products.

As I said, this hearing is of special importance to me, because I was a practicing clinician for 20 years before I joined Lilly. After completion of my training as an endocrinologist in 1992, I opened the first endocrine clinic in North Mississippi, serving a very large rural population of patients with type 2 diabetes. I've co-authored multiple publications on diabetes research and clinical care

considerations for patients with diabetes.

Lilly has been committed to diabetes care for nearly a century. In 1923, when a diagnosis of diabetes was virtually a death sentence, Lilly introduced the world's first commercially available insulin product. In 1982, we introduced human insulin, the world's first medicine made using recombinant DNA technology. In 1996, we lost Humalog, the first approved insulin analog, and more recently, in 2015, we obtained approval for Basaglar, the first follow-on insulin biologic.

Over the years, we have helped advance innovation in how insulin is administered, going from the classic administration in vials and syringes to today's pens and pump delivery systems. We believe the future standard of care for patients with diabetes will continue to evolve and will move into connected diabetes ecosystems made up of insulin along with digital health technologies and connected delivery systems. I will address each in turn.

Lilly strongly supports FDA's efforts to promote innovation, competition and access with regard

to insulin products. My comments today are very much in line with the principles of the final interchangeability guidance that FDA issued last week, particularly the Agency's recognition that more detailed guidance is needed on interchangeability considerations that are specific to each product presentation. Lilly plans to submit written comments as well, addressing a broader range of issues.

Lilly agrees with FDA that a robust showing of biosimilarity is the first step in demonstration of interchangeability. We recommend that FDA develop the requirements for interchangeable insulin products based on a case-by-case assessment of the strength of the biosimilarity data. In the case of insulins, the ability to characterize the molecule as a part of the biosimilarity data package may reduce uncertainty at the time of assessment of interchangeability. This should include a particular focus on those portions of the molecule known to affect immunogenicity. The demonstration of fingerprint-like similarity and functional binding as compared to the reference product may further reduce uncertainty.

Beyond biosimilarity, interchangeability requires evidence to ensure safe substitution in the absence of prescriber oversight. Switching studies provide additional confidence that there will be no meaningful increase in immunogenecity from switching or alternating between the biosimilar and originator product. However, Lilly believes that FDA could take steps to make the conduct of switching studies more efficient and feasible. Most importantly, given the lack of dose linearity with insulins, we recommend that FDA consider whether an efficacy endpoint might be more appropriate for these studies as compared to the pharmacokinetic endpoint being recommended.

Furthermore, FDA could provide proactive guidance on key elements of protocol design, including patient population, such as whether data from a type 1 population is generalizable to a type 2 population, and duration of each switching period. We are committed to continue working with FDA to simplify switching studies for insulin products, and will provide additional details in our written comments.

The experience of interchangeability

determination is that the patient receives an insulin product at the pharmacy that is different from the product prescribed by their healthcare professional and potentially different from one that they have ever previously used. And all of this is done without the oversight of the prescriber. This underscores the importance of assessing any patient-facing components of a proposed interchangeable insulin product, such as the delivery device, to ensure that no additional training or prescriber oversight is needed for the switch.

Components of a connected diabetes ecosystem may include beyond the insulin itself, a number of digital health technologies -- connected pens, mobile medical applications, connected, continuous glucose monitors, cloud-based data storage, data analytics and dosing algorithms, as well as a pump-based artificial pancreas system. Improved outcomes can be accomplished by providing tools to patients and physicians for better monitoring, insulin management and patient motivation, which links to improved treatment adherence and individualized patient care by

providing aggregate data that leads to a better understanding of the disease, and by enabling data-driven conversations between a patient and their healthcare provider to optimize and tailor treatment plans. In circumstances where an insulin is delivered in a connected ecosystem, FDA should consider that specific system in assessing interchangeability. How the insulin product functions within the ecosystem will be relevant to whether a biosimilar may be substituted for the reference product safely and effectively without the involvement of the prescriber.

We do not believe that this assessment of treatment ecosystem should represent a barrier to interchangeability of the more classic routes of insulin administration. We recommend that FDA assess interchangeability for insulins in current presentations, such as vials, pens and pumps, separately from interchangeability within a connected system. This approach will enable FDA in the short term to focus on biosimilarity and interchangeability of insulins in current presentations, and at the same time enable FDA to proactively assess the complex

questions presented by the evolving connected ecosystem of diabetes care, with a focus on promoting innovation and competition.

FDA should consider the following questions in assessing interchangeability where an insulin product is part of the connected system. Will the applicant seeking interchangeability have its own connected ecosystem? If so, how do the components of this system, and the system overall, compare to those of the reference product? How do patient outcomes compare between these systems? How will switching from a product within one ecosystem to another affect the continuity and stability of care for the patient, and the datalink to their healthcare chain? How will interchangeability affect data security and data integrity of the reference product's secure ecosystem?

As I close today, I share Lilly's recommendations of the key issues FDA should consider when crafting insulin interchangeability standards for now and in the future. In the near term, we believe that FDA should focus on biosimilarity and interchangeability of insulins in current

presentations. And in the future, interchangeability for biosimilar insulins within a connected ecosystem should be assessed separately. Ideally, this could be part of the FDA's upcoming guidance on presentation-related interchangeability issues. Lilly stands ready to assist FDA with these new standards to help promote patient access to insulin products. Thank you for the opportunity to provide my comments, and I welcome your questions.

MR. KOSLOWSKI: So, regarding this concept of an ecosystem, so the way you've described it, there are multiple different ecosystems. Like, currently patients move from one type of insulin to another or across-the-board. Wouldn't it seem to make sense that there would be one large ecosystem considering all the different components in this? And you mention that this won't be a barrier. I mean, potentially, if large companies can create their own ecosystem, right, it could be a tremendous barrier, because basically you can't switch to anything else because you're kind of fixed in that system.

DR. MARTIN: So, I think there are two parts

to the question. The first is, will there be universal interoperability between connected ecosystems that are being developed? And I think we don't know the answer to that question today, but I think we need to prepare for the fact that there could be interoperability, whereas, one would need to understand did a biosimilar insulin function as well within another system? Is there the possibility that there will not be interoperability in some systems? I think that's also possible, and in that case, when a patient is in a particular system, say, for instance, using a connected pen that has an algorithmic-driven dose, if they were to be moved to a vial and syringe presentation, would that be a feasible alternative for that patient? No, there would be a problem there. Because the patient would then be asked to move into a system where they didn't have the dosing prompt that they had before, perhaps didn't have the connection to continuous glucose monitoring. So, we do believe that this does represent a new and more complex for our side of the regulatory environment and the production environment. The goal is that it actually, in the

right system that a patient has been prescribed and has been trained on, simplifies their care.

MR. KOSLOWSKI: So, as you said, clinicians for decades who has taken care of diabetic patients, wearing that clinician hat, would you like an ecosystem that's interoperable?

DR. MARTIN: The ecosystem that I will be looking at as a clinician is does it deliver the outcomes that I would expect for a patient? The interoperability I think will be dependent on what are the methods of that ecosystem, the container closure, other kinds of aspects that may exist within these systems in the future. But I'll be looking at outcomes. Thank you.

MS. TEMKIN: Thank you very much. I believe it's time for us to take a break, so we will reconvene at 10:40.

[Break.]

MS. TEMKIN: Welcome back. I hope everyone enjoyed their break, and we are now pleased to welcome Dr. Luo.

DR. LUO: Good morning, everyone. Can you

hear me? Great. My name is Jing Luo. I am an instructor of medicine at Harvard Medical School, and a faculty member in the Division of Pharmacoepidemiology and pharmacoeconomics, which is located within the Department of Medicine at the Brigham and Women's Hospital. I'm also a practicing physician. I am licensed to practice in the state of Massachusetts. It's a pleasure to be with you all on this rainy day. Here are my disclosures.

So, I've been following the pharmaceutical market for about 15 years, and doctors are notoriously bad at making prognosis, but let me go out on a limb and make one important prediction this morning. The approval of biosimilar, non-interchangeable insulins will be insufficient to address existing failures in the US insulin market. Therefore, I will focus the bulk of my talk about issues specific to interchangeability. I have three points for FDA's consideration and our esteemed panelists.

First, minor differences in insulin efficacy may not be clinically significant for patients. Second, be cautious but pragmatic about claims of

safety when you do hear them. And, third, a small pre-approval switching study, I believe, can meet all statutory requirements regarding interchangeability.

This is an advanced audience, so I do not need to spend much time, cost-related insulin underuse is common even in contemporary cross-sectional studies for which I have participated in. We estimate somewhere between 1 in 4 patients who use insulin experienced this in 2019. It's associated with worst clinical outcomes and, uncommonly, death. The global need for insulin is staggering. I will note cite all of the figures, but I'll just conclude this part by saying that the reason this is such an important topic is because this is a serious disease. Not using insulin is universally and rapidly fatal for patients who require it.

The status quo is a boon for industry but a disaster for patients and for healthcare providers. Why do I say that? First, there is limited competition for insulin. There is a research letter by Emma Hernandez out of Pittsburgh published in JAMA this year.

Second, patients do not benefit from rebates or discounts negotiated between insulin manufacturers and payers. I should put in parentheses, currently benefit, because there are talk about making that no longer be an issue.

Third, the private contracts that decrease net prices for insulin are extremely unkind towards frontline healthcare providers and patients. I don't need to tell you about all of this because you are all well aware that it's quite a headache to deal with things like formulary restrictions, prior authorizations, step therapy, quantity limits. I have to fax forms to payers that say that my patients have failed X, Y and Z for six months before they'll pay for certain insulin pens. This is ridiculous.

Fourth, Band-Aid solutions, like copay cards, discounts, authorized generics, they do not work for the majority of Americans, and we have published a large number of studies on this particular issue. I put up some references for you to read later.

Interchangeable insulins are the most efficient solution for the US market, because we don't

have rational centralized strategies to control prices. We must rely on things like the market-based solutions of which interchangeability will be very, very important. The remarkable success of the generics market in the US is primarily due to two things: Hatch-Waxman, which was enacted the same year I was born, 1984; and second-stage generic substitution laws, which are really, really important in this space. Existing state laws on biosimilar medicines only allow substitutions of biosimilars that are designated as interchangeables by you at the FDA. Therefore, interchangeable insulins represent a profound opportunity for FDA.

Three points. Point No. 1, minor differences in efficacy, that is potency, may not be clinically significant for patients. Insulin is titratable by definition. Additionally, someone has already mentioned this, but medication switches happen all the time in clinical medicine. It is a huge nuisance for our patients and for providers such as myself. I just list a couple of switches that happened today, of which there is no regulatory concern. Levothyroxine

to levothyroxine, which are rated by the FDA as therapeutic equivalent rating of AB. Second, rapid-acting analog, such as lispro to aspart, or vice-versa; glargine to detemir, or vice-versa; glargine to glargine, or vice-versa.

And, finally, even happens between analog and human insulin products in the market. I was able to participate in one of these studies. You can read about it in JAMA. It came out in January of this year, and we looked at things like utilization, expenditures, hemoglobin A1c, no major difference that I'd be willing to share with you, even switching between analog and human insulins for type 2 diabetes.

Point No. 2. Be cautious but pragmatic about claims of safety. Some claims of safety may be unverified or unsubstantiated by the totality of the scientific evidence. What do I mean by that? Multiple people have stood up today and talked about immunogenicity. Let me remind you, immunogenecity is not part of the statute. You cannot find that word anywhere in the BPCIA, okay? It's been made up. We're talking about it now because people believe it's

theoretically important, yet I would argue that the development of anti-insulin antibodies, even neutralizing antibodies, often have no or very little clinical significance. We are talking about looking at a biomarker which hopefully is associated with a surrogate marker, which is probably associated with a clinical outcome. Okay, we're looking at a biomarker for A1c which is probably a validated surrogate outcome that is meaningful for patients. This is what we're talking about right now.

Additionally, their clinical events may be impossible or impractical to identify in approval studies and thus may require post-marketing observational studies that include things like traceable real world evidence. Our division is quite good at doing these types of studies, but you don't have to do observational studies. You can also do them through registries or through the US sentinel program.

Finally, this point at the bottom, it's buried there but it's super-important. People will talk about unusual, idiosyncratic, unpredictable

clinically meaningful safety events. These will always happen irrespective of the product being considered. However, these can always, always, always be mitigated in the status quo because the provider can simply check off dispenses written or brand name medically necessary on his or her prescription.

Here's some examples of things we can look at for safety events using observational data. I have three minutes. Let me just skip to the second point, which is I quote some statute here. The risk in terms of safety or diminished efficacy of switching between the use of interchangeable products and reference products are not greater than the risk of using the reference product alone without a switch.

I will propose to you one hypothetical study design, which you can see here, which is my interpretation of the draft guidance, because I don't think I've had a chance to review the final guidance, which came out after these slides were prepared. But here's one hypothetical switching study for demonstrating insulin interchangeability that uses no less than three switches between the reference and

biosimilar product.

Let's say after you screen an appropriate patient population that may or may not already be using insulin. Is there a laser on here? On the far left you'll see that patients after screening are entering a two-week run-in phase -- that number of weeks is variable -- where they're using the reference insulin product. On day zero they're randomized to the top, where there's a no-switch arm, or the bottom, where they are switched to a biosimilar insulin. Subsequently, after a certain number of days, let's say it's 10 days, which is about the amount of time that one pen lasts, they are switched to a reference insulin. That's switch No. 2. Ten more days they are switched to a biosimilar insulin, and at the end of a certain number of period, let's say it's 3.5 half-lives, you compare the PK endpoints, clinically relevant endpoints, the dose, the immunogenicity, and safety risk, comparing the top versus the bottom randomized arms. This is one potential study design, and I would suggest something on the range of 30 patients, let's just say. I'm not covering this

slide. And I'll finish with this story in my last minute.

Okay. I guess my animations didn't come through, so you can't see the most important picture here. Ninety-seven years ago a 5-year-old boy named Teddy Ryder was first treated with insulin in Fred Banting's group at the University of Toronto. He came in as -- in a wheelchair. Sometime later you see a picture of him as a rotund, healthy boy, okay? And he writes this letter, which currently a copy of which sits on my desk. "Dear Dr. Banting. I wish you could come see me. I am a fat boy now and I feel fine." This is a picture of Ted Ryder. He survived well into his seventies, dying in the 1990s, holding up a picture of what he looked like shortly after receiving insulin.

I believe, personally, that it is a travesty we're nearing the 100-year anniversary without any true generic insulin in the US market. The time to act is not today, it was two years ago, when Alex Smith died for rationing his insulin and dying unfortunately of complications related to DKA, okay?

I urge you, I thank you for being here today, but let's not mistake ourselves, it's time to act. Thank you.

MS. YANOFF: Thank you so much. For your interchangeability study, a couple questions. One is the number of patients you're thinking, and also the considerations about the duration of the study comparing that to what we know about insulin dosing and how long it takes to titrate for glycemic control. So, how do you reconcile the short duration of the trial with the fact that a lot of the patients would be dose titrating still at that point?

DR. LUO: Yeah, I mean, I'm not as familiar with the average length of titrations in pre-approval studies for insulin. I imagine they're relatively short. In clinical practice we kind of draw it out a little bit because we're concerned about risk of hypoglycemia and we want to give patients time to kind of get familiar with it. But I would argue that in a randomized trial setting, where you have people who are monitoring safety events, that you should be able to titrate up pretty aggressively. And, of course,

there are different titration algorithms that are out there. I would argue for something aggressive, like treat to target, where you can get to your fasting goal relatively quickly.

The number of patients should be driven by the science based on your primary outcome. So, if your primary outcome is PK related, I believe those studies can be extremely small. And why do I believe that? Because, I'll just reference you guys to the pivotal trial which led to the approval of intranasal Narcan, where there were 30 patients.

MR. KOSLOWSKI: I just wanted to ask if you could comment on something a little bit different. I noticed in the publication this was a switching approach from a human -- from an analog to human insulin, and I guess just more broadly, if you could comment on some of the other barriers at the patient level or physician level concerns that might occur from implementing availability of interchangeability, why would you think there will be concerns from either patients or physicians around switching from one form of insulin to another?

DR. LUO: Yeah, I mean --

MR. KOSLOWSKI: And how would you suggest we consider those and mitigate them?

DR. LUO: -- I think history repeats itself. I think the arguments you heard about switching between levothyroxine from one manufacturer and generic levothyroxine from another manufacturer, those same arguments will come again and we will have to beat them back with rigorous science. It could be pre-approval studies and it could be a combination of pre-approval and post-approval required or suggested studies, which can come from real world evidence.

I think you'll probably get a lot of resistance from patients or from healthcare providers that have a lot of skin in the game. If they're making a lot of money off the brand-name pharmaceutical industry, I believe that they'll probably have really strong arguments about why switching is really, really bad for them. However, I believe if you really focus on the science and you get those endpoints right, that we should be able to back those biased hypotheses.

MS. TEMKIN: Thank you. I wanted to ask a little bit more about your discussion of claims of safety. I'm wondering if you can explain a little bit what kinds of claims you're talking about, who's --

DR. LUO: Yeah. I mean, I've heard of comments from senior leadership at FDA talking about things like, well, if you do repeated switching between reference and biosimilar products, and between different biosimilar manufacturer's products, that will [pound] the immune system and make it really, really problematic in terms of immunogenicity.

What science undergirds those claims? Neutralizing antibodies are quite common. Non-neutralizing antibodies are also quite common after the use of insulin, but they have little or no clinical impact, not on dose, not on its associations with glycemic control, certainly not on hard clinical endpoints. So, when we say things like that or even hear things like that, it seems really important, because it's about safety of our patients, but, really, what evidence support those claims? That's what I mean about claims about safety.

And, actually, when I first read about the guidance and I heard that piece in the Federal Register, when I thought FDA was thinking about safety, I thought you were referring to hypoglycemia risk. But it's become apparent to me that safety can also include things like immunogenicity, and I would just argue that, well, you know what? My patients probably care more about their risk of having a hypoglycemic event than developing an antibody for which clinicians do not even check in routine clinical practice. These are subspecialty lab results that are almost never ordered unless you are a researcher. That's why I think they don't have very much clinical significance, and that's why I think you should probably down-weigh that particular endpoint when you think about regulating these products.

MS. TEMKIN: I just want to unpack a little bit which guidance you're talking -- are you talking about biosimilarity, interchangeability?

DR. LUO: Well, how do you interpret the statute? Do you interpret -- do you think the statute mentions anything about immunogenicity?

MS. TEMKIN: It does, yeah. So, --

DR. LUO: Can you quote that line to me?

MS. TEMKIN: Sure. In Section 351(k)(2)(A)(i)(cc).

DR. LUO: And what is the line?

MS. TEMKIN: It's in defining the content that's required for a biosimilarity demonstration, and it mentions a clinical study or studies, including the assessment of immunogenecity and pharmacokinetics or pharmacodynamics --

DR. LUO: Okay.

MS. TEMKIN: -- sufficient to demonstrate safety, purity and potency.

DR. LUO: So, it sounds like it's more for interchangeability -- I'm sorry, for biosimilarity than interchangeability.

MS. TEMKIN: Well, and then biosimilarity, of course, is incorporated into the definition of interchangeability.

DR. LUO: Yeah.

MS. TEMKIN: So, I'm just trying to understand --

DR. LUO: Yeah. Well, based on that statute, it sounds like you probably do have to evaluate immunogenicity. Whether you can do it in a PK study or whether you'd have to do it as a large pre-approval clinical study -- let's say a small pre-approval clinical study, would be up to you.

MS. TEMKIN: Thank you.

DR. LUO: Thanks.

MR. KOSLOWSKI: So, you had mentioned that immunogenecity is low risk, and there's a lot of evidence for that. So, clearly, even though the statute mentions immunogenicity, obviously it's based on the risk and understanding the risk of immunogenecity what the expectations with that would be. So, clearly, if you have information -- and there's a lot of information about this -- that supports the lack of importance of immunogenecity for insulin, it's important to include that in the docket or to share that with us.

DR. LUO: Sure. I'll find those studies and summarize them for you.

MS. TEMKIN: If there are no additional

questions, thank you very much.

DR. LUO: Thank you.

MS. TEMKIN: And Christine Simmon, thank you.

MS. SIMMON: Hi. Thank you for the opportunity to speak at today's hearing. I'm Christine Simmon. I am the -- oh, yes, of course. I actually don't have slides, so I will be happy to -- there we go. So, I'm Christine Simmons, Vice President of Policy and Strategic Alliances at the Association for Accessible Medicines, and the executive director of the Biosimilars Council, which is a division of the association that represents the manufacturers of biosimilars. I have no disclosure to make today. Most significantly, I do not intend to disclose the year I was born, but I will put my glasses on, so that might give you a clue.

So, as former FDA Commissioner Gottlieb noted, regulating insulin under the Public Health Service Act will allow for more efficient development of biosimilar and interchangeable insulin for America’s 7.5 million diabetes patients who rely on insulin to manage their disease, a population that has

doubled in the past two decades. And we have seen in the biosimilars space to date that competition works to bring down monopoly prices for costly biologics. Marketed biosimilars are currently, on average, coming into the market discounted at 47% below their respective reference products list price, and 18% lower in terms of net price, ASP, in Medicare Part B.

As Congress has noted, competition is sorely needed in the insulin space, and we look forward to working with the Agency and policymakers to achieve this goal.

The insulin market in the United States is a direct reflection of issues facing biosimilars more broadly. The current insulin market lacks significant competition to the detriment of patient access and health and has been characterized as a public health crisis. The combination of regulatory challenges, over-patenting to stave off competition, and anti-competitive rebating and contracting tactics by brand firms are some of the reasons for this lack of competition.

Six of the most highly utilized brand name

insulins increased in list price by more than 500% from 2006 to 2015. Because patient cost-sharing is often based on the list price before rebates or discounts, increases in list price directly impact a patient's ability to afford their medicines and can cause increased patient abandonment and lower adherence. In addition, in Medicare Part D, annual out-of-pocket costs for insulin nearly doubled from 2007 to 2016, from $324 to $588, according to the Kaiser Family Foundation.

Given the acute need for competition in the insulin market, we absolutely applaud the FDA's recent efforts in this space to ensure insulin biosimilars are able to efficiently be developed and come to market post-March 2020. We support the Agency's timely guidance on interchangeability, particularly its streamlined data and study design requirements that allow flexibility and the use of the global comparator products to support applications. We also appreciate the removal of the ambiguous fingerprint-like regulatory standard.

Now, while the interchangeability designation

does not confer any additional quality or safety attributes for approved biosimilars, the statutory requirement, as others have pointed out, under BPCIA makes the designation necessary for automatic substitution at the retail pharmacy. Interchangeability will therefore be particularly important in the insulin space.

As the agency stated recently in a response to a letter from senators voicing concern over the final guidance on the implementation of the deemed to be a license provisions of the BPCIA, FDA has considerable expertise and experience safely and effectively regulating insulin, and with the highly similar regulatory standard that is applied to brand biologics after manufacturing changes as well as to biosimilars.

Further, insulin is a simpler molecule than other, more complex biologics such as monoclonal antibodies, and has been extensively characterized and significant real-world evidence related to the safety and efficacy of insulin exists. To that end, we support the Agency’s step-wise approach to

interchangeability outlined in the final guidance.

Contrary to all too prevalent misinformation campaigns around the safety and efficacy of biosimilars driven by some brand manufacturers, stakeholders to not need to wait for interchangeable biologics to use biosimilars with their patients. Significant evidence exists that a physician-led transition from a reference product to a noninterchangeable biosimilar does not result in a loss of safety or efficacy.

In the insulin space, brand-to-brand switches across insulin types occur frequently at the direction of the provider, and given the highly similar nature of a biosimilar to its reference product, the risk of diminished safety or efficacy from a transition is minimal.

Availability of biosimilar insulin is likely to increase patient access and savings. To that end, in terms of the Agency's educational efforts on biosimilar insulin, we would like you to continue emphasizing that a transition from a reference product to a noninterchangeable biosimilar will not result in

changes to safety or effectiveness.

Finally, at the risk of piling on, I want to add our voice to the chorus of the stakeholders who also believe the uptake -- excuse me, the updated FDA guidance on naming does act as a barrier to biosimilars. We've commented on this previously, but the FDA policy that requires four-letter random suffixes be added to the biosimilars INN purportedly to support pharmacovigilance and despite a global consensus that a suffix only leads to patient and prescriber confusion is disappointing to those of us seeking to increase patient access to biosimilars.

FDA recently announced that it will abandon its prior commitment to add suffixes to previously approved originator biologics, which includes insulin products. Different requirements for originator biologics and biosimilar competitors will create patient and provider confusion, compounding reference biologic manufacturer-supported misinformation campaigns. And this is going to be particularly challenging for insulins approved as interchangeable biologics. It will differentiate the automatically

substitutable interchangeable biologics from their reference products and undermining interchangeability designation. The policy further erodes confidence in biosimilars and results in billions in lost savings if interchangeable biologics are not automatically substituted for the reference product. So, we really urge the Agency to reverse its policy on the random suffixes, really, just rescind the guidance and kind of come into line with the rest of the globe.

With that, I guess I would just conclude with a few recommendations. FDA has significant experience with insulin and highly similar regulatory standard, and should apply that experience to biosimilar insulin development. We'd like the Agency to continue to highlight for stakeholders that interchangeability does not confer quality but is a statutory standard for automatic substitution at the pharmacy.

We'd like the Agency to continue to emphasize that a transition from a reference product to a noninterchangeable biosimilar will not result in changes to safety or effectiveness.

Thank you for the opportunity to speak today

and your leadership in ensuring the development of a competitive biosimilar market in the US. I look forward to answering your questions and submitting additional comments for the docket.

MS. TEMKIN: It seems that we don't have questions at this time. Oh, I take it back.

MR. KOSLOWSKI: So, earlier on we heard about sort of this broader insulin ecosystem. What is AAM's position on sort of how insulin fits into a broader world with all kinds of apps and electronic links?

MS. SIMMON: Well, that's, you know, I think that's the first time I've heard, really, that application of the ecosystem analogy to insulin, and from Lilly, so, we had an opportunity to discuss among the members of our trade association. But I would say that it does look that developing the ecosystem with different parts that involve different products will therefore likely involve additional patents. And as parts of the ecosystem or the delivery system, in the ecosystem are patented -- we do know that patent tickets, over-patenting rebates, the rebate trap and other patent issues are a big barrier to biosimilar

adoption. So, we would definitely want to know more about it and take a look at it from that perspective.

MR. STEIN: You mentioned prescriber-initiated switching based upon -- with biosimilars that were not interchangeable. Can you speak a little bit about your views on the potential success for biosimilars that are not interchangeable, the value of interchangeables with regard to increased use of that product? And, also, well, maybe start with that?

MS. SIMMON: Okay. Yes. I mean, certainly, biosimilars that have not -- or biosimilar applicants who have not sought the interchangeability designation but have their biosimilar approval should be successful in the market, notwithstanding the confusion around, you know, what interchangeability really means from a layperson's perspective and from a patient perspective. And the idea that interchangeability sounds like a quality attribute, when, of course, we know that it's not, and the FDA has been very clear about that and we appreciate that.

Right now, because the market is mainly in Part B, it's less of a concern. As the market moves

to Part D, hopefully, and the ongoing approvals of more biosimilars, we do expect there to be some challenges surrounding that, and certainly our manufacturers are concerned.

MR. STEIN: And the second part I was going to ask is in terms of the timing of it. Do you think that it would be important for the Agency to come out as interchangeable or sequentially biosimilar and then interchangeable? Does that pose any differences in likelihood of success of the product?

MS. SIMMON: Well, I think to the extent that they could be contemporaneous would be helpful. But we would support the idea that I think was mentioned by others, that interchangeability, you know, in the EU is a component of biosimilarity, it's not a separate designation. And interchangeable biologics, the interchangeability is already, from a product perspective, is built in. So, ideally, while we know it exists in the statute, it would be something that could be weighted a great deal less.

MR. UNLU: I have a question. All morning we've heard about interchangeability two ways. One is

describing the existing market, we've heard a lot about how the existing market is de facto interchangeable in ways, for example, driven by insurance or prescriber decisions. And then we're also talking about interchangeable insulins and how they're really important. I guess I'm a little confused. If the existing market is exhibiting aspects of interchangeability as the prices keep rising, what additional aspect of the interchangeable approvals would help those prices come down? And how many of those would we need? Because I also understand that there are a handful of insulins currently on the market and are apparently being used interchangeably in many ways. So, can you shed some light on that?

MS. SIMMON: Possibly. I think that, you know, the degree to which interchangeability designations will help drive down prices is directly, of course, correlated to the degree to which those are products that will be available at the pharmacy and will be, therefore, automatically substituted. The success of the generic industry in terms of market

penetration is primarily based on automatic substitution at the retail pharmacy level. That's why we're at 90% of the market. So, you know, that's really, if you have interchangeability but not retail availability, then you may not see -- certainly, you won't see as rapid price competition, and that will affect, I think, the rate of price competition, if not the level.

MS. TEMKIN: Great. Thank you.

MS. SIMMON: Thank you.

MS. TEMKIN: Dr. Ramanan?

DR. RAMANAN: Good morning. My name is Sundar Ramanan. I am vice president of global regulatory affairs for Biocon. Thank you for the opportunity this morning to present our policy position today.

The reason why we are passionate about this topic is because our chairperson defines blockbuster as being accessible to a billion patients, right? This vision has enabled us, Biocon, to be a pioneer in affordable access to biologics. Patients in over 120-plus countries benefit from our high quality

biotherapeutics, both innovative and biosimilars. In 2019 alone, we expect to improve more than 2.6 million patient lives, which 2.5 million will be diabetic patients. Patent metrics presented here also demonstrate our commitment to innovation.

When it comes to insulin, we have been serving diabetic patients globally for over 15 years. Specifically with recombinant human insulin, patients have benefited from more than two billion doses, which correspond to more than 730 million patient days of exposure in over 40 countries. Our products cover the entire spectrum of patient needs with recombinant human insulin, basal and bolus, available in vials, cartridges, as well as disposable and reusable pens.

The Agency has asked for feedback on four questions, and this is our presentation on question 1(a) specifically on biosimilarity.

One, insulins are small proteins relative to mAbs, and they can be completely characterized. Second, both efficacy and safety can be adequately evaluated using highly sensitive in vitro methods. Third, insulins have a PD marker, which means they can

evaluate efficacy in a clinical pharmacology setting along with safety. That leaves very little uncertainty with regards to immunogenicity. We have specific suggestions on factors to consider to address any theoretical or any residual uncertainty coming from analytical similarity exercise.

Unlike mAbs, which are large and complex, insulins are simple proteins. We can completely characterize the drug product using multiple orthogonal methods and up to a molecular level. Therefore, once we do the characterization with adequate sensitivity, we can also quantify residual uncertainty risks. Specifically, the point I want to drive home on this slide is there are no unknown risks after we complete analytical similarity exercise.

Second, once we complete the structural characterization using physiochemical methods functionally, incidents, the mycogenic as well as metabolic effects, efficacy and safety component can be adequately characterized using in vitro methods that are highly sensitive.

Therefore, as we go through the step-wise

process, once we address the quality components as well as nonclinical components, coupled with the clinical pharmacology exercise, very little residual uncertainty remain with regards to immunogenicity and perhaps in most cases it's only a theoretical risk.

So, now we have specific considerations with regards to immunogenicity. First, multiple studies have shown absence of correlation between insulin antibodies and insulin resistance. In long-term follow-up studies of children with type 1 diabetes, neither the presence of insulin autoantibodies nor the development of insulin antibodies caused an increased need for insulin dose requirements.

Second, many clinical studies have shown absence of significant correlation between insulin antibodies and average glycemia. Therefore, insulin antibodies are not correlated with loss of efficacy or safety issues.

Now, when it comes to a biosimilar product, we can characterize the immunogenecity risk into two categories. One is product-related factors and patient-related factors. Insulin molecule is well

established to have multiple T cell epitopes that can elicit adaptive immune response, and which is a balance between effector and regulatory T cell response. Since the T cell response or to the linear peptides, and given the amino acid sequences identical between the reference product and biosimilar product, switching between these two is not expected to produce differential T cell response. The goal of biosimilarity is not to reestablish safety, is something I would like to remind here -- only to assess differential safety. Second, using high order structure using NMR and x-ray crystallography, they can further enhance the confidence that move differential risks exist.

Lastly, for products where the excipients are identical, no differential immunogenecity risks exist.

Moving on to patient-related factors, multiple long-term clinical studies in type 1 diabetic patients, their 70% of patients had a basal anti-insulin antibody, and in type 2 diabetes patients evaluating anti-insulin antibody formation, after exposure to human insulin and insulin analogs indicate

that anti-insulin antibody does not have a major impact on patient safety and efficacy.

Now, lastly, the question of immunogenicity, how do we go about addressing that? If we are to look at treatment-emergent adverse reaction rates from multiple clinical studies, from different sponsors for the same reference product, it ranges from 1.9% to 40%. Such large observed differences have been found to have no impact on efficacy or safety. Therefore, specifying a certain margin which results in a clinical trial size is non-value-added. A 300-patient trial can produce the same level of confidence as a 500-patient trial. Therefore, we recommend that the comparative immunogenecity specifically neutralizing antibody and its effect on glucodynamic effect should be viewed from a totality of evidence perspective. Any residual uncertainty can be addressed using this -- a single, approximately 300-patient trial.

Now, for products that have multiple formulations and then the label of the reference product for the safety section is the same, then the immunogenecity assessment for the formulation of the

highest theoretical risk should be sufficient. They should then be able to extrapolate safety and immunogenecity to the other formulations. Similarly, if the product has two different concentrations, they should be able to extrapolate safety and immunogenecity from one study to another based on scientific justification.

For over-the-counter products, by the way, insulin, recombinant human insulin is designated as over-the-counter product. Safety and immunogenecity data for a biosimilar product from a foreign controlled trial, even if the reference product is different, should be considered to watch toward the totality of evidence with scientific justification. Likewise, global pharmacovigilance data must be considered towards totality of evidence for biosimilarity.

Now, transitioning into the interchangeability question, unlike other biologics, insulin is the only protein to have been designated as over-the-counter product. Here, we compare the crystal dimensions and crystal morphology in terms of

length and width between two reference products, which are largely different. Despite the large differences in product characteristics, the Agency has allowed switching between these two products. What this does is that the effective therapeutic range is wide and the same. The dosage is identical on a unit-for-unit basis.

Now, interchangeability has three considerations, the first one being biosimilarity; the second one being same clinical effect for any given patient, and the risk in terms of diminished efficacy. Once we establish the biosimilarity, our position is that there is no differential need for evidence between biosimilarity and interchangeability, and here's the reason.

Every patient currently takes the drug that is titrated to their needs, and comparison of GAR equivalent proves the drug is effective in any given patient. So, it's irrelevant the same clinical effect in any given patient criteria outlined primarily for perhaps fixed dose product is irrelevant for insulins.

Second, risk in terms of diminished efficacy,

unlike mAbs, loss of efficacy due to anti-drug -- antibody formation, as I demonstrated just now, is not a concern for diabetic patients. Also, unlike mAbs, vary the frequency of dose between the first and second maybe weekly, monthly, or even longer, insulins are taken daily and the single switch or a three-switch study is not needed, and the immunogenecity assessment can be done in parallel study as well.

There are multiple reference products or biosimilars available to patients today, and these products are frequently switched to each other, either because of OTC rating or other drivers. Therefore, we are asking the Agency to consider that when a biosimilar is approved, it should be deemed as interchangeable to all the reference products.

Now, when it comes to continuous infusion pumps, if you systematically evaluate the risk, starting with product-related factors and in terms of device-related factors, we have already demonstrated that there are no risks in regards to product-related and device-related. So, the only residual component is the compatibility. Compatibility study and

extractable leachable should be sufficient.

In terms of patient experience, we request the Agency to allow patient experience or patient preference data to be utilized towards enabling approval, access and adoption of biosimilars.

And, lastly, with regards to education, we request the Agency to provide a level playing field for both the reference product and biosimilar. Any educational or promotional material casting aspirations on the biosimilarity or interchangeability should be discouraged.

And, lastly, sometimes loss of efficacy is attributed to handling, so we request the Agency to enhance education on handling of these products so that there is no misattribution of loss of efficacy due to biosimilars or switching.

In conclusion, insulins are simple proteins and the regulatory requirements should reflect that. Residual uncertainty can be accurately identified and quantified. Such residual uncertainty can be addressed in a single trial. The totality of evidence required for biosimilarity and interchangeability is

the same, and therefore we request the agency to designate all insulin biosimilars as interchangeable.

Comparability studies are necessary and sufficient to address any residual risks, and patient experience data should enable quicker access to biosimilars. If you put patient first and science-based regulations, that will ensure efficient development of biosimilar and interchangeable products. Thank you for the opportunity, and I'm happy to take questions.

MR. KOSLOWSKI: So, you mentioned patient experience should be a factor. So, are you saying that whatever the expectations are, that patient experience changes those expectations?

DR. RAMANAN: The patient experience in terms of real world evidence, pharmacovigilance data globally, if available, we request the Agency to consider that towards totality of evidence.

MR. KOSLOWSKI: Right. So, that would be a factor going into what the expectations might be in a particular case?

DR. RAMANAN: I wouldn't say it should be the

expectation, but if the data is available from global data, we request the Agency to consider that towards totality of evidence. Requiring a new study, you know, should not be needed if the data exists, clinical data exists.

MR. KOSLOWSKI: And following up on another, in your slide you had a comment in the characterization slide that there are no unknown risks.

DR. RAMANAN: Yeah.

MR. KOSLOWSKI: A pretty bold statement.

DR. RAMANAN: Yeah.

MR. KOSLOWSKI: So, I want to explore that a little bit further. So, does that mean there's no unexpected risks or that all risks we could think of, including immunogenicity, are dealt with?

DR. RAMANAN: So, words matter, right? So, after we complete the analytical characterization, we can actually -- and using MS technique, we will -- we know exactly what the risks are. Unexpected risks can come from either the product or patient-related factors. What we are saying here is from a product-

related factors there will be no unknown risks.

MR. STEIN: If you could speak a little bit to the proposal for the 300-patient study to look at immunogenicity. So, in a prior slide you had mentioned that the differential immunogenecity between a biosimilar and a reference molecule would be minimal, at low risk and therefore the immunogenicity differential would be minimal, and yet you're proposing a 300-patient study. Can I ask you two questions about that? First of all, if you are suggesting that the risk of differential immunogenecity is minimal and the impact of immunogenicity, if it were to occur, is minimal, what was the reason that you were proposing the study? And, secondly, where did you come up with the 300 number? Is that based upon experience or a particular calculation?

DR. RAMANAN: Yeah, happy to answer that. So, the clinical study that we are proposing is to address any public health risk, theoretical or otherwise, could exist, right? So, that's where the study is coming from. The number 300 is -- what we're

seeing is right now the 500-patient trial that -- you've seen all these studies have been close to 500-patient trials. Comes from a certain tier rate margin. What we are saying is, it doesn't really matter -- we should be looking at it from a comparative setting. You can take a lower number and can still get the same level of confidence from a 500-patient trial. So, if you increase the margin, the sample size will decrease, and so long as it's in a comparative setting, comparative totality of evidence requirement, the number should be fine.

MR. STEIN: Just to explore that a bit more, you said to look at other potential risks. So, are you primarily proposing the study with 300 patients to look at the residual risk of immunogenicity, or are there other factors that you would specifically look at, and what would the endpoint of the study be?

DR. RAMANAN: That's a good question. So, from a -- if you were to go by the step-wise process, what we are left with is the theoretical or any known risk coming from the analytical characterization. And the study that we are proposing is primarily only will

be for the immunogenicity.

MS. YANOFF: I'm also interested in this same issue. So, working backwards, you say there's no impact on safety and efficacy of the anti-insulin antibodies. Then working backwards, what is the relative importance of this tier rate percent, that you're saying, well, we can sort of compare the same number with fewer patients. But what exactly -- what number are you exactly wanting to compare and why?

DR. RAMANAN: We will provide those specific comments to the docket, and the scientific rationale.

MR. KOSLOWSKI: So, you made a comment about interchangeability that should not be an additional standard of biosimilarity for insulins or not require additional information. You also mentioned interchangeability should occur with all reference products. I kind of wondered what you meant by that, since biosimilarity is typically to a single reference product?

DR. RAMANAN: So, from a -- it has two components, right? First, even if the reference product are many, the amino acid sequence is

identical, practically, right? So, what we are saying is, from a differential risk, when we demonstrate interchangeability to one, we should practically get interchangeability to other reference products as well.

MS. TEMKIN: I had a very similar question. So, I'll just ask, and you may not have thought of this. But have you given any consideration to the regulatory framework for the -- you know, you say when a biosimilar is approved, it should be deemed as an interchangeable. And this idea that it would be interchangeable to multiple reference products, have you thought at all about the regulatory structure of that?

DR. RAMANAN: We will look into it and will provide comments to the docket.

MS. TEMKIN: That would be great. Thank you.

DR. RAMANAN: Yeah.

MS. YANOFF: And also for the docket, perhaps if you could expand on why you think immunogenecity assessment should include neutralizing antibody assessment, because you mentioned that on one of your

slides but didn't really discuss it much.

DR. RAMANAN: Okay.

MS. YANOFF: And, also, if you have any information on why the apparent large immune response in terms of anti-insulin antibodies in some trials has absolutely no impact on safety and efficacy?

DR. RAMANAN: Okay.

MS. YANOFF: If you have information that could explain what the reasoning is for that scientifically, that would be helpful.

DR. RAMANAN: Okay.

MS. TEMKIN: I think that's all the time we have to pepper you with questions.

DR. RAMANAN: All right. Appreciate it.

MS. TEMKIN: Thank you. Coby Watier? Okay. Maybe we have more time to pepper you with questions, but we won't do that. Dr. Marinac? Thank you.

DR. MARINAC: Good morning. My name is Marjana Marinac, and I'm speaking to you today as a staff member for the nonprofit JDRF. I'm also here as a pharmacist, and most importantly as a person who has lived with type 1 diabetes or T1D for 29 years.

Because of both my personal and professional background, the safety, effectively, availability and cost of insulin are of great importance to me. I am honored to be here today on behalf of JDRF.

As I've just mentioned, my disclosures are that I am a full-time employee of JDRF International. First, a little bit about our organization. JDRF was founded almost 50 years ago by moms and dads of children with type 1 diabetes. We work to achieve our vision by accelerating life-changing breakthroughs to cure, prevent and treat type 1 diabetes and its complications.

Since our founding, we have funded over $2 billion towards T1D research globally, and increasingly through clinical trials. Overall, 7.4 million people with diabetes rely on insulin every day, and I cannot stress enough the importance of insulin for the over 1.25 million Americans who have type 1 diabetes, a condition which is fatal without it.

JDRF is grateful to the FDA for holding this public hearing and for recognizing the importance of

affordable insulin and the role that regulatory policies can play in access to medical products. Access to and affordability of insulin is vitally important to people with T1D. The cost of insulin has soared in recent years. As an example, the Healthcare Cost Institute found that among people with type 1 diabetes, the per-person annual spending on insulin, as well as the point of sale price has doubled between 2012 and 2016. This has led people with diabetes to go to drastic measures, such as rationing insulin to meet those soaring costs, which can lead to devastating and life-threatening consequences. No one should suffer or die because they cannot access insulin.

Through our coverage to control campaign, JDRF has been rallying our community to call on companies to lower the price of insulin and for health plans, employers and the government to take steps to lower out-of-pocket costs. As FDA has acknowledged, an important part of those efforts is ensuring that there is a healthy, competitive and innovative insulin ecosystem. JDRF encourages the FDA to adopt policies

that will encourage biosimilar development, to increase competition in the insulin market while at the same time fostering innovation to continue to improve the care for people with diabetes.

I'd now like to address some important aspects of the diabetes patient experience with insulin that FDA should consider as they evaluate potential biosimilar or interchangeable products. Let's begin with hemoglobin A1c, a metric that people with diabetes usually discuss with their healthcare provider and an important indicator of the risk of developing long-term complications. A biosimilar or interchangeable insulin product should show consistent HbA1c results; however, this is not something that is central to a patient's daily experience with insulin.

People with T1D are on intensive insulin regimens and must closely monitor and take into account many factors in determining their insulin dose, such as their glucose levels, their carbohydrate, protein and fat intake, and the amount of insulin they have taken and what remains in their body, also known as insulin onboard. These factors

and many others are oftentimes considered on a minute-by-minute basis.

The reason for this close monitoring is to try, to the extent possible, to avoid hyper- and hypoglycemia, or said another way, to remain in a certain glycemic range, often 70 to 180 mg/dL, as measured by blood glucose meters or increasingly as shown here by continuous glucose monitors.

Because insulin has a narrow therapeutic index, a biosimilar or interchangeable insulin product should demonstrate consistency in the incidents of hypoglycemia and hyperglycemia with existing insulins.

In order to get these clinical outcomes, there are insulin management regimens that people with diabetes develop with their healthcare team to calculate insulin dose, including insulin-to-carb ratios, insulin sensitivity factors, and basal rates. Patient experience with these ratios should remain consistent for a biosimilar or interchangeable insulin.

Injecting insulin multiple times a day or continually infusing insulin through an insulin pump

has an impact on a person's body that includes site irritation or burning sensation. Any biosimilar or interchangeable insulin should not introduce new site impacts that existing insulins do not. Additionally, biosimilar insulin products should be able to be delivered in the same manner -- injection and, for some, through an infusion pump.

Storage and handling conditions should be similar and should maintain the safety and efficacy of the biosimilar insulin product.

As insulin is transitioned to being regulated as a biologic next year and as new types of biosimilar and possibly interchangeable insulins are approved in the coming years, it is imperative that information resources be available for patients, clinicians, pharmacists and other healthcare providers.

It will take a community-wide effort to have a comprehensive communication strategy and plan. FDA is, of course, an important stakeholder in this, but JDRF also calls on our fellow patient organizations, clinician organizations, industry and insurers to all play a role in the development and implementation of

effective communication and education strategies.

The type of information that needs to be communicated includes what a biosimilar or interchangeable insulin is; how to know what the insulin is biosimilar for or interchangeable with; an explanation of how these types of products are named to avoid administration errors; and, finally, how patients or providers can get help or more information.

Allow me to elaborate more on the importance of naming related to insulin products. Patients with T1D may often use some combination of short- and long-acting insulin that can either be injected or pumped, and can come in various presentations, such as vials and pens. Particularly for T1D, oftentimes all these types and presentations of insulin may be on-hand. Looking in my refrigerator this morning, they were all there.

Biosimilar or interchangeable insulin products, when available, would be, in part, identified by nonproprietary names. Those nonproprietary names are not commonly used today with

people with diabetes and may present challenges in identifying the correct insulin to use at the right dose and at the right time. We need to work together to ensure that patients can clearly and without doubt identify and understand which insulin they are taking. Mistakenly administering a dose of short- or rapid-acting insulin with a dose meant to be of long-acting insulin because of naming confusion could have potentially dire consequences.

Steps to ensure all labeling from not only the manufacturer but also pharmacy-affixed labels are clear, concise and understandable will help to ensure the safe use of biosimilar or interchangeable products.

We foresee that patients may receive information from many different sources, so this should be taken into consideration as communication and education strategies are developed. Certainly, some of this information should be included in patient labeling for products, but we also need to ensure that all healthcare providers caring for patients taking insulin are fully informed and have resources

available. Healthcare providers, including primary care physicians, endocrinologists, nurses and pharmacists need to be equipped with appropriate resources to keep patients with diabetes safe. We also need to consider how patients who use mail order pharmacies will get the information they need to safely use future biosimilar or interchangeable insulin products.

In short, all of this points to the need for a comprehensive and continuous education campaign. Thank you for the time to speak with you today on this important topic. JDRF appreciates the work FDA does, and we stand ready to help make the transition of insulin as smooth as possible, and we look forward to the day when there is a thriving, competitive, and innovative market for insulin that provides people with diabetes with more choices for safe, effective and affordable options of this lifesaving drug. I'm happy to take any questions.

MR. KOSLOWSKI: So, you had mentioned the importance for patients in their day-to-day life that the insulin behaves the way that they expect. So, how

do you see demonstrating that, and is there any concern that with the expectations you've heard about today, which varied to some extent, but the expectations in terms of characterization and being highly similar, and whatever additional clinical studies are necessary, that that remain -- does that remain an uncertainty?

DR. MARINAC: I think patients -- there are many factors, and I only listed a few, and I've seen data published, or I've seen that oftentimes there are 42 different factors that can be taken into consideration when a patient is trying to figure out what insulin to dose. So, I think we're expecting, or what we would like to see is that day-to-day experience not vary so much that rates of hyper- and hypoglycemia aren't so drastically different between a reference product and a biosimilar product that is causing issues. If it is, then we need to ensure that physicians and patients are educated and they understand what they need to do and where to go for help to get more information.

MR. KOSLOWSKI: I think that there are so

many, probably, different factors, as you mentioned, stress, a whole slew of things, that it might be extremely difficult, right, to be able to compare things, because so much of it will be a patient factor and not a product factor.

I also wanted to follow up on, I mean, you talked about ecosystem a few times. So, from patient groups, like JDRF, what are your thoughts, right? In other words, in terms of the system. Because part of that helps potentially with confusion about products and other things to have systems in place that better link products and understanding of their use.

DR. MARINAC: I think it's going to be really important that patients understand what a biosimilar insulin or what they're similar to or interchangeable with. And having that information I think is going to be an important part of ensuring that those products can be used safely.

MR. SCHILLER: We heard from a number of previous speakers that there's a fair amount of switching that goes on in the market today. From a patient perspective, how do you view existing levels

of switching compared to what it might look like in a world with biosimilars and interchangeables?

DR. MARINAC: Right. So, I think today, if you look at the switching that's happening, those are all happening with, you know, the proprietary products that are available today. We haven't introduced biosimilars or interchangeable products, which now there might be multiples of. So, that adds another layer, I think, of -- once those do become available, that additional switching now. You know, switching between Humalog and NovoLog because, let's say, formulary issues. Yes, that does happen today, and sometimes patients, when they potentially run out or have to go to an OTC product, yes, they are doing some of that today. But I think you add some complexity and some additional layers when you introduce now biosimilar products of those, where there might be some additional switching going on in the future that isn't happening necessarily today.

MS. LIAS: So, I was interested in the part where you talked about multiple medications in the refrigerator, for example, and that patients may

inadvertently grab the wrong medication. In Devices we call that human factors. Do you have any ideas of ways that we should consider making it easier for patients to avoid those mistakes?

DR. MARINAC: Some thoughts. Some clarity around what's a short-acting insulin versus a long-acting one. That information isn't really sort of -- it's probably buried in insulin information that's included with an insulin product, but I think ways to clearly identify what's a rapid or short-acting insulin versus what's a long-acting one. I think there's also a lot of things that can be done with color-coding. I think if we could look at -- I used to work for a generic injectables manufacturer, and oftentimes we'd receive complaints about color-coding and things for pharmacists were too close in name and color on the shelf, and sort of those medication errors that could come from that. So, I think even working with the community on potentially coloring systems, right, for short, rapid, long, that might also help avoid some of the future potential errors.

MS. TEMKIN: Thank you very much.

DR. MARINAC: Thank you.

MS. TEMKIN: I think we have time for one more presenter before lunch, if Dr. Ratner is ready.

DR. RATNER: Thank you very much. I'm Robert Ratner. I'm a trained endocrinologist who was involved in patient care directly for 35 years. I'm now professor of medicine at Georgetown University in the Department of Medicine, and I represent the American Diabetes Association today, for whom I served as the chief scientific and medical officer for five years.

Diabetes is a unique disease. The true primary care provider for a person with diabetes is the person with diabetes. It's unique because we ask our patients, these people with diabetes, to monitor their glucose by drawing blood, doing an analytical test, deciding how much of a treatment they need of a drug that has a very, very narrow therapeutic window, and then administering that drug multiple times a day via parenteral route. You can't say that about a whole lot of diseases.

This isn't new information. It was

identified by Elliott Joslin the year after insulin was actually introduced, saying that it's a remedy primarily for the wise and not for the foolish, and he drew no distinction between doctors and patients. It takes brains to live long with diabetes, but to use insulin successfully requires more brains.

Where we are today is a very confusing state for trying to treat diabetes, and that's because it's a very complex environment. You're looking at basal insulin rates that control the glucose during the fasting state and between meals, and then you see a bolus of insulin that's required with each meal. And all of this varies day-to-day on the basis of stress, exercise, and what you decide to eat at that particular meal. So, it gets to be complicated. It's led us in the profession to develop a basal-bolus insulin concept, where we separate out the long-acting, or basal insulin, from the mealtime, or prandial bolus insulin, and try and individualize it for each and every patient. We do that with a variety of different insulin products. And as has been mentioned multiple times, none of these are identified

as interchangeable, and yet we see the changes at the level of the pharmacy or the health plan or the formulary on a regular basis. What that does is it adds confusion; it really makes life lots more difficult in deciding which insulin you're taking; and what its dynamics are because, despite the fact that we can call things intermediate-acting or long-acting, the PK/PD of these products are not the same and the result is variability in glycemic control. So, let me just demonstrate a little bit of this.

Regular human insulin versus two of the insulin -- short-acting insulin analogs. You can see the remarkable difference in terms of the time action curves of these particular insulins. You look at long-acting insulins, whether you're looking at NPH human insulin, insulin glargine, or insulin detemir. And the PK and ultimate PD is very, very different. If you ask patients, and I've done this for 35 years, when the formulary changes and they suddenly get switched from glargine to detemir, or detemir to glargine, or glargine to degludec, everything changes. More telephone calls to the physician; more blood

glucose testing in order to readjust; more mild hypoglycemia because of the peaks. It becomes highly problematic and results in confusion and poor outcomes. Not long-term outcomes, because once insulin is in the blood, it all works the same way. It gets to the receptor, turns the receptor on, and that's what signals insulin action. It's before it gets to the receptor that's different, and that's what affects day-to-day management of diabetes.

You look at the variability here with the long-acting insulins and it really becomes highly problematic. We've seen one new insulin, branded insulin, come onboard that actually has part of its package insert citing safety from hypoglycemia. Degludec actually has a much different PK and PD as compared to any of the other insulins. They should not be interchangeable. Even with glargine, the concentration effects the PK and the PD, so that these should not be interchangeable, either.

In essence, what I'm saying is that we really don't need more insulins; we need better insulins and we need insulins that are more predictable, and we

need insulins that are more reliable, more accessible, and cheaper.

What's important to people with diabetes? They want to know that the insulin they take today will work the same way tomorrow and the day after that and the day after that. And that's really talking about reproducibility. This was brought up by one of the panelists just -- in one of the recent presentations. You want to be able to demonstrate reproducibility of a given dose in a given patient. The more narrow this range, the more predictable the biologic response is going to be.

So, having more insulins on the market isn't necessarily going to help things; it's going to confuse things. That doesn't mean we don't need better insulins on the market, and it doesn't mean that we don't want interchangeable insulins on the market; we clearly do. But currently, insulin is the leading cause of drug-induced adverse effects resulting in ER visits. Part of it is the narrow therapeutic window; part of it is the wide variety of products with different PKs and PDs; and part of it is

human error. We can't -- we have to be able to deal with the products on the market today and make sure that they are predictable, make sure they are reliable, make sure they are accessible, and make sure they are inexpensive.

The expense may be gotten to by the interchangeability. I would second Dr. Luo in saying biosimilar in the absence of interchangeability is of no benefit of all. It's going to add to the confusion, it's going to add to patient errors, pharmacy errors and human errors. So, I would say go directly to interchangeability and have the requirements there be what's really required. That's not all that difficult. This study looking at glargine by reference product and a second product coming to market demonstrates overlapping PKs, overlapping PDs.

This is what's needed for interchangeability. To have products like this on the market that are interchangeable at the level of the pharmacy will tend to bring down costs, make insulin more available; it will make insulins cheaper; it will improve care. A

simple approval process basically demonstrated here with the two forms of insulin glargine can really get us to the point of having biosimilar-interchangeability that actually benefits both patients and providers. Thank you very much. I'm happy to answer any questions.

MR. KOSLOWSKI: So, this is kind of following up on what we heard from JDRF, too. So, if, in fact, errors that you've mentioned really are from confusion, then do you have any suggestions about how to avoid that? Because, again, you might have interchangeable insulins that meet whatever criteria are necessary, will deliver the same patient experience, but what would be involved in making sure there is no confusion between reference products, between interchangeable products, etc.?

DR. RATNER: So, much of that is beyond the scope of the FDA, because it really gets to the issue of how the health plans or the formularies are really developed. I think that interchangeability needs to be product-by-product. So, the comment that was made earlier about once you have a biosimilar to one, let's

generalize it, I would vigorously disagree with. I think it needs to be one-for-one with interchangeability, because the PK and the PD and the variability are the same, and that's then, hopefully, what will happen is rather than switching from detemir to glargine, or glargine to degludec, the switch will be made from one form of glargine to another form of glargine, or one form of degludec to a different form of degludec.

MR. STEIN: Can you comment on what you think is necessary for interchangeability beyond a PK/PD matching? So, you're showing nicely that on average in a comparison you're seeing overlapping PK and PD. You didn't mention the need for looking at differences in immunogenicity. Do you think this is sufficient or would you also suggest the need to look at immunogenicity?

DR. RATNER: I think looking at reproducibility is much more important than looking at immunogenicity. I would agree with prior speakers that immunogenicity has not been a major clinical issue. I understand that there are certain safety

functions that need to be met within the regulatory sphere. I think that can be done within the framework of relatively small Phase 1 PK/PD studies and reproducibility studies.

MR. STEIN: You mentioned reproducibility, although this is looking at comparison rather than within patient reproducibility of the effect. Were you also suggesting that reproducibility criteria for interchangeability would be necessary? That is to say, that the biosimilar have a similar coefficient to variation to the reference drug? Is that a criteria you were suggesting?

DR. RATNER: I think that that would be worth looking at. It is certainly important to both providers and to people with diabetes to have that reproducibility and predictability. To do the analyses of reproducibility is not difficult in a Phase 1 trial.

MR. STEIN: So, you're suggesting that would be sort of a four-period trial with the reference and the biosimilar candidate both being tested twice?

DR. RATNER: Correct.

MR. STEIN: I see. Thank you.

DR. RATNER: Thank you very much.

MS. TEMKIN: Thank you. We will take a break for lunch and reconvene at 12:55.

[Lunch break.]

MS. TEMKIN: Welcome back, everyone. I hope you had a nice lunch, and we are pleased to start again with a presentation by Robert Geho.

MR. GEHO: Close enough. Close enough. So, thanks, everybody, for being here, and thanks to the FDA for the opportunity to speak today. I'm here as a representative of Diasome Pharmaceuticals, which is a Phase 2b stage clinical development company that is working on a novel additive to any form of commercial insulin. And the point of this additive is to address the very abnormal biodistribution of all forms of injected insulin therapy. And so our point in being here today is that on the one hand we're very supportive. Because we are insulin-agnostic and we are an additive to any form of commercial insulin, we're very supportive of the switch to biosimilar regulation. At the same time, we have focused for the

last several years of our development on our material, which we call hepatocyte-directed vesicles, or HDV, being a candidate for a 505(b)(2) pathway. So, my remarks are all focused on the issues associated with this transfer from a regulatory pathway that's coming up in March 2020, and potentially losing a 505(b)(2) type pathway.

Much has already been said about the rising costs of insulin. As a type 1 patient myself for the last 27 years, I know full well the cost of managing type 1 diabetes, in particular from an insulin point of view, from a continuous glucose monitoring point of view, insulin pump costs. David Nathan is quoted as recently as last year somewhat provocatively as saying that there really hasn't been a lot of change in the insulin molecule itself. I think that insulin developers in this room would probably take issue with some parts of that. It is the case, however, that once insulin molecules get out of the subcutaneous tissue and into the peripheral circulation, they all act exactly the same way. So, peripheral fat and muscle cells do not distinguish between a glargine

molecule and a NovoLog molecule.

One of the points, though, is that injected insulins are not working. And I put working in terms of my remarks in quotations, as someone who takes insulin and is in good health, insulin does work for me. At the same time, the recent data from the first quarter of this year from the type 1 diabetes exchange shows that insulins are really struggling to get patients under good control. Essentially, 80% of all type 1s across all age groups as a class are not able to reach ADA treatment goals from an A1c point of view. And for the patients who had data in the outcomes study authored by Roy Beck and others, who had data from 2010 to 2012, and then 2016 to 2018, mean HbA1cs shockingly have gone from 7.8% to 8.4%. The bulk of that increase is attributed to much poorer A1c outcomes in children, young adults and the elderly.

Before I move on from this slide, I do acknowledge that A1c is a fairly rudimentary marker of overall glycemic control. I along with others in the insulin development space are very much focused on the

importance of time and range and other measurements. Nevertheless, A1c is still the outcome that FDA is primarily concerned with. So, the reason why we say that insulins aren't working is we're still struggling to get people anywhere close to healthy A1cs. And we should all remember that the number of type 1s who have A1cs of 4.9, 5%, 5.1, is alarmingly small.

So, the question is, why is this the case? We believe that, in addition to just the routine complexity of managing type 1 diabetes, the fact of the matter is that type 1 patients cannot inject enough insulin safely to get some of that injected insulin to the liver. Novo published what we think is one of the most important papers, coauthored by Alan Cherrington at Vanderbilt, of the last several years just a month or two ago, in which they say that the data clearly demonstrate that it is impossible to normalize the glucose distribution between the liver and muscle when regular insulin is administered peripherally. So, then the question is, why is this important? It's important because the liver, and the hepatocytes in the liver specifically, are the only

cells -- and I underline that and put it in bold -- the only cells in the entire body system that can both store glucose at the time of a meal in response to an insulin signal from the pancreas, and then release that stored glucose into the peripheral circulation in response to pancreatic glucagon in order to counteract hypoglycemia. So, if we want to fix the hypoglycemia problem in a physiologic way, it is our opinion, and it's supported by this Novo research, that getting insulin to the liver preferentially is critically important. The liver stores glucose during a meal, thereby preventing hyperglycemia, and so an insulinized liver should have a big impact both on timing range and A1c. And then very importantly as a physiologic way of addressing hypoglycemia, that increased store of mealtime glucose should be releasable into the peripheral circulation, but that will only happen if the liver is seeing insulin.

Novo goes on to say in this paper, hepatic and nonhepatic glucose metabolism could be fully normalized by a hepato-preferential insulin analog. Our position is that while improvements can be made in

terms of access to insulin, cost of insulin, even more rapid-acting insulins, slower-acting insulins, the fact of the matter is, until all of those insulins have some form of hepato-preferential cell targeting, patients are going to be at a significant disadvantage.

In summary for this part of my remarks, insulin really has to have three different components in order to be successful for patients. How much is determined by blood glucose monitoring, insulin pumps, artificial pancreas technology, the ecosystem that was described in the morning session. The question of how fast or how slow or for how long is being, I think, addressed by the insulin producers in the industry. We are unique at this stage, in our opinion, in seeking to address the question of where. You know, just as in real estate, it's location, location, location; the same thing is absolutely true, in our opinion, in terms of insulin therapy. Where that injected insulin goes is critically important. I think it's the case now that both Lilly and Novo have abandoned their hepato-preferential insulin programs,

at least from a clinical development point of view, that we are alone in this. And so this question of 505(b)(2) pathway for us is critically important, even if it's singular for us right at the moment.

So, how do we get insulin to the liver? We develop this material, it's a 20 to 50 nanometer phospholipid-based, Frisbee-shaped disk. It is comprised of two different forms of phospholipids, a small amount of cholesterol that's kind of a chemical glue, and then the secret sauce component of this, if you will, is a special form of the vitamin biotin, which is embedded in the phospholipid matrix. We use biotin because liver hepatocytes have an abundance of biotin in their natural cell biology, and so biotin becomes part of the Trojan horse aspect of this.

Importantly, for the 505(b)(2) consideration, when we add 8/10 mL of liquid HDV, which is manufactured under CGMP conditions at commercial scale now, 10 mL vial of standard commercial insulin, we bind about 100 insulin molecules passively to that Frisbee-shaped disk. It does nothing to change the underlying structure of that insulin, making the HDV

system, from our perspective, anyway, ideal for a 505(b)(2) type pathway. HDV is specifically designed to be added to any form of commercial insulin. As I said, it's acceptable for pens, pumps, we've done the leachable and extractable testing, and our goal is to add, as I said, HDV, either by the patient or a pharmacist, or by a commercial insulin manufacturer to any form of commercial insulin.

So, our request is for consideration as to how a technology like this and other technologies that could impart things like liver preferential targeting to already approved insulins, and any form of biosimilar insulin as an equivalent, so that we can take advantage of this type of pathway. Our entire process has been predicated on the relatively inexpensive development cost that should accrue to a (b)(2) type pathway, and our concern, because of the switch from the drug to the biologic side is that if we lose this, it could impede the significant progress that we especially have made over the last few years.

So, with that I'll conclude my remarks and I'm very happy to take any questions. Thank you.

MS. TEMKIN: I was wondering if you have given any thought to the post-transition regulatory framework and how you see this type of pathway working, or whether you have a vision for what it would look like and how it would work?

MR. GEHO: Well, I think at a simple level, we'd like to be able to attach our application to whatever form or class of insulin that we're adding the HDV technology to, which is why the (b)(2) pathway is so attractive to us. If we're not able to do that, then we would have to switch to an adjunctive or combination product pathway, which has different layers of complexity, from our point of view. So, as we've analyzed the entirety of the potential pathways for us, we continue to think that the (b)(2) pathway is the most straightforward for us and would enable us to move as quickly and efficiently as possible.

MR. KOSLOWSKI: This may be kind of more of the same, but what would you envision actually needing for, say, a combination product pathway that you wouldn't need in a (b)(2) pathway?

MR. GEHO: So, at this point, I'd prefer to

just provide those comments in written form. We're in the process of analyzing that right now with our entire regulatory pathway team, so we're trying to figure out the pros and cons of those different pathways. But I would say that up to this point, everything that we've done has been predicated on the (b)(2), and if we lose that, our sense is it will add complexity and time.

MS. YANOFF: It would also be helpful if, when you discuss the (b)(2) pathway, comment on whether you would need to rely on another product or whether there's a literature-based approach, or how you envision the specific detail?

MR. GEHO: Part of that depends on whether or not we've partnered with an insulin company or whether we're going to market as a standalone. And so that would also be something that we would have to factor in when we head into Phase 3.

MR. KOSLOWSKI: So, this is more general, but aside from the regulatory pathway, what are things you think could be helpful for innovating in this area as sort of the -- you know, you said this is one example

of a kind of innovation, the targeting system, but to really encourage this type of innovation, any thoughts about that?

MR. GEHO: I think, generally speaking, it's our sense that the current insulins that are available, if they can get where they're going, to put it in the vernacular, are very appropriate insulin therapies and can be made a lot safer. So, I think, generally speaking, an emphasis on using already approved insulins or their biosimilar equivalents as the backbone of incremental improvement -- and by incremental, I don't mean in terms of the dramatic effects of, for instance, what we're seeing with hepatic-specific insulin. But finding ways to use the backbone of current insulins in a straightforward way where we can add things, like tissue specificity, like changing the absorption rate from a speed and duration point of view without having to change the underlying insulin itself would be very helpful to companies like Diasome, who are trying to add things to existing products. And, again, the fear is that if we lose that, it could really impede that kind of novel

development.

MS. YANOFF: So, is there -- what are the business considerations for partnering versus having a pathway where you wouldn't need to partner?

MR. GEHO: Our position is that if we can be approved as a standalone additive that, for instance, could be added by a pharmacist, then it enables us to be independent of needing an insulin partnership, which would by definition be the fastest way to get into Phase 3 and then be approved. And so we would like to be able to maintain that independence until such time as it makes good business sense and good sense from other perspectives to do an insulin partnership. And we recognize that even as we are pursuing that pathway from a product development point of view, that that is entirely unique in the industry. I'm not aware of any other company that is able to formulate a product that could be added in a single step to a commercial insulin. And so those -- the pros and cons of partnering with an insulin company are many. On the other hand, if we did have an insulin partnership, then the 505(b)(2) pathway

wouldn't be quite as much of an issue for us, because we could simply attach our information to the originator insulins already approved documentation.

MR. KOSLOWSKI: This may be a bit more technical, but obviously insulins are formulated in very, very different ways. If you wanted to have something standalone that you could kind of add a variety of insulins to achieve this, how would you deal with the fact that, in fact, there are very different formulations, which may really interact with your lipid bilayer in different ways?

MR. GEHO: So, our position is that it is certainly incumbent upon Diasome, in this case as an innovator, to ensure to the Agency that when we add HDV to every one of those insulins it behaves in the same way. We have the same amount of binding; we don't do anything to negatively affect insulin stability; we don't do anything to negatively affect the utility of that new combined product and all of the approved pumps, for instance. So, we view that as incumbent upon us. Our preference is that we would be able to do that across classes, so that if we do it

with Humalog, then we can do it with NovoLog in a more simple, streamlined bridging study. But we understand that it's incumbent upon us to demonstrate all of the things that you would want to see in terms of safety, stability and efficacy.

MS. TEMKIN: Okay. Thank you very much.

MR. GEHO: Thank you.

MS. TEMKIN: Dr. Socal?

DR. SOCAL: Hello. Good afternoon. My name is Mariana Socal. I'm a medical doctor. I have a PhD in health systems from Johns Hopkins University, a master's in public policy from Princeton. I currently work as an assistant scientist in the Department of Health Policy and Management at Johns Hopkins. I am speaking today on my own behalf and with the collaboration of my colleague, Dr. Jeremy Greene. Professor Greene is a medical doctor, a professor of medicine and a chair in the Department of History of Medicine at Johns Hopkins. Our statement today does not represent Johns Hopkins. We do want to thank our Arnold Ventures for supporting our research, although Arnold Ventures has had no role in us preparing our

remarks today.

We would like to provide commentary on how the FDA could improve the scientific standards for evaluating interchangeability of insulin products. We would like to start by defining that human insulin is the first successful product of the modern biotech industry. It has been on the market since 1982. Human insulins are biological products because they require living organism bacteria to be produced, but in the broader sense, insulins have been biologic drugs even before the biotech industry has developed. We view the upcoming transition of insulins into the regulatory framework established by the Biologics Price Competition and Innovation Act of 2009, BPCI Act or BPCIA, in 2020, with concern. We contend that if exceptions are not made, the transition will deepen the great challenges that currently affect access and affordability of insulins in America.

To encourage the production of high quality, affordable insulins, we propose that an exception should be made such that proof of biosimilarity should be considered ground for interchangeability in the

case of insulins. Transitioning insulin to the BPCIA framework means that if a generic insulin were to come into the market in or after 2020, it would not be considered a substitute to the existing product, even if they were demonstrated to be the same molecule, without additional trials. The FDA just issued last week the final guidance explaining these requirements that are placed on biosimilar competitors in order to gain interchangeability. For generic drugs in the small molecule space, these requirements do not exist. In our view, there is no substantial differences between insulin products and large molecule biologics that provide adequate grounds for our proposal.

First, immunogenecity in loss of efficacy, the more substantial concerns driving the requirements for interchangeability on large molecule biologics that exist today have not been a major concern across different insulins after decades of monitoring. Although insulin is a biologic, it's a relatively small molecule comprised of about 50 amino acids, much smaller than other drugs, like Humira, at about 1300 amino acids. Even though autoantibodies may be

developed by people utilizing human insulin, we have seen no evidence to date that these autoantibodies are associated with any clinically important changes. For example, changes in glucose control, hypoglycemia rates, or changes in dosage requirements for insulin.

There is also no evidence that development of autoantibodies if and when it occurs, is associated with any long-term complications of diabetes. Today, the American Diabetes Association guidelines, to the pharmacologic approach to diabetes, recommends the use of insulins according to the therapeutic onset and duration of effect. In other words, the standards of care in diabetes already acknowledge that insulins within the same class, for example, fast-acting insulins or intermediate-acting insulins, and so on, they're similarly effective and can be selected at the physician's discretion. While patients may have preferences and experience with different brands, the clinical literature supports equivalence across treatments.

Second, in the case of insulin, even if a theoretical risk of noninterchangeability were to

become a concern, the nature of diabetes management with robust biomarkers mitigates the possibility of clinical failure going unnoticed. The day-to-day, hour-to-hour effectiveness of insulins is quickly and easily measured via blood glucose levels by patients and their physicians. Many patients also have continuous glucose monitors that can provide immediate feedback.

If in theory a biosimilar insulin were for some reason to provide inadequate clinical effect, patients should be able to identify within the hour and correct it. This is not a case of autobiologics, for which if a clinical failure occurs, by the time it is identified, it may be too late to address it and complications may have already ensued. Therefore, in the case of insulin, we contend that there is no justification or credible evidence mobilized for requiring additional studies for interchangeability. There is no reason to indiscriminately apply a principle of the BPCIA that in the case of insulin would apply to concerns that are merely theoretical at this point.

In addition, we also believe that the differentiation between biosimilarity and interchangeability that will be imposed by transitioning insulins into the BPCIA framework has unintended consequences that could be harmful to patients, providers, and to the broader pharmaceutical market.

To patients, the negative consequences will be as follows. Under the current regulation, there is substitutability across some products, insulin products, as long as prescribers do not indicate a proprietary name, and as long as no proprietary administration device is involved, like a pen, for example. When a provider prescribes a human insulin by its nonproprietary name, say, for example, NPH human insulin, the pharmacy may dispense any of the existing brands of insulin to fil that prescription.

This substitutability prerogative is very important in light of the very real harm that already comes from rationing due to unaffordable prices in the insulin market. An insulin-dependent patient who ran out of their drug, they may not afford the time needed

to go back to the doctor and procure a new prescription. In some cases, just a few hours without insulin may be enough to send a person to the emergency room for a serious exacerbation. Patient safety would suffer if this pattern of direct substitutability were to change. It's also unclear if, under the new regulation, the availability of insulins over-the-counter or without a medical prescription would be maintained.

Diabetes is a lifelong condition, and patients are very well educated to its management in diverse occurrences. They know that fast-acting insulins share a given therapeutic profile and long-acting insulins are a different one. Introducing the intricate and arbitrary divide between biosimilarity and interchangeability to insulins will increase complexity, decrease patient autonomy, and decrease self-management abilities. This can have serious consequences for treatment adherence and overall glycemic control.

Insulin products are used by vastly more patients than any other biologic drug. Nearly two

million Medicare beneficiaries use glargine alone, a long-acting insulin. This is five times more than the users of the top five biologics combined. We're talking about Humira, Rituxan, Enbrel, Herceptin and Avastin combined.

If, due to increased barriers to access, hospitalization risks were increased by even a minor percentage, given the immense population of insulin users, the additional cost to the system and the loss of quality of life would be significant. To providers who are familiar with the current practice, adding an arbitrary divide between biosimilarity and interchangeability for insulins would generate confusion and uncertainty. It also has the potential to generate liability concerns. The additional four-letter suffix will further add complexity to prescribing and potentially restrict competition.

To the pharmaceutical market, increasing complexity would increase uncertainty regarding new products, and would further increase barriers to new entrants. Interchangeability requirements would also increase the cost to bring a new product into the

market without adding real gains. This also may contribute to increasing prices.

Instead, we suggest that the FDA has enough authority to issue guidance on its own, modifying the criteria for insulin interchangeability. While the criteria established by the BPCIA may be important in order to monitor and safeguard the public in relation to new complex moles of larger sizes, we contend that this criteria should not be blindly applied to older and smaller molecules, like insulin, that happen to be produced through biological pathways.

Insulin is not Humira. There is no evidence that the increased complexity would increase safety or effectiveness for insulin users, as compared to current standards. The FDA can and should consider insulin to be an exceptional product to which the rules of the BPCIA should be carefully reinterpreted, if applied at all, in order to maximize benefit, affordability and access to insulin for all Americans living with diabetes. Thank you.

MR. KOSLOWSKI: Did I hear you correctly that you said that the current market allows for direct

substitutional insulins?

DR. SOCAL: In certain cases.

MR. KOSLOWSKI: In the same class?

DR. SOCAL: For the same product. So, I gave the example of insulin, human insulin NPH. So, if the prescriber prescribes like the nonproprietary name, the pharmacist is able to dispense either, for example, Novolin or Humulin, for example, if the prescriber does not indicate the brand.

MR. KOSLOWSKI: So, I think we heard earlier from Dr. Ratner that there are significant differences between PK/PD profiles. Are they are the same insulins that are being substituted today, or can you say more about that?

DR. SOCAL: So, what I was saying is, insulin patients, they are extremely well educated about -- and they become well educated about their condition over time. So, it's very possible that different patients, they will have different experiences with their insulin. They're going to become more familiarized, they know what to expect with their brand. And we're not advocating that a patient, you

know, would be arbitrarily receiving one or the other product just because the pharmacist decides so. What we are saying is that given the current challenges that exist for affordability of these products and really access of these products in the market, maintaining these safeguards of substitutability is important, and not removing them through, you know, generating these additional complexities and additional differentiations in the market. It's very important for the patients, for their self-management, for prescribing, from the prescriber perspective, and also generally to the market.

MR. KOSLOWSKI: So, just to add on a little bit. So, is that substitution through state pharmacy laws, or that's basically pharmacy practice?

DR. SOCAL: It could be both. And also because there are -- there is also the possibility -- currently, there is the possibility that patients will purchase the drug without a prescription. There is also substitution there.

MS. YANOFF: So, you sort of allude to this at the end when you said the BPCI Act maybe shouldn't

be applied to insulin, but I want to make sure I understand what your position is on the evidence needed for biosimilarities. So, I understand your position that if you establish biosimilarity, you don't think any more should be done. But can you clarify what --

MS. SOCAL: Yeah, I was just running out of time. But I meant interchangeability. I didn't want to exceed the time. I was not discussing the BPCIA requirements in terms of biosimilarity. [I was] specifically referring to interchangeability.

MS. YANOFF: I think we have a couple minutes of time, if you could clarify what you think the standards should be for biosimilarity.

MS. SOCAL: My sentence was, the FDA can and should consider insulin to be an exceptional product. So, we think to changeability rules of the BPCIA should be carefully reinterpreted.

MS. TEMKIN: I want to ask a couple of questions maybe about the consumer confusion aspect of what you're talking about. Are you not concerned about consumer confusion in the face of

interchangeable insulins; it's the distinction between biosimilar and interchangeability that you're worried about? And can you explain sort of why one and not the other?

DR. SOCAL: Yes, and I think this -- you know, this sort of conversation is the most important conversation to have, because at the end of the day we want to establish regulation. We want to, you know, have the highest possible standards, but we also want to be responsive to patients' needs first and foremost. And the discussion between interchangeability and biosimilarity adds some uncertainty to patient self-management. One example that I recently came across was in having a conversation with a manufacturer of originated biologics. This was not in the insulin space; it was another sort of set of manufacturers. And the manufacturers told us this: Payers are really more excited about products that have interchangeability designation. And we were thinking to ourselves, what does that actually even mean, if you're a payer and you have to establish a formulary? Like, what does

that even mean to be more excited about a product with interchangeability designation? So, we believe from this and other narratives that separating what is a biosimilar and what is an interchangeable biosimilar, yes, there are safety reasons and there are multiple advantages in some cases for some drugs. But specifically for the case of insulins and specifically with a long history that insulin has in the market and in people's lives, having this dichotomy between these two concepts as we envision new products coming into the market in the future, patients asking themselves, well, I was prescribed by my doctor this insulin, but I had these -- I read that it's not interchangeable with the previous one that I'm using. Well, my doctor selected, but I'm not very confident that it will work for me, even though, let's imagine, it has a biosimilar designation.

So, we believe that, you know, separating these two concepts for the case of insulin will have much more complexity and more unintended consequences, potentially, than really increasing safety standards, efficacy standards, and other -- bringing other

positive aspects to patients and providers.

MS. TEMKIN: Thank you. I take it from the change of slides that we're moving into the open public speaker section of our day. Our first registered public speaker is Dennis Cryer. I think if you step up to the microphone. Okay. Maybe Dennis Cryer has decided not to step up to the microphone. Karin Hehenberger?

DR. HEHENBERGER: Yes, thank you. So, my name is Karin Hehenberger. I an MD, PhD, and I trained as a post doc at the Joslin as a JDR fellow, so my life has been about diabetes research. And for the past 20 years I worked on the industry side of diabetes innovation and really assessing new technologies. I also have a very personal reason to be involved in this. This summer it's going to be 30 years since I was diagnosed with type 1 diabetes. So, it wasn't a purely unselfish act to spend this much time; I also wanted to find better ways to treat myself.

MS. TEMKIN: I'm very sorry to interrupt. Would you mind taking a step towards the microphone?

DR. HEHENBERGER: Okay.

MS. TEMKIN: Thank you.

DR. HEHENBERGER: Is this better?

MS. TEMKIN: Yes.

DR. HEHENBERGER: So, despite all this education and commitment to the space of diabetes, and I really am very grateful for the discovery of insulin and all the manufacturers who spend so much time and money in creating all these great products for people like myself, it's not easy to handle the disease. And as reflected by my own problems, I needed a kidney transplant 10 years ago. So, despite having all this access and all this education, and being in the best environment you could be, I still failed in my own disease, and I think that's, of course, an N of 1.

But five years ago I decided to start my own company called Lyfebulb, which is a patient empowerment platform which bridges patient communities with industry, really, to bring the insights and the solutions from people like myself, who are living on a daily basis with different conditions, chronic conditions -- diabetes being our first area of

interest -- to industry to try and enable better products to reach the marketplace, to really address these daily problems that are so very important when it comes to delivering better outcomes.

So, in the case of diabetes, we've seen very little discovery, very little advancement beyond the insulin, especially for type 1 diabetes, especially if you compare to other disease areas, such as cancer, multiple sclerosis, and so on. So, what I urge -- what I would like a message to be today is that we should encourage these wonderful companies who have worked so hard in delivering insulin to so many people to try to take it one step further and see what else we can do for people like myself and others with diabetes, and try to create better, new innovative products that are beyond insulin, and enable insulin to be accessible and affordable to everyone who needs it.

And one step to do that -- there are several different steps. We need to fix the healthcare system with the payers, the PBMs, and all the different margins, but we also need to increase competition in

the marketplace. And I believe we've heard today already how relatively simple among all the biologics insulin is. So, creating an environment for biosimilar insulin where the biosimilar insulin is interchangeable with the reference product I think is a very important first step.

I also think that we need education and we need programs surrounding all incidents so that people know how to use it. I think in contrast to maybe some of the speakers, I don't think all people with diabetes are educated and know everything about their insulins, and it's not that easy.

So, we need to have a, really, a community effort when it comes to enabling people with diabetes to live better lives. But let's move the discussion, also, toward better innovation so that we do not have to see the severe complications and the negative outcomes that we still see today, 100 years later, after the discovery of insulin. So, thank you so much.

MS. TEMKIN: Thank you. Our next speaker is Zoe Kullah (ph). Zoe? No? Brooklyn McGowin (ph)?

Christine Simmon? Brianna Tianga (ph)? Coby Watier again? No? Kelly Close?

MS. CLOSE: I was No. 8, so I wasn't expecting to get here so quickly. Thank you, everyone, for being here. It is amazing to see the influence that FDA is just putting on diabetes, proudly speaking. So, I just wanted to start with that. It is really big, and you have so much impact on global regulatory agencies and on everyone in the US.

So, just wanted to start by saying that and thank you so much to all of the patient advocates, to all of the researchers, to all of the manufacturers, to everyone working more toward working together with collective impact to improve life for people with diabetes.

So, I'm under the diaTribe Foundation and also Close Concerns. Our disclosures are that at Close Concerns we put out a daily newsletter that goes to 10,000 different people. Many of them are manufacturers as well as nonprofits working in the field. And the diaTribe Foundation also has donations

from the Helmsley Charitable Trust, as well as a number of manufacturers and other healthcare and other businesses.

So, just want to start out by saying, you know, I think everyone would agree that people with insulin need to have access to this lifesaving drug. This should be a human right. And, by the way, even all of the references today to the people who require insulin to insulin-requiring patients, way more people would benefit from insulin if it were easier to take, easier to prescribe, easier to dose, and all of that. So, I don't -- I think it's important to note that it's probably a lot higher than 7.5 million people who would benefit from it if we could improve the system in different. And I love FDA working on barriers. So, that is amazing. Thank you.

The current status quo is far from the place where everyone has access, and so we really applaud Dr. Sharpless and before him, Dr. Gottlieb's focus on changing this and expanding FDA's work on this front. And thank you to CDER, CDRH, folks on the nutrition side with the improved labels. There are many pieces

that need to come together to improve life. And we absolutely need to start with insulin affordability and access. There is major momentum here. And, again, this is a human right. No one would dispute that.

Reducing friction, though, is just essential in all parts of diabetes. So, it would be great to see policies looking through that lens, and increasingly more of them are. So, thank you, again, and how can we all work as stakeholders to reduce friction? The visibility that you are giving patients with diabetes speaks volumes on this, but nonetheless, acquiring insulin right now is a high friction experience. Paying for it is high friction; prescribing it is high friction; taking it is high friction; knowing when to change your dose is high friction; and knowing how to work with all the progress that has been made in the last two decades. It's amazing, including so much work by FDA. And I will say, insulin is not the same drug as it used to be 100 years ago. You know, I've been in the emergency room 24 times over 12 years taking NPH, and

I was very lucky for all the work that FDA and others did to create analogs. And we want analogs to be made available to everyone that needs them.

And just for more acknowledgement to be -- one size doesn't fit all. When we're asked what's the patient perspective, there are so many different patient perspectives and understanding the diversity of patients is absolutely critical. So, thank you to the work on FDA's front for encouraging much more diversity in clinical trials.

In the largest continuous glucose dataset ever shared, this is in almost half a million people, 500,000 users in 26 countries. The typical person with insulin spent 56% of the time in the range that we all have agreed is at least the right range for research to use, 70 to 180. Over half an hour a day was spent below 54. That is an incredibly dangerous level, and four hours a day were spent over 240. And these are people with CGM. We know that reality of global insulin users is far, far worse, and so a really small percentage of people with diabetes get to that over 70% place right now, and time and range is a

tool that is increasingly discussed by many researchers. And we are a tool that is so grateful with CGM, who brought it to market quickly so patients can understand time and range. We also think along with insulin knowing how much insulin to take can greatly be -- can really greatly be improved.

Also, as a side note, you are now seeing a lot of work on the closed loop front. Many people in clinical trials, their time and range is 80%, 90% and above. That is because they are getting -- their insulin delivery is being enabled by technology, and that is amazing. And that FDA is helping make that happen is something we're really grateful for. And we so need faster insulins and better insulins, and we still need those investments.

I think most would probably agree that immunogenecity is not really any longer a real issue that there is tremendous worry about. I would also like to just remind people that there was a lot of work and a lot of investment that went into this by major manufacturers over the past decade so that we don't have to worry about that as much. And we need

to make an environment where that kind of resources can still be put into safety.

MS. TEMKIN: I have to pause you, I'm very sorry that we are over time on this.

MS. CLOSE: That's okay.

MS. TEMKIN: And invite you to please put in all of your comments to the docket. We're very interested to hear what you have to say and would appreciate you doing that.

MS. CLOSE: Thank you very much.

MS. TEMKIN: And Lynn Young, if you're here.

MS. YOUNG: My name is Leigh Young (ph). Since I think there is a time limit, I'll have to make it quick. I don't know if it was insulin, but I think a lot of medicines, prescription, has been misused, abused and prescribed by doctors just as a tool in hospitals or rehab center, this type of setting. So, I'm just wondering, instead of saying you have to push the medication since it is in high demand, we had better examine instead of what's wrong that caused so much use of insulin or any other prescription. A lot of time I can see in the hospital or rehab center,

those patients probably are not supposed to be there, including the mental hospital and VA. A lot of VA send to the hospital, a mental hospital or rehab center. They use their benefit to benefit themselves, to benefit the health provider or social services, social workers. Those are a big group of what I call robberism. If you put all this work together, robberism equal official misconduct and government gain, murder for all crime in just the network operation. So, if you can examine those, we can save a lot of healthcare costs, because those are not really demanded.

And also a lot of prescription will be misused, prescribed to a patient. The patient, they don't need it, but they are forced through judicial administration, administrative procedure and even there's not many corrected, even made patients request it, they will not release it. So, if you request it, I can't send you to jail or something, handcuff or shackle you. So, a lot of misuse and that can even cause tensions in their life, and even if it's not their life, they take all your property, you're

homeless, everything possible.

So, and this also related to a PPP, public-private partnership. Just especially now I realize FDA is related to PPP, especially in economic development. But this is system-wide it's related, so it's related to community development in this area that can cause a problem with the patients. Again, it's not the patient, they don't need the medicine and then they are just misused and they want to take their property, so they send them to mental hospital, they send them the insulin, even patient run, they don't want it. That doesn't -- several people grab in bed and injection and the medicine, they will not even give the medicine or any label, and so eventually they are close to death or it is because uncomfortable and cannot even sleep, and deprivation of their sleep is a problem and the deprivation of their food. And especially the diagnosis of diabetes, why they are suffering depressions, a big huge bowl of really sweetness and sweeter than anything else that you can imagine in the world. And I don't think this is the way to treat diabetes patients. From the way they do

things and they always use force denying the patient through their good exercise and good recreational activities. They try to isolate them so they can control them. And this is -- the whole thing is to isolate the people and they don't allow them to go home or go to anything that they need. They don't want to stay in hospital, they don't want to stay in the jail. They don't want to be in rehab center. Everything is there.

We must do something about it, and I emphasize again, this is system-wide, I think the FDA and the public has to do something, but FDA is a good start. You are concerned about the prescription, about healthcare, you're concerned about all these people's health and life, and I see why you can work with other agencies concurrently. Almost every agency is with PPP, that's public-private partnership and the better, the best example of PPP is in the Rockville Town Center project, which I've been testified almost every segment of their PPP.

So, you will see why I'm here just like a dead man crusading, because they take all my property,

everything away, they treated me as a dead man. So, they don't want me to speak everywhere. They don't allow me to speak in a lot of cities, mayor and council, they don't allow me to go to Montgomery County Council --

MS. TEMKIN: I'm sorry, I have to interrupt you. We're over time again, but thank you very much for your comments.

MS. YOUNG: Thank you for this opportunity. Appreciate it. We will work together. And I think you mentioned that number you announced --

MS. TEMKIN: Yes. In my closing remarks I will give you all additional information about submitting to the docket.

I think unless we've missed someone who signed up and then wasn't present when their name was called, that we are ready to close the hearing. So, on behalf of the whole panel here, I'd like to thank all of the presenters and everyone in the audience, whether you attended in person or via webcast, for participating in today's public hearing. We greatly appreciate your attention and your interest in this

topic and in today's presentations.

As a reminder, we do encourage everyone to submit comments to the docket, which will be open until May 31st. If you would like details on how to submit to the docket, we placed copies of the Federal Register notice announcing this hearing at the registration table outside the doors. The Federal Register notice contains those details.

A transcript from the hearing will be posted to the website. It should be within 30 days, and we will provide copies of today's presentations upon request. Contact information is also at the registration table. And on that note, I am closing this public hearing. Thank you.

CERTIFICATE OF NOTARY PUBLIC

I, KEVON CONGO, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

KEVON CONGO
Notary Public in and for the
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