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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

DATE: Monday, May 13, 2019  
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1 MS. TEMKIN: Good morning. My name is Eva  
2 Temkin. I am the acting director for policy in the  
3 Office of Therapeutic Biologics and Biosimilars at  
4 CDER here at FDA, and I'm going to be the presiding  
5 officer for the hearing today.

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

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

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

9           The subject of today's public hearing,  
10 facilitating the efficient development of biosimilar  
11 and interchangeable insulin products tackles this  
12 challenge in part. Insulin is a life-saving medicine.  
13 The essential role in treating diabetes mellitus has  
14 been known since the time of Banting and Best in the  
15 1920s, and as an internist I can say that no condition  
16 is more satisfying to treat than diabetic  
17 ketoacidosis. You would have these patients come in  
18 so profoundly sick and we give them 10 or 20 units of  
19 regular insulin, and these patients would rise like  
20 Lazarus and then tell you they wanted to go home so  
21 quickly. So, it was a great -- it makes it evident  
22 how important that drug is for patients in that

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

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

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

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

1           One study from the Schaefer Center documented  
2           the average list price of four insulin categories  
3           increased on the order of 16% per year from 2001 to  
4           2015, and a report released late last year by the  
5           Congressional Research Service noted a list price of  
6           one type of insulin had increased nearly 600% from  
7           2012 to 2016. It hardly needs to be said that these  
8           kinds of whopping and steady price increases make it  
9           increasingly difficult for many insulin-dependent  
10          patients to afford basic medicines they need to  
11          survive. As a physician, I find this intolerable. No  
12          patient should have to choose between paying for their  
13          medicine and paying for their rent.

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

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

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

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

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

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

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



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

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

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

1 promise for insulin products.

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

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

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

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

1 evaluation?

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

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

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

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

1 Before we begin, here come the administrative  
2 announcements.

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

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

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

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

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

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

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

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

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

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

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

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

3 Public hearings are public administrative  
4 proceedings and are subject to FDA policies and  
5 procedures for electronic media coverage.

6 Representatives of the electronic media are permitted,  
7 subject to certain limitations, to videotape, film or  
8 otherwise record FDA's public proceedings, including  
9 the presentations of today's speakers. This hearing  
10 will also be transcribed, and copies of the transcript  
11 can be ordered through the docket or accessed on our  
12 website approximately 30 days after today's hearing.

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

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

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

10 Please remember that the hearing is being  
11 transcribed, so please be sure to use the microphone  
12 when speaking. If you didn't register to make an oral  
13 presentation but you would like to do so at the end of  
14 the hearing, you may be able to speak during the open  
15 public comment period, which is scheduled to begin at  
16 1:45 p.m. If you're interested, please sign up at the  
17 registration table outside the meeting room no later  
18 than 10 a.m. for one of the available three-minute  
19 speaker slots. We also strongly encourage you to  
20 submit to the docket. The Federal Register notice has  
21 details on how to submit comments to the docket.  
22 Extra copies of that notice are also available at the



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

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

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

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

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

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

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

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

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

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

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

11           It can actually be argued that the primary  
12 purpose of Phase 3 trials is to create marketing data  
13 for physicians in an effort to be able to increase  
14 claims in market share rather than truly to detect the  
15 inherent safety of a biosimilar drug. A robust CMC  
16 package in Phase 1 clinical trial should leave little  
17 uncertainty as to biosimilarity. Insulin, which is a  
18 small, extensively studied protein discovered almost  
19 100 years ago, is particularly amenable to this  
20 approach.

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

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

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

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

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

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

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

10 DR. OSHMYANSKY: Oh, sure.

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

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

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

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

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

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

1 for that?

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

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

12 DR. OSHMYANSKY: Thank you, guys.

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

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



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

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

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

1 other biologic molecules.

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

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

22 Since 2010, Vizient has provided ongoing

1 training and education on the biosimilar paradigm to  
2 its membership and other audiences in the form of over  
3 200 in-person presentations and web conferences, has  
4 developed evidence-based clinical resources to support  
5 members in their formulary evaluations of approved and  
6 pending biosimilars, and has worked with existing and  
7 future biosimilar manufacturers on contractual  
8 relationships to maximize the value and cost-savings  
9 opportunities for our membership.

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

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

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

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

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

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

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

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

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

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

1 biosimilar insulin products.

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

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

22 First, Vizient is working with its members

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

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

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

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

22 In addition to these recommendations, Vizient



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

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

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

1 refrain from introducing additional barriers.

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

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

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

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

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

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

6 MR. KOSLOWSKI: Thank you.

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

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

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

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

1 quality pharmaceutical supply chain that we have in  
2 the US.

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

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

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

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

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

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

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

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

18 DR. LUCIO: Sure.

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

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

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

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

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



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

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

11 DR. LUCIO: Yes.

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

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

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

5 MS. TEMKIN: Thank you very much.

6 DR. LUCIO: Sure. Thank you.

7 MS. TEMKIN: Dr. Barve?

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

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

1 seeing the results of these efforts with many firsts.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

1 delivery devices.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

16 DR. BARVE: Correct.

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

22 DR. BARVE: I think some of these will

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

3 MS. LIAS: Thank you.

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

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

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

1 considerations for patients with diabetes.

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

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

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

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

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

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

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

22           The experience of interchangeability

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

18 [Break.]

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

22 DR. LUO: Good morning, everyone. Can you

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

1 biosimilar product.

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

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

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

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

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

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

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

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

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

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



1 DR. LUO: Yeah, I mean --

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

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

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

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

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

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

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

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

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

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

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

3 MS. TEMKIN: Sure. In Section  
4 351(k)(2)(A)(i)(cc).

5 DR. LUO: And what is the line?

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

11 DR. LUO: Okay.

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

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

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

20 DR. LUO: Yeah.

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

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

7 MS. TEMKIN: Thank you.

8 DR. LUO: Thanks.

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

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

22 MS. TEMKIN: If there are no additional

1 questions, thank you very much.

2 DR. LUO: Thank you.

3 MS. TEMKIN: And Christine Simmon, thank you.

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

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

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

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

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

22 Six of the most highly utilized brand name

1 insulins increased in list price by more than 500%  
2 from 2006 to 2015. Because patient cost-sharing is  
3 often based on the list price before rebates or  
4 discounts, increases in list price directly impact a  
5 patient's ability to afford their medicines and can  
6 cause increased patient abandonment and lower  
7 adherence. In addition, in Medicare Part D, annual  
8 out-of-pocket costs for insulin nearly doubled from  
9 2007 to 2016, from \$324 to \$588, according to the  
10 Kaiser Family Foundation.

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

22           Now, while the interchangeability designation



1 does not confer any additional quality or safety  
2 attributes for approved biosimilars, the statutory  
3 requirement, as others have pointed out, under BPCIA  
4 makes the designation necessary for automatic  
5 substitution at the retail pharmacy.

6 Interchangeability will therefore be particularly  
7 important in the insulin space.

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

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

1 interchangeability outlined in the final guidance.

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

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

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

1 changes to safety or effectiveness.

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

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

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

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

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

22             Thank you for the opportunity to speak today

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

9 MS. TEMKIN: Great. Thank you.

10 MS. SIMMON: Thank you.

11 MS. TEMKIN: Dr. Ramanan?

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

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

1 biotherapeutics, both innovative and biosimilars. In  
2 2019 alone, we expect to improve more than 2.6 million  
3 patient lives, which 2.5 million will be diabetic  
4 patients. Patent metrics presented here also  
5 demonstrate our commitment to innovation.

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

15           The Agency has asked for feedback on four  
16 questions, and this is our presentation on question  
17 1(a) specifically on biosimilarity.

18           One, insulins are small proteins relative to  
19 mAbs, and they can be completely characterized.

20           Second, both efficacy and safety can be adequately  
21 evaluated using highly sensitive in vitro methods.

22           Third, insulins have a PD marker, which means they can

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

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

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

22 Therefore, as we go through the step-wise

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

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

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

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

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

15           Lastly, for products where the excipients are  
16 identical, no differential immunogenicity risks exist.

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

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

3 Now, lastly, the question of immunogenicity,  
4 how do we go about addressing that? If we are to look  
5 at treatment-emergent adverse reaction rates from  
6 multiple clinical studies, from different sponsors for  
7 the same reference product, it ranges from 1.9% to  
8 40%. Such large observed differences have been found  
9 to have no impact on efficacy or safety. Therefore,  
10 specifying a certain margin which results in a  
11 clinical trial size is non-value-added. A 300-patient  
12 trial can produce the same level of confidence as a  
13 500-patient trial. Therefore, we recommend that the  
14 comparative immunogenicity specifically neutralizing  
15 antibody and its effect on glucodynamic effect should  
16 be viewed from a totality of evidence perspective.  
17 Any residual uncertainty can be addressed using this -  
18 - a single, approximately 300-patient trial.

19 Now, for products that have multiple  
20 formulations and then the label of the reference  
21 product for the safety section is the same, then the  
22 immunogenicity assessment for the formulation of the

1 highest theoretical risk should be sufficient. They  
2 should then be able to extrapolate safety and  
3 immunogenicity to the other formulations. Similarly,  
4 if the product has two different concentrations, they  
5 should be able to extrapolate safety and  
6 immunogenicity from one study to another based on  
7 scientific justification.

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

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

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

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

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

22           Second, risk in terms of diminished efficacy,



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

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

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

1 extractable leachable should be sufficient.

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. RAMANAN: Yeah.

11 MR. KOSLOWSKI: A pretty bold statement.

12 DR. RAMANAN: Yeah.

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

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

1 related factors there will be no unknown risks.

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

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

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

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

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

1 be for the immunogenicity.

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

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

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

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

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

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

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

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

18 DR. RAMANAN: Yeah.

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



1 slides but didn't really discuss it much.

2 DR. RAMANAN: Okay.

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

7 DR. RAMANAN: Okay.

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

11 DR. RAMANAN: Okay.

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

14 DR. RAMANAN: All right. Appreciate it.

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

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

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

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

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

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

1 affordable insulin and the role that regulatory  
2 policies can play in access to medical products.  
3 Access to and affordability of insulin is vitally  
4 important to people with T1D. The cost of insulin has  
5 soared in recent years. As an example, the Healthcare  
6 Cost Institute found that among people with type 1  
7 diabetes, the per-person annual spending on insulin,  
8 as well as the point of sale price has doubled between  
9 2012 and 2016. This has led people with diabetes to  
10 go to drastic measures, such as rationing insulin to  
11 meet those soaring costs, which can lead to  
12 devastating and life-threatening consequences. No one  
13 should suffer or die because they cannot access  
14 insulin.

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

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

5 I'd now like to address some important  
6 aspects of the diabetes patient experience with  
7 insulin that FDA should consider as they evaluate  
8 potential biosimilar or interchangeable products.

9 Let's begin with hemoglobin A1c, a metric that people  
10 with diabetes usually discuss with their healthcare  
11 provider and an important indicator of the risk of  
12 developing long-term complications. A biosimilar or  
13 interchangeable insulin product should show consistent  
14 HbA1c results; however, this is not something that is  
15 central to a patient's daily experience with insulin.

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

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

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

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

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

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

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

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

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

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

1 effective communication and education strategies.

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

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

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

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

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

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



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

9 In short, all of this points to the need for  
10 a comprehensive and continuous education campaign.

11 Thank you for the time to speak with you today on this  
12 important topic. JDRF appreciates the work FDA does,  
13 and we stand ready to help make the transition of  
14 insulin as smooth as possible, and we look forward to  
15 the day when there is a thriving, competitive, and  
16 innovative market for insulin that provides people  
17 with diabetes with more choices for safe, effective  
18 and affordable options of this lifesaving drug. I'm  
19 happy to take any questions.

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

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

8 DR. MARINAC: I think patients -- there are  
9 many factors, and I only listed a few, and I've seen  
10 data published, or I've seen that oftentimes there are  
11 42 different factors that can be taken into  
12 consideration when a patient is trying to figure out  
13 what insulin to dose. So, I think we're expecting, or  
14 what we would like to see is that day-to-day  
15 experience not vary so much that rates of hyper- and  
16 hypoglycemia aren't so drastically different between a  
17 reference product and a biosimilar product that is  
18 causing issues. If it is, then we need to ensure that  
19 physicians and patients are educated and they  
20 understand what they need to do and where to go for  
21 help to get more information.

22 MR. KOSLOWSKI: I think that there are so

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

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

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

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

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

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

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

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

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

22 MS. TEMKIN: Thank you very much.

1 DR. MARINAC: Thank you.

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

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

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

22 This isn't new information. It was

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. RATNER: Correct.

1 MR. STEIN: I see. Thank you.

2 DR. RATNER: Thank you very much.

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

5 [Lunch break.]

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

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

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

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



1 molecule and a NovoLog molecule.

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

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

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

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

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

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

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

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

1 at least from a clinical development point of view,  
2 that we are alone in this. And so this question of  
3 505(b)(2) pathway for us is critically important, even  
4 if it's singular for us right at the moment.

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

1 development.

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

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

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

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

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

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

6 MS. TEMKIN: Okay. Thank you very much.

7 MR. GEHO: Thank you.

8 MS. TEMKIN: Dr. Socal?

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

1 remarks today.

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

1       substitutional insulins?

2                   DR. SOCAL:   In certain cases.

3                   MR. KOSLOWSKI:   In the same class?

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

1 positive aspects to patients and providers.

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

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

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

1 DR. HEHENBERGER: Okay.

2 MS. TEMKIN: Thank you.

3 DR. HEHENBERGER: Is this better?

4 MS. TEMKIN: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

11 In the largest continuous glucose dataset  
12 ever shared, this is in almost half a million people,  
13 500,000 users in 26 countries. The typical person  
14 with insulin spent 56% of the time in the range that  
15 we all have agreed is at least the right range for  
16 research to use, 70 to 180. Over half an hour a day  
17 was spent below 54. That is an incredibly dangerous  
18 level, and four hours a day were spent over 240. And  
19 these are people with CGM. We know that reality of  
20 global insulin users is far, far worse, and so a  
21 really small percentage of people with diabetes get to  
22 that over 70% place right now, and time and range is a

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

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

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

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

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

5 MS. CLOSE: That's okay.

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

10 MS. CLOSE: Thank you very much.

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

12 MS. YOUNG: My name is Leigh Young (ph).

13 Since I think there is a time limit, I'll have to make  
14 it quick. I don't know if it was insulin, but I think  
15 a lot of medicines, prescription, has been misused,  
16 abused and prescribed by doctors just as a tool in  
17 hospitals or rehab center, this type of setting. So,  
18 I'm just wondering, instead of saying you have to push  
19 the medication since it is in high demand, we had  
20 better examine instead of what's wrong that caused so  
21 much use of insulin or any other prescription. A lot  
22 of time I can see in the hospital or rehab center,

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

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

1 homeless, everything possible.

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

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

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

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

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

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

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

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

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

1 topic and in today's presentations.

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

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

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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

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SANDRA TELLER

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