Biosimilar insulin concepts

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Multiplicities of interest

- Consultant/advisor: Astra Zeneca, Merck, Novartis, Boehringer Ingelheim, Sanofi
- Stockholder: Johnson & Johnson, Humana, Novartis
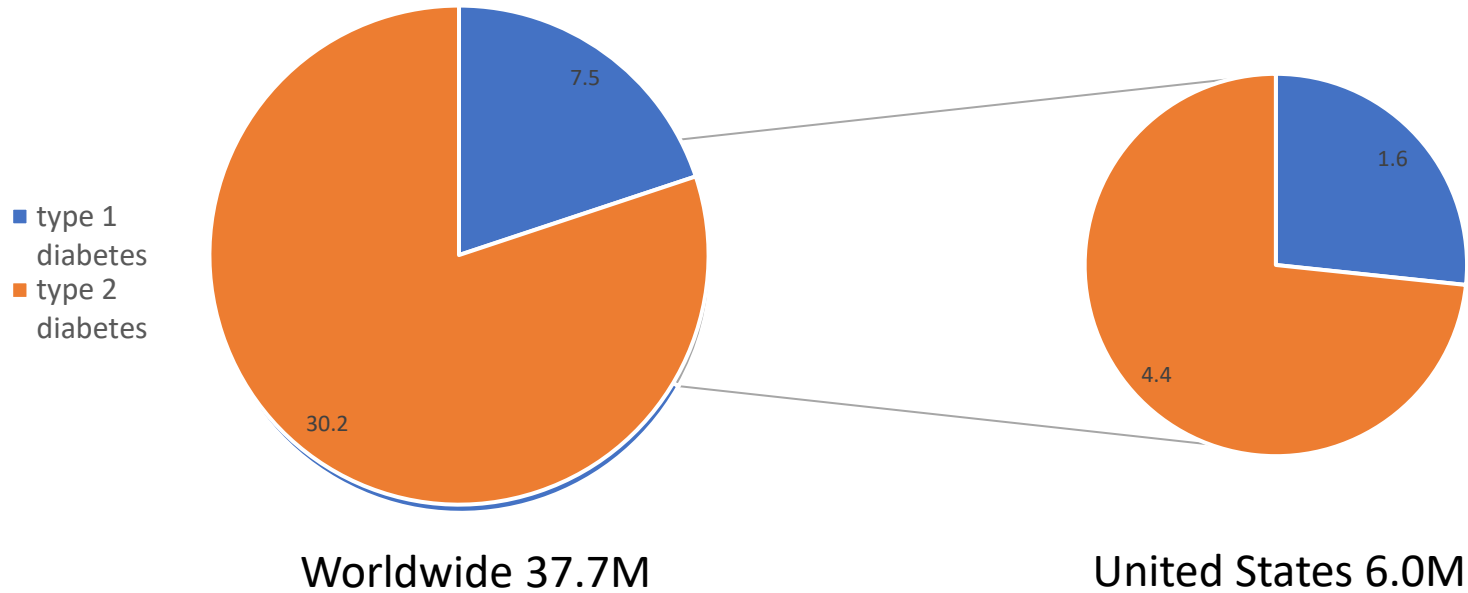
Biosimilar insulin concepts

- Rationale for encouraging biosimilar insulin development

- Issues with stressing interchangeability as criterion

- Effectiveness of existing biosimilar insulin preparations

- Immunogenicity as potential biosimilar insulin safety issue

- Other biosimilar insulin safety issues

Rationale for encouraging biosimilar insulin development
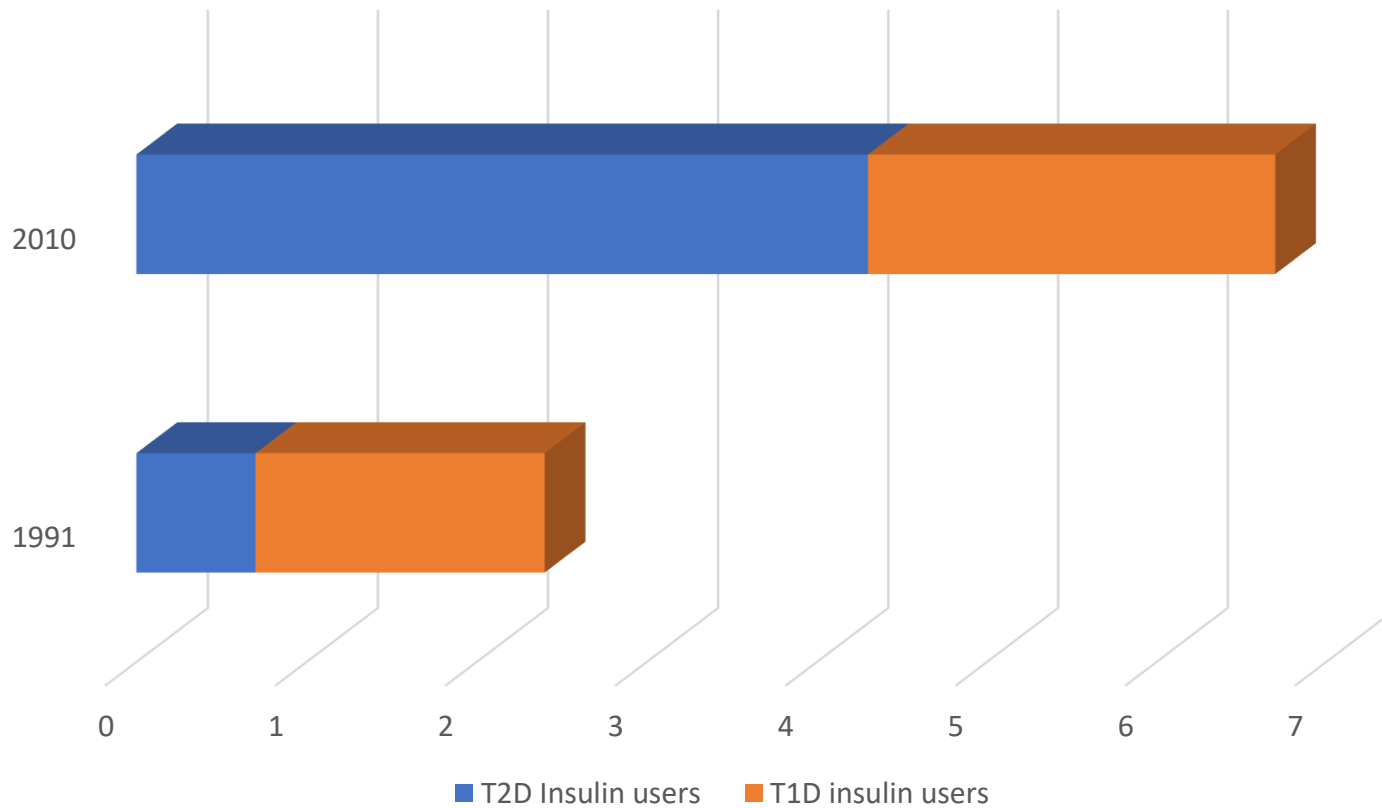
Biosimilar insulin concepts

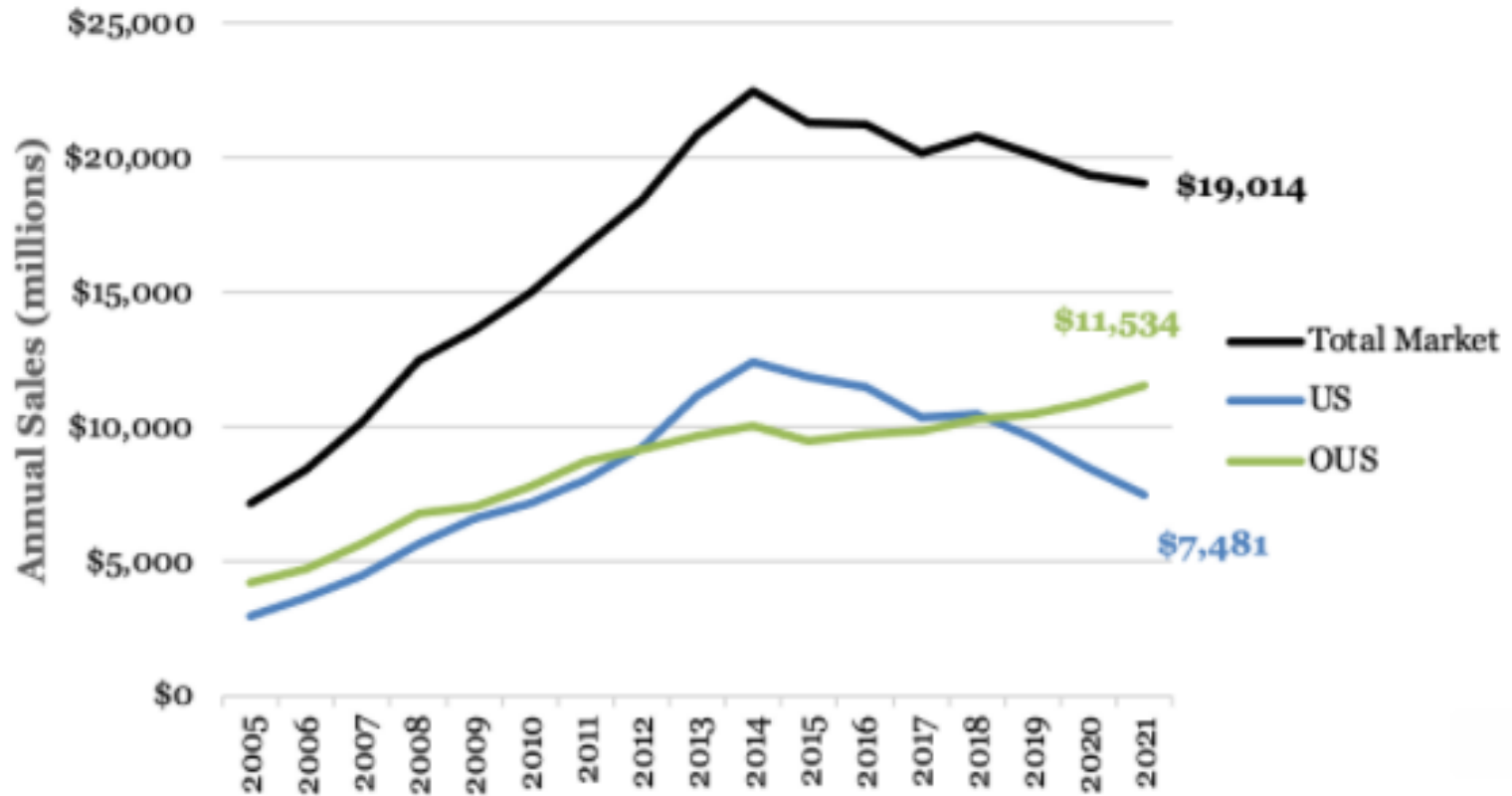# Insulin users, worldwide and US

Insulin-treated persons, millions

Worldwide 37.7M

United States 6.0M

Basu S et al. Lancet Diabetes Endocrinol. 2019 Jan;7:25-33; Mobasseri M et al. . Health Promot Perspect. 2020;10:98-115

UK insulin use 1995-2020

UK insulin users per 1000 adult population

Beran D et al, Diabetologia 2022

World insulin market, 2005-2020
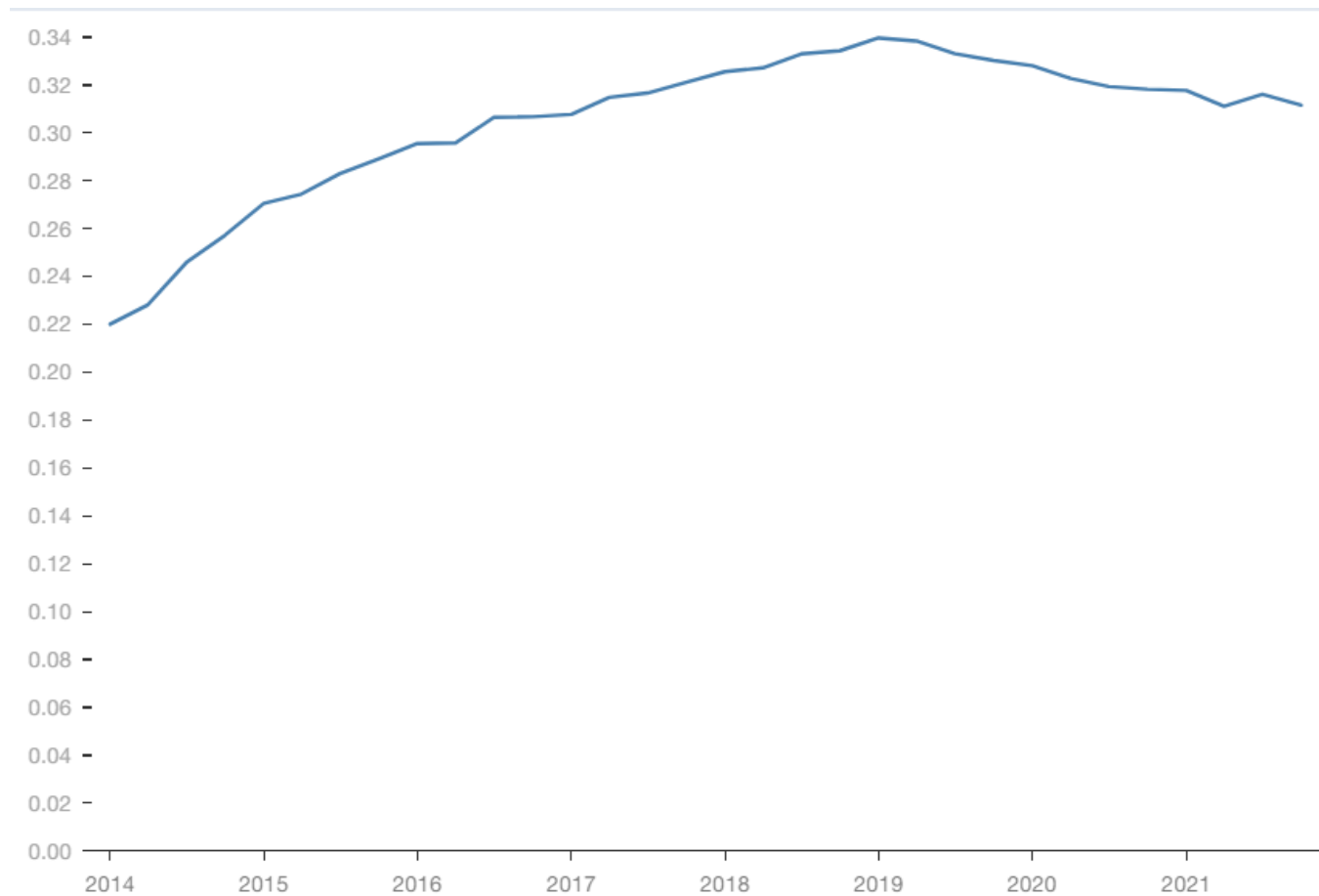

Close Concerns, 2022

US vs ex-US insulin cost 2018

Figure 2.9. Average Price per Standard Unit, by Insulin Timing Category, Selected Comparisons, 2018

OECD, Organisation for Economic Co-operation and Development
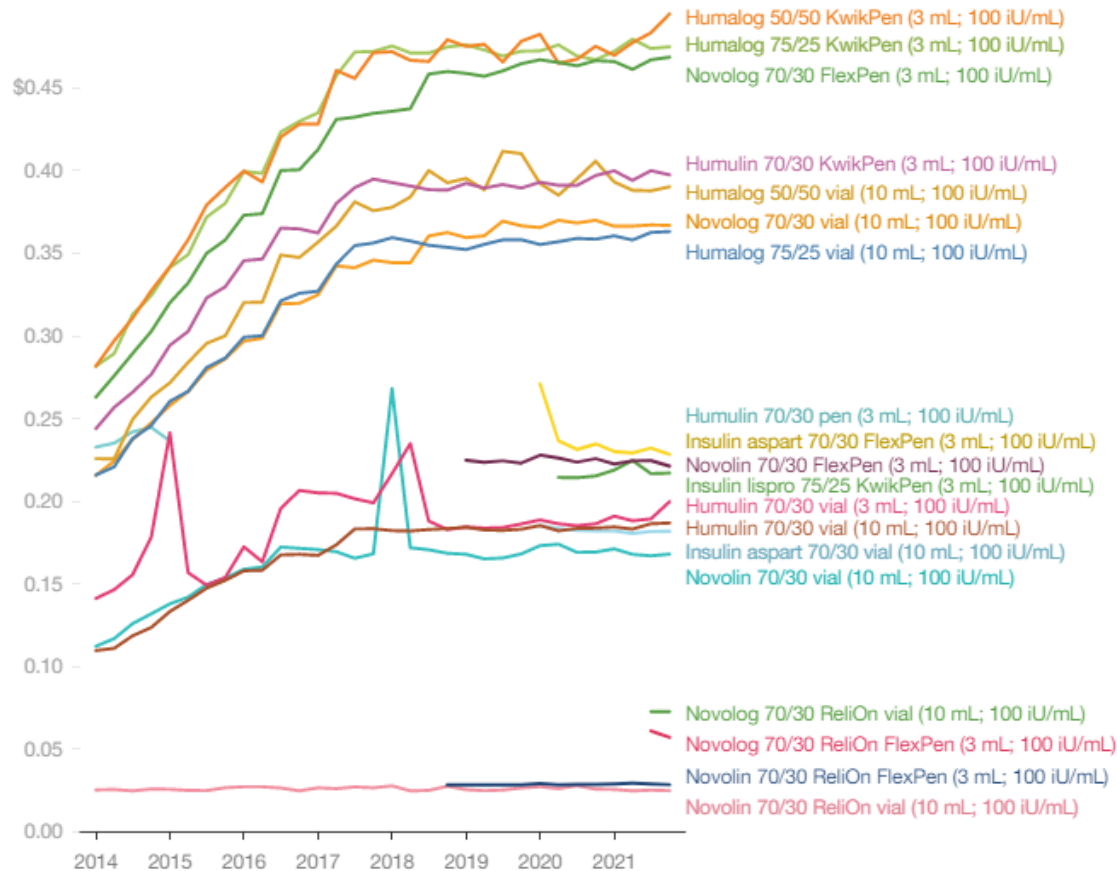

Mulcahy AW et al, www.rand.org/pubs/research_reports/RRA788-1.html

Average insulin cost, US, 2014-2021

Benita Lee, How Much Does Insulin Cost? https://www.goodrx.com/healthcare-access/research/how-much-does-insulin-cost-compare-brands

# Mixed insulin cost, US, 2014-2021

Benita Lee, How Much Does Insulin Cost? https://www.goodrx.com/healthcare-access/research/how-much-does-insulin-cost-compare-brands
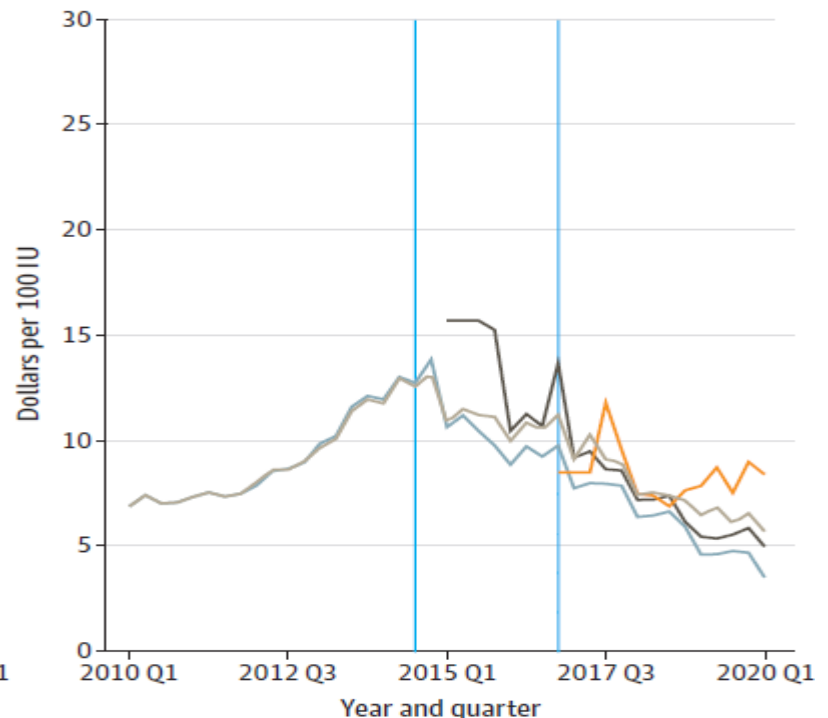
List Price and Estimated Net Price* of Insulin Glargine Products

❖*from the SSR Health Drug Database, containing quarterly list prices and estimates of net prices after rebates*

Levy J et al. JAMA Intern Med 2021;181:1405-6
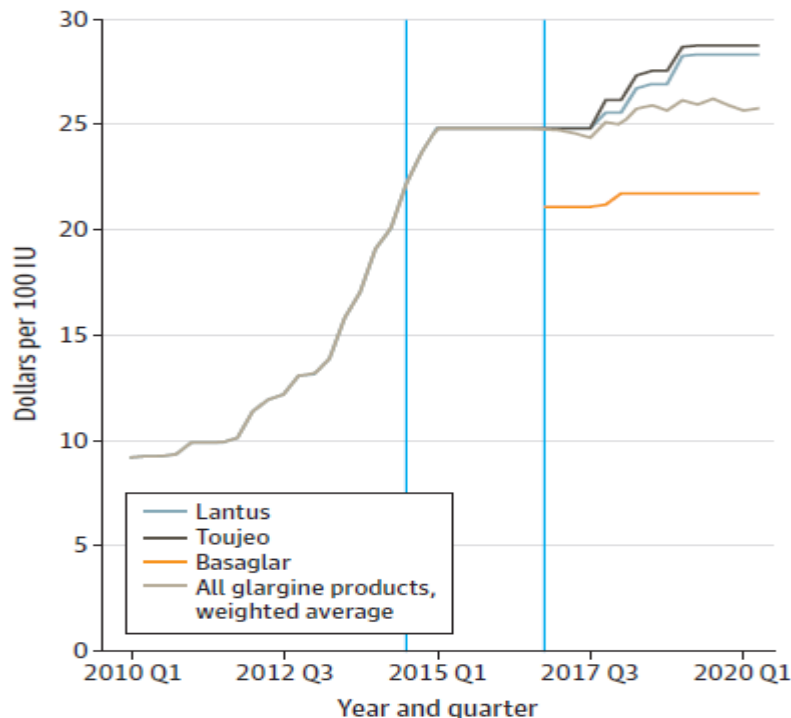
Insulin analog retail cost, US

	Name	Manufacturer	Cost/ 10ml	price/unit (vial)	Cost/ 5x3ml	price/unit (pen)
insulin aspart	Novolog	NovoNordisk	$369.41	$0.37	$593.00	$0.40
insulin aspart	ReliOn	Walmart	$72.88	$0.07	$85.88	$0.06
insulin aspart		Sanofi				
insulin lispro	Humalog	Lilly	$274.70	$0.27	$530.40	$0.35
insulin lispro	Lilly insulin	Lilly	$43.43	$0.04	$78.27	$0.05
insulin lispro	Admelog	Sanofi	$270.48	$0.27	$405.34	$0.27
insulin glargine	Lantus	Sanofi	$375.00	$0.38	$454.00	$0.30
insulin glargine	Basalglar	Lilly			$326.30	$0.22
glargine-yfgn	Semglee	Mylan	$269.38	$0.27	$404.00	$0.27

From goodrx.com and additional google searches, March 18, 2022

Insulin analog retail cost per unit, US

Mean adult dose, type 1, 50 U/day, type 2, 75 U/day (range <10 to >400 U/day); at mean $0.24/U, cost/year: 10U $874, 20U $1747, 50U $4368, 100U $8735

From goodrx.com and additional google searches, March 18, 2022

The new generic insulin isn't as cheap as you thought

- Bob Herman

The new generic insulin isn't as cheap as you thought

Insulin — the new battleground for drug pricing

Outrage over the cost of insulin is driving drug-pricing reform. Industry must do more to support patients dealing with spiraling out-of-pocket costs for biotech medicines.

Check for updates

editorial

The new generic insulin isn't as cheap as you thought

Insulin — the new battleground for drug pricing

Outrage over the cost of insulin is driving drug-pricing reform. Industry... with spiraling out-of-pocket costs for biotech medicines.

Check for updates

editorial

...support patients dealing

	Average annual insulin price per patient, United States
2014	$3,819
2019	$5,917

The new generic insulin isn't as cheap as you thought
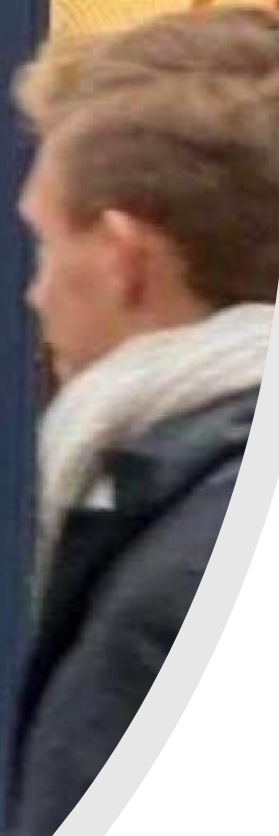
Insulin —

Outrag...

BMJ Global Health **Production costs and potential prices for biosimilars of human insulin and insulin analogues**

We estimated that, if there were a competitive biosimilar market, treatment with biosimilar insulins could cost US$72–133 per year or less.

...port patients dealing

2014	$3,819
2019	$5,917

Definitions: 3 levels of similarity

- Follow-on biologic - sufficiently similar to FDA-approved biologic to permit reliance on existing scientific knowledge about safety/effectiveness (determined on case-by-case basis).

- Biosimilar - "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and "no clinically meaningful differences from reference product in safety, purity, and potency."

- Interchangeable expect the same clinical result as reference product in any given patient and "the risk in terms of safety or diminished efficacy of alternating or switching between use of the [biosimilar] and the reference product is not greater than the risk of using the reference product without such alternation or switch."

Fonseca, Bloomgarden et al Endocr Pract 2017

Issues with stressing interchangeability as criterion

Biosimilar insulin concepts

"Insulin is a remedy primarily for the wise and not for the foolish, whether they be patients or doctors."

Elliot Joslin, 1923

Is the biologic action of existing insulin preparations consistent?

Table 2. Pharmacokinetic/pharmacodynamic characteristics of basal insulin analogs.

	Peak (hours)	Duration of action (hours)	Half-life (hours)	Dosing frequency
NPH Insulin	4–8	8–14	4	Once or twice daily
Insulin detemir 100 U/mL	4–7	Up to 24	5–7	Once or twice daily
Insulin glargine 100 U/mL	8–12	Up to 24	12	Once daily
Insulin glargine 300 U/mL	Close to peakless	>24	19	Once daily
Insulin degludec	Close to peakless	26+	25	Once daily

Goldman et al. Current Medical Research and Opinion, 2017;33:1821-1831

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Insulin glargine 300 U/mL	Close to peakless		19	Once daily
Insulin degludec	Close to peakless	26+	25	Once daily

- The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH insulin, and 24 hours (range: 10.8 to >24.0 hours for insulin glargine (Lantus PI http://products.sanofi.us/lantus/lantus.pdf)

Goldman et al. Current Medical Research and Opinion, 2017;33:1821-1831

Is a given individual's insulin requirement consistent? T1D

12-week closed loop insulin requirement relative to baseline n=32


Ruan Y et al. Diabetes Care 2016;39:830-2
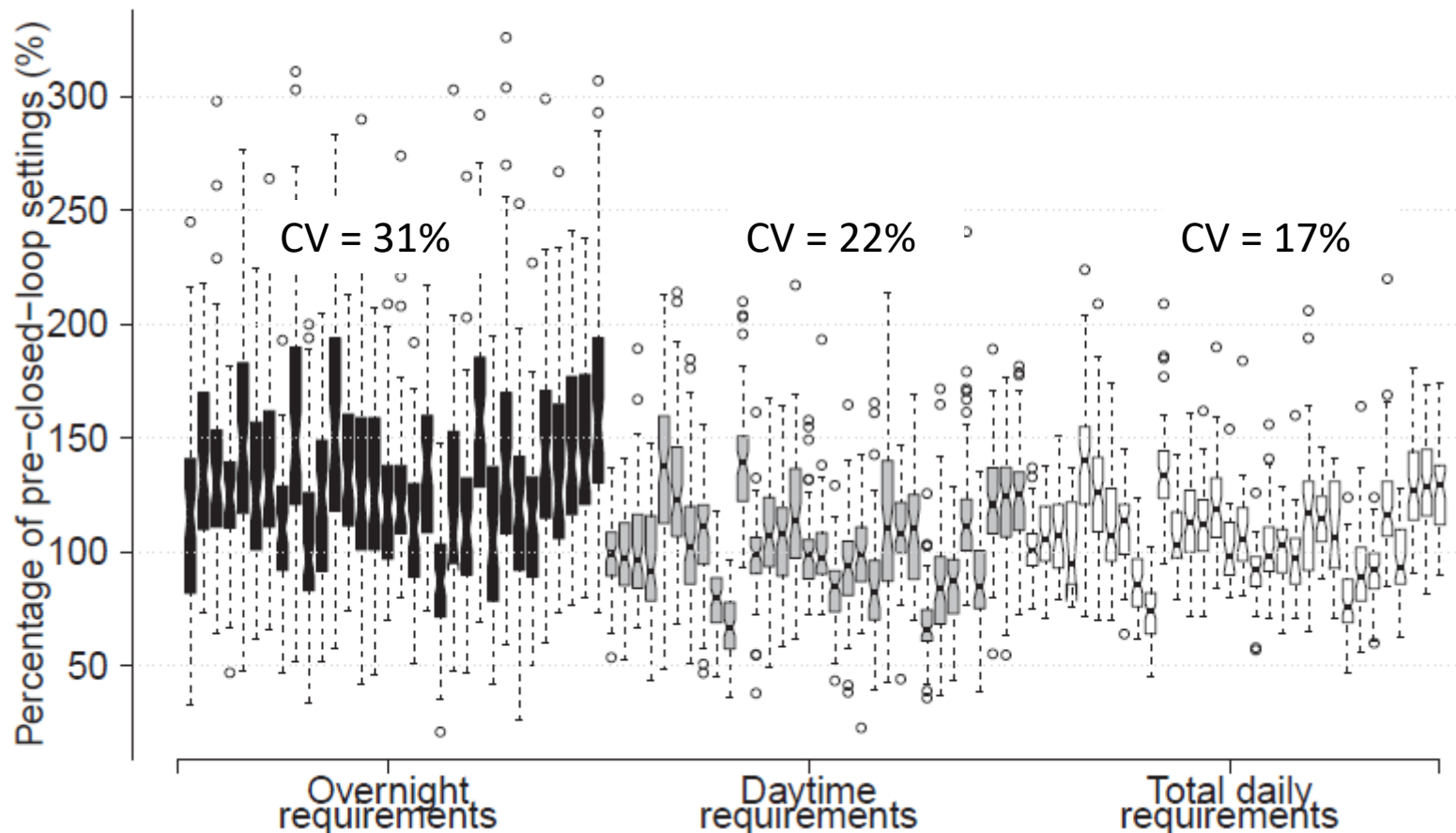
Is a given individual's insulin requirement consistent? T2D

CV of 4-15 day closed loop insulin requirement n=67 hospitalized persons

Boughton CK et al Diabetes Obes Metab. 2021;23:1978–1982
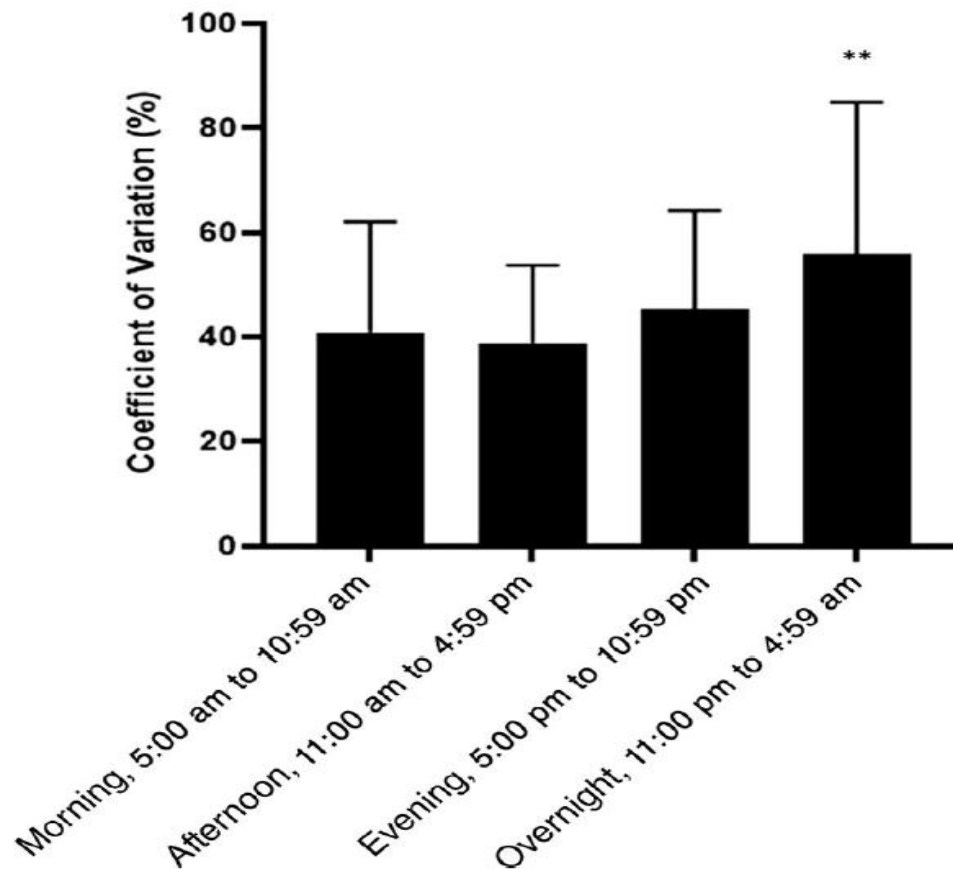
Fasting SMBG variability with maintenance insulin regimen

SMBG SD tertiles of persons receiving fixed glargine-100 or degludec doses after titration
T1D (FBG 7.5 DGLDC; 8.3 GLA) low 3[ile] 0.016-0.367, mid 3[ile] 0.367-0.463, high 3[ile] 0.464-1.050
T2D (FBG 6.1 mM/L):low 3[ile] 0.013-0.116, mid 3[ile] 0.117-0.190, high 3[ile] 0.191-0.589

DeVries JH et al Diabetes Obes Metab. 2019;21:622-630
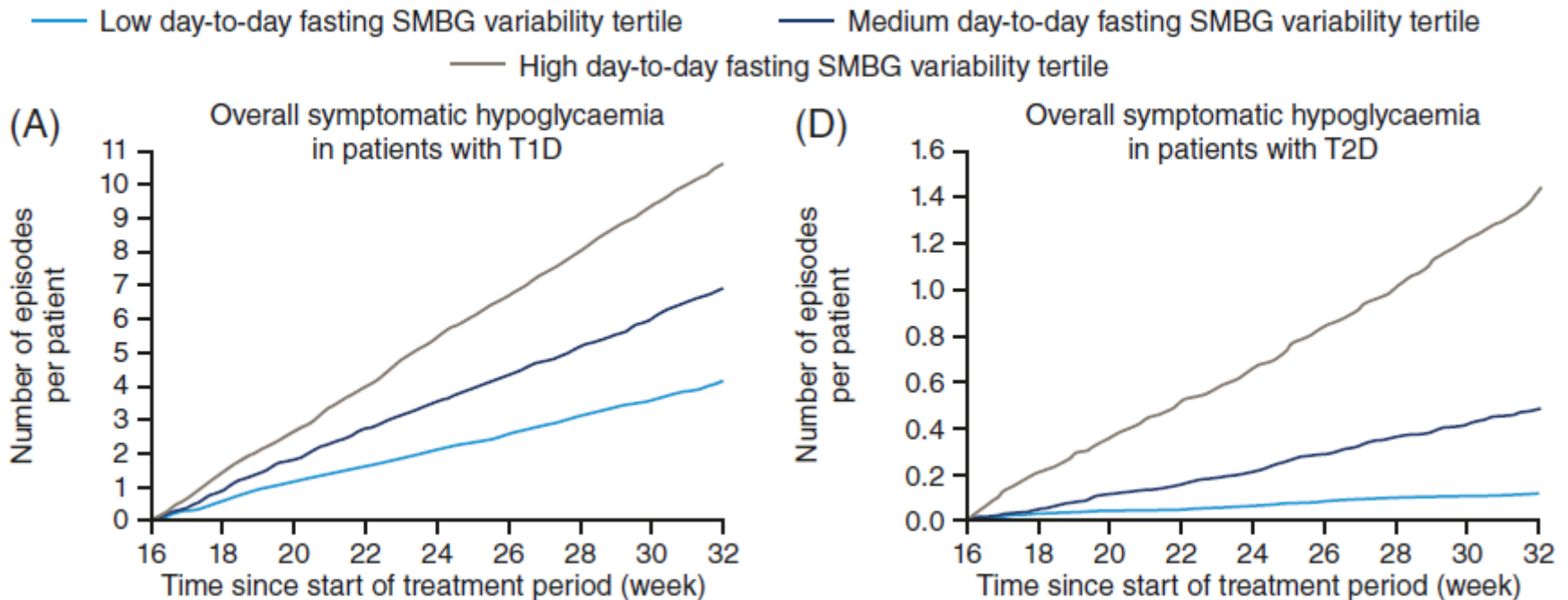
Effectiveness of existing biosimilar insulin preparations

Biosimilar insulin concepts

How to show biosimilar effectiveness?

FDA Works to Ensure Smooth Regulatory Transition of Insulin and Other Biological Products
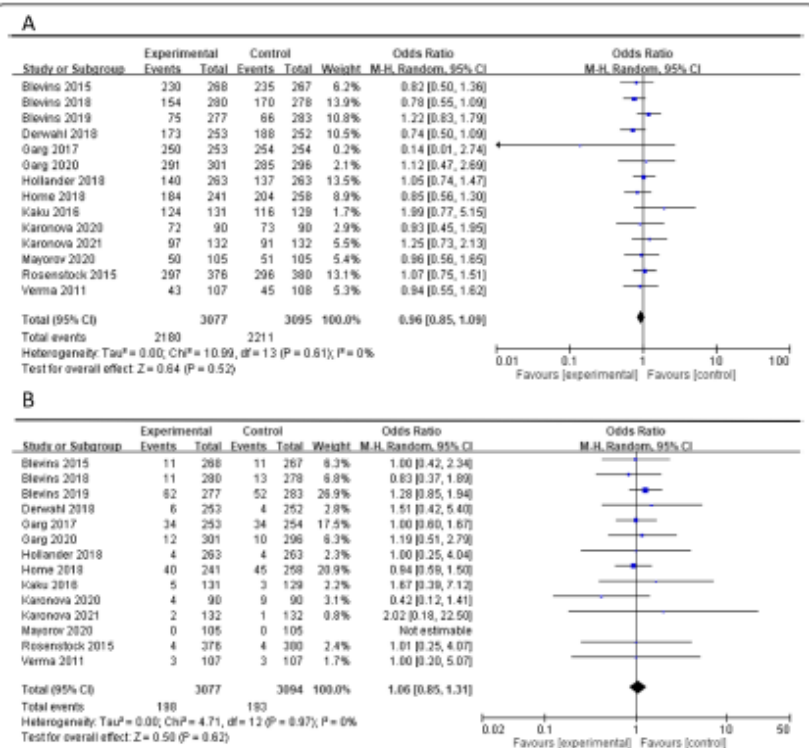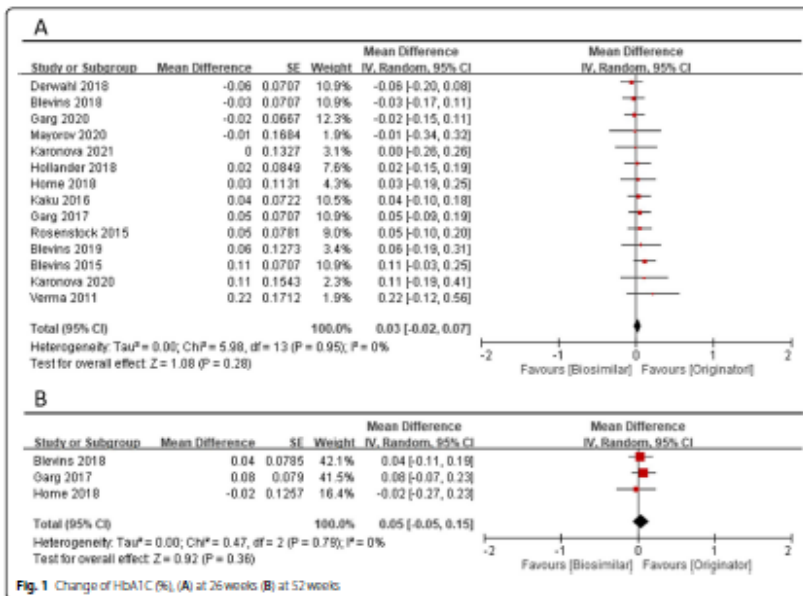
- "Getting safe and effective biosimilar and interchangeable products approved will help ensure that the market is competitive, and patients may have more affordable access to the treatments they need."

FDA News Release, February 20, 2020

Insulin biosimilar efficacy and safety meta-analysis

HbA1c (A) 24-wks (B) 52-wks

Hypoglycemia (A)

Severe Hypoglycemia (B)

Fig. 1 Change of HbA1C (%), (A) at 26 weeks (B) at 52 weeks

Fig. 5 Hypoglycemia (A) Hypoglycemia ≥1 event (B) Severe hypoglycemia

Yang LJ et al. BMC Endocrine Disorders (2022) 22:35l,

Biosimilar SAR342434 Insulin Lispro

- SORELLA 1 multicenter, 2-arm, parallel-group, open-label phase 3 study in T1DM treated with MDI of insulin lispro/aspart + GLA-100 randomized to SAR-Lis (n=248) or Ly-Lis (n=252) with GLA-100

- SORELLA 2 similar T2D study with SAR-Lis (n=245) or Ly-Lis (n=248)

- No differences in lispro or glargine doses, A1c, FPG, SMBG, hypoglycemia, weight change

- Anti-insulin Ab baseline positive 51.4% of T1D, 22.7% of T2D taking insulin prior to study, among negative group, 22.6-24.2% of T1 and 14.5-18.8% of T2 became positive and in positive group ~12-20% had ↑Ab, insulin doses were comparable, not influenced by Ab development or ↑, no association with hypoglycemia

- No switch study reported

Garg S et al Diabetes Technol Ther 2017 19 516-526;
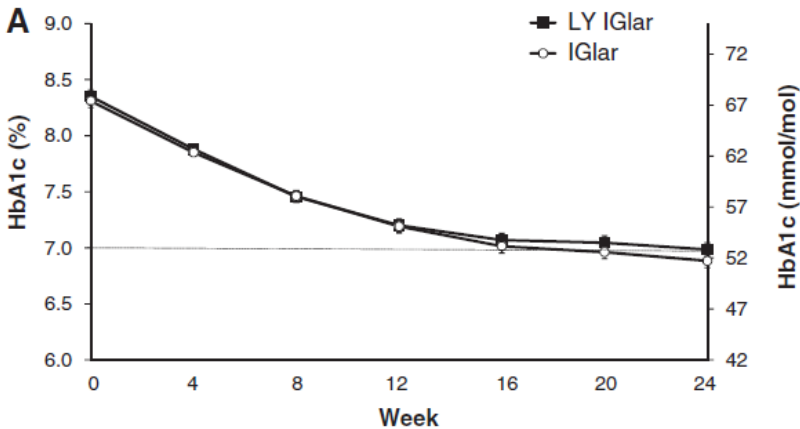Home P et al Diabetes Technol Ther 2018 20 160-170

Biosimilar SAR341402 Insulin Aspart

- N=597 insulin aspart or lispro-treated T1D or T2D randomized to NN-aspart vs SAR341402 – no difference in hypoglycemia or insulin Ab formation
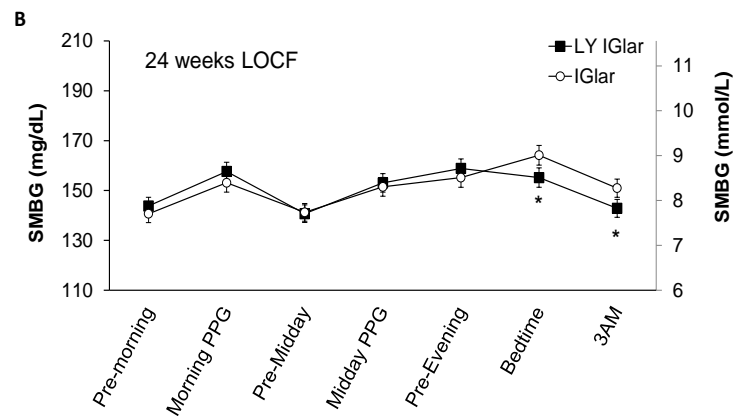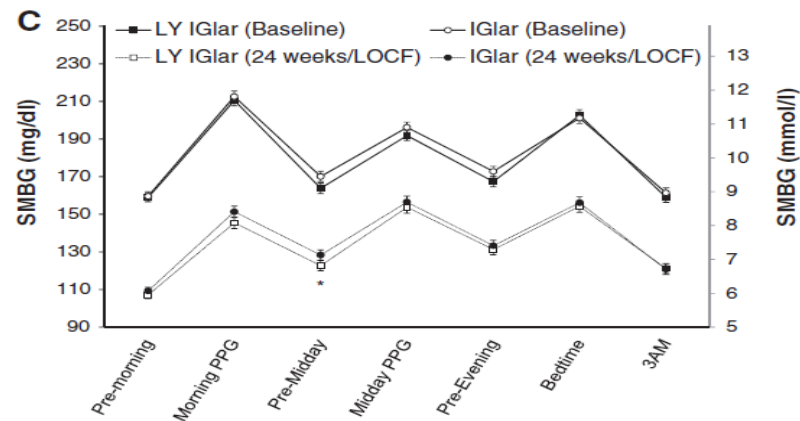
HbA1c change

Prandial insulin

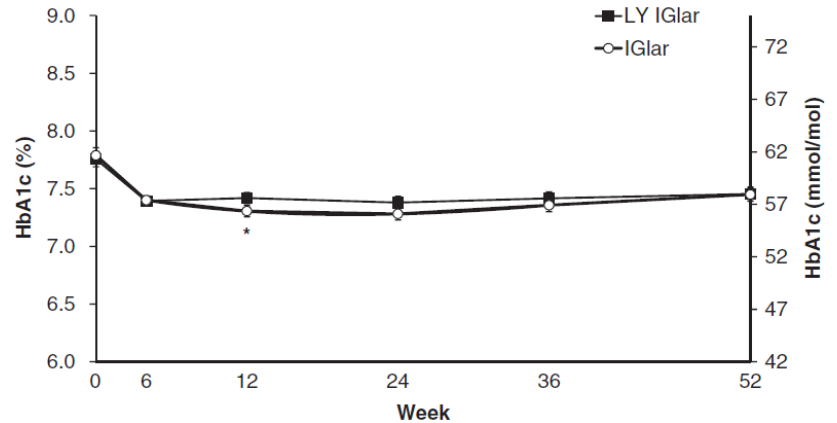Shah V et al Diabetes Ther (2021) 12:557–568
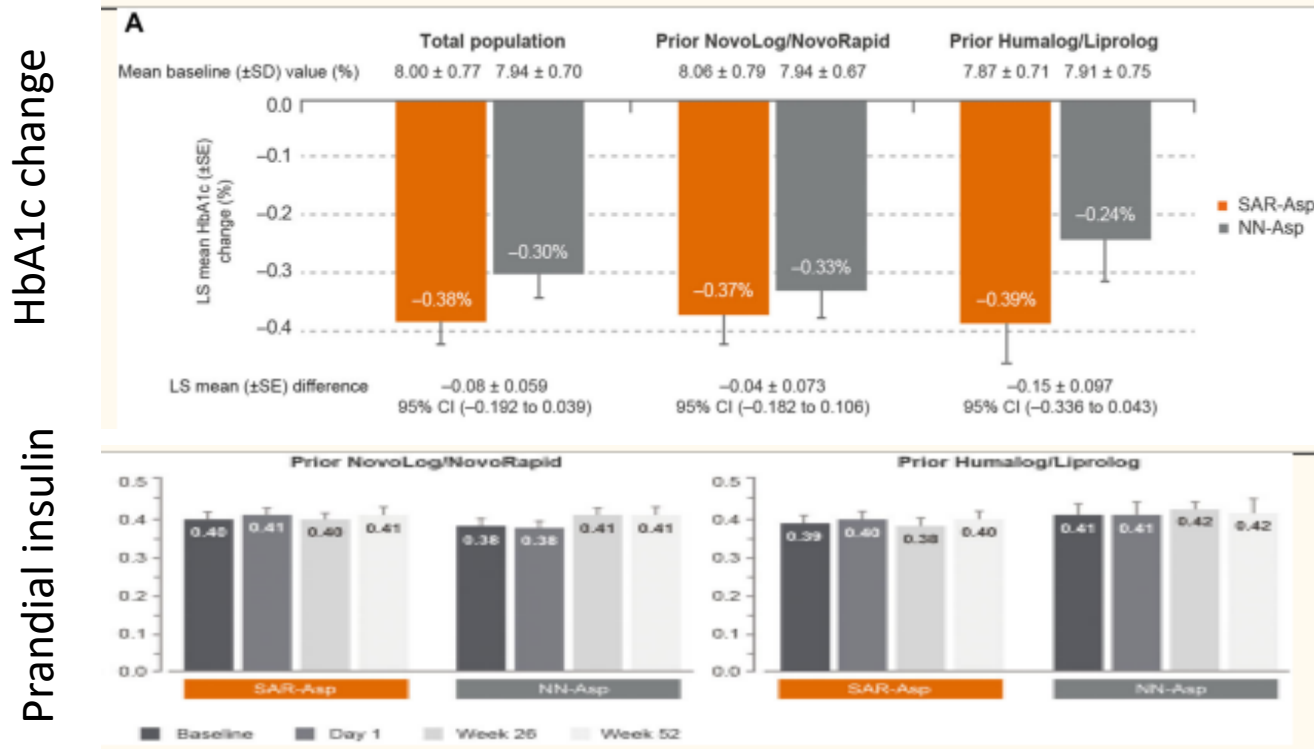
Biosimilar LY2963016 insulin glargine

T2D

T1D

Rosenstock J et al Diabetes Obes Metab. 2015 Aug;17(8):734-41;
Blevins T et al Diabetes Obes Metab. 2015 Aug;17(8):726-33

Biosimilar Basalin Insulin glargine

- 100 T2D on stable glargine dose >0.2U/kg/day treated with blinded 2-day plus 2-day crossover from glargine-Basalin to glargine-Lantus or vice versa with Medtronic continuous glucose monitoring

Table 3 Parameters of glucose variation calculated from CGMS

Glargine	24hMBG (mmol/L)	24hSDBG (mmol/L)	24hMAGE (mmol/L)	24hNGE (number)
Basalin	9.35 ± 2.39	2.17 ± 0.88	5.22 ± 2.71	1.99 ± 1.716
Lantus	9.67 ± 2.75	2.24 ± 0.96	5.50 ± 2.69	2.06 ± 2.119
p	0.378	0.563	0.474	0.797

Glargine	1 h before breakfast MBG (mmol/L)	1 h before lunch MBG (mmol/L)	1 h before dinner MBG (mmol/L)	10 P.M. to 6 A.M. MBG (mmol/L)
Basalin	7.55 ± 2.10	8.95 ± 3.19	9.01 ± 2.81	8.75 ± 2.48
Lantus	7.73 ± 2.38	9.26 ± 4.01	9.33 ± 3.45	8.79 ± 2.77
p	0.562	0.559	0.489	0.905

Li HQ et al J Endocrinol Invest (2018) 41:179-184
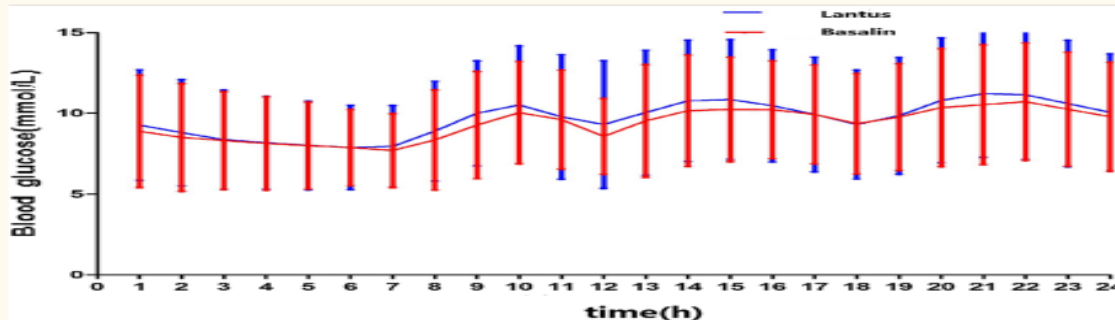
Biosimilar Ezelin (Basalin) Insulin glargine

- 133 T2D with baseline HbA1c 9.7% randomized to EZL vs LAN x 6 mos, insulin dose at study end 0.28 vs 0.25 U/kg, weight gain 2.15 vs 20.4 Kg, minimal hypoglycemia and immunogenicity – no difference


Tarigan T et al Diabetes Metab Syndr Obes 2021 14 107
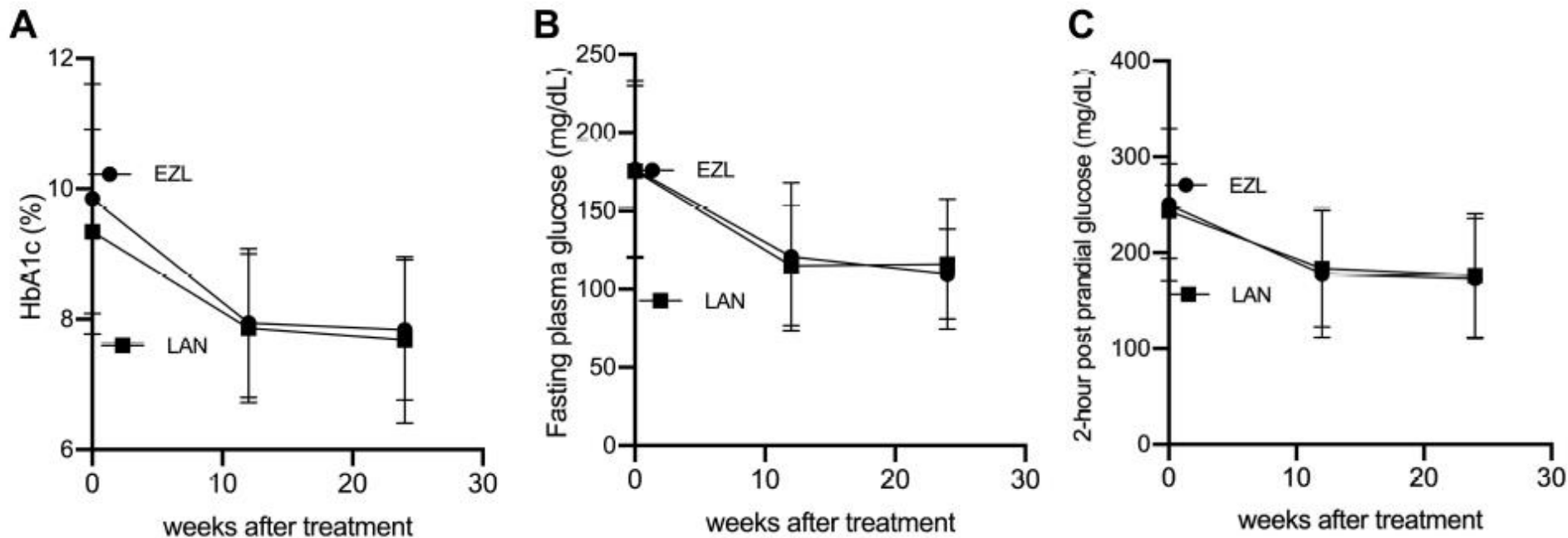
How to show interchangeability?

- "a switching study or studies should assess the impact of switching or alternating between use of the proposed interchangeable product and the reference product on clinical PK and PD"

FDA interchangeability guidance, FDA-2017-D-0154-0061
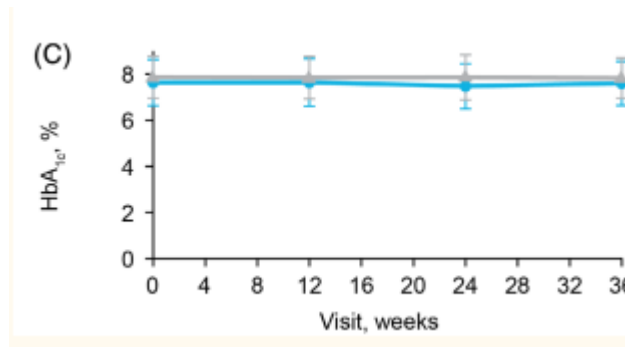
Biosimilar MYL-1501D Insulin glargine

- 113 C-peptide-negative T1D had three 30-hr Biostator clamp studies 48 hrs post-last basal insulin, 24 hr post-NPH, 1-6 hr baseline regular insulin±glucose infusion to stabilize at 5.5 mM/L, administered 0.4U/kg MYL-1501D, European and US formulations of insulin glargine
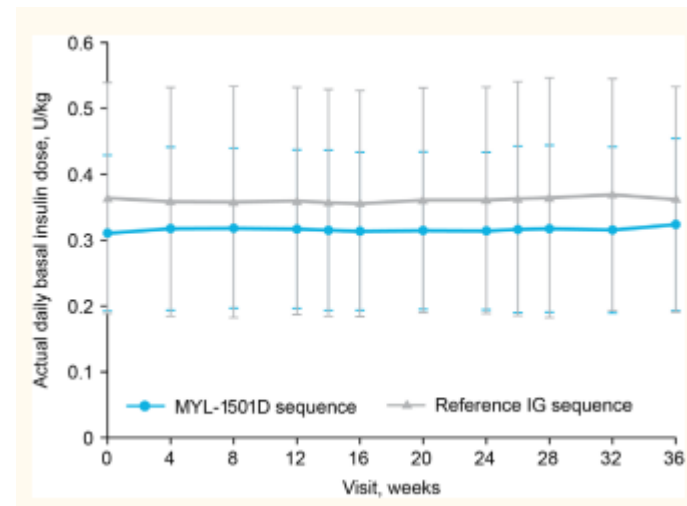

Heise T et al Diabetes Obes Metab 2020 22 521-529
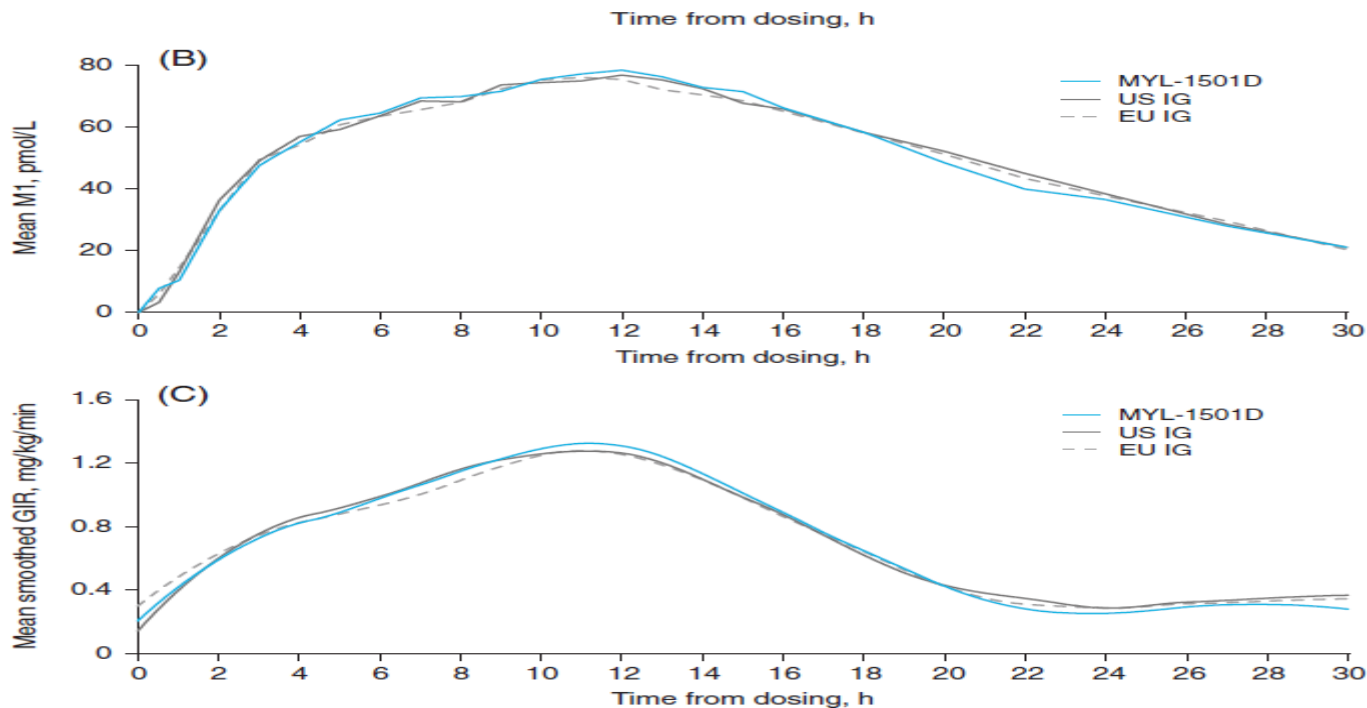
Biosimilar MYL-1501D Insulin glargine: INSTRIDE 3 phase 3 switch study

127 T1D treated with insulin glargine randomized to continue GLA or use MYL-1501D x12 wks, GLA x12 wks, and then MYL-1501D x12 wks

HbA1c

Daily basal insulin dose

In T1D 24 weeks, (n=558) and T2D (52 weeks, n=560), MYL-1501D and reference insulin glargine had similar immunogenicity profiles

Blevins T et al Diabetes Obes Metab. 2020;22:365-372;
Sun et al. BMC Endocrine Disorders (2021) 21:129

# Biosimilar MYL-1501D Insulin glargine: new nomenclature

Semglee® (henceforth, referred to as insulin glargine-yfgn) was developed by Biocon Biologics and is distributed by Viatris (formerly Mylan). Insulin glargine-yfgn is a longacting recombinant human insulin analog approved by the FDA as a biosimilar of reference insulin glargine on June 11, 2020. As simply a biosimilar, Semglee®'s nonbranded name is insulin glargine U100. But as an interchangeable biosimilar, a suffix has been added to the nonproprietary name; in this case, Semglee® is referred to as "insulin glargine-yfgn U100."

Matli MC et al, Journal of Diabetes Science and Technology 2021

Immunogenicity as potential safety issue

Biosimilar insulin concepts

Insulin biosimilar immunogenicity meta-analysis

Anti-insulin Ab

Fig. 6 Anti-insulin antibody positivity (%)

Yang LJ et al. BMC Endocrine Disorders (2022) 22:35l,
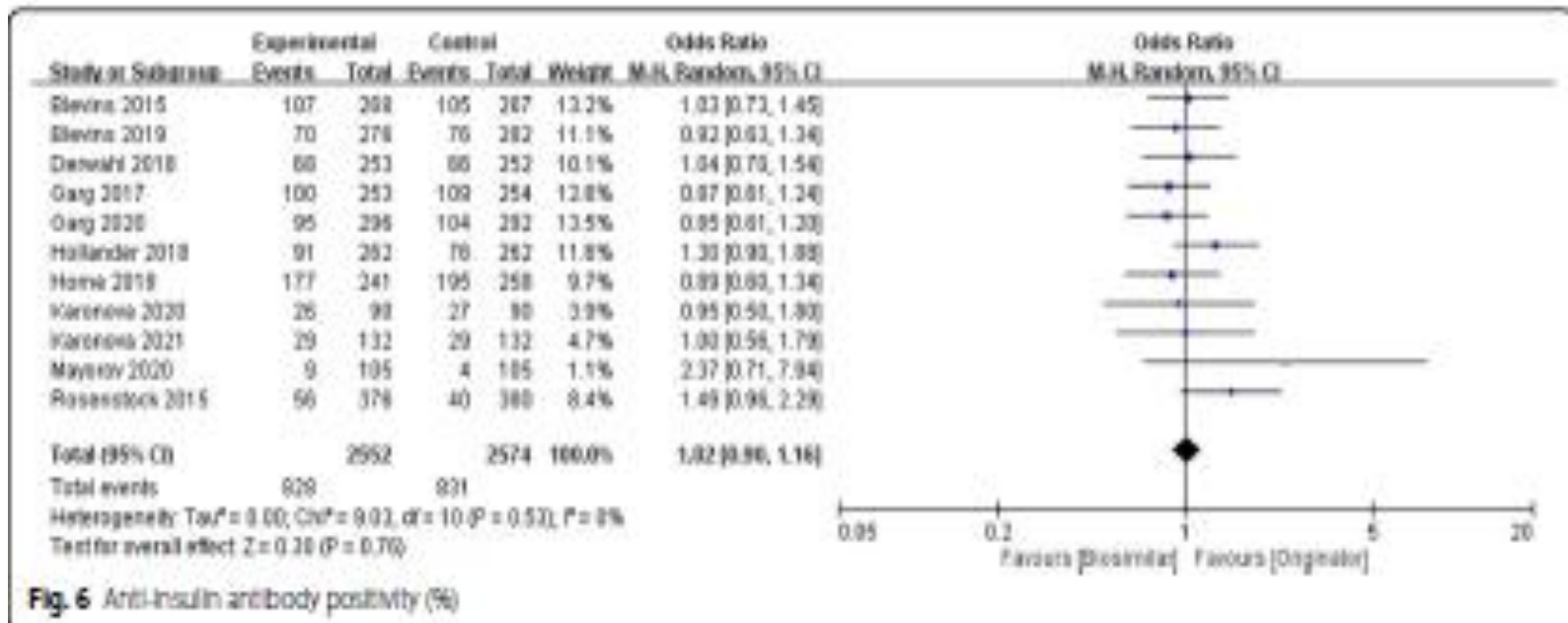
Immunogenicity?

CASE REPORT

Hypersensitivity reaction to a biosimilar insulin glargine

Héctor GARCÍA-NARES,[1] María Isabel LEYVA-CARMONA,[2] Neftalí PÉREZ-XOCHIPA[1] and Erwin CHIQUETE[3]

Departments of [1]Endocrinology, and [2]Immunology, Regional Hospital 1st of October, ISSSTE, and [3]Department of Neurology, The "Salvador Zubirán" National Institute of Medical Sciences and Nutrition, México, DF, México

"In Mexico, two insulin glargine formulations are commercially available... Lantus® ... and a noninnovator version, Bonglixan® ... manufactured and distributed in Mexico by Landsteiner Scientific (Toluca, Mexico)... Some differences in secondary structure were found." [Escobedo-Moratilla A et al. J Diabetes Sci Technol. 2016;10:616–617.]

Other biosimilar insulin safety issues

Biosimilar insulin concepts

Accessibility of Low-cost Insulin From Illegitimate Internet Pharmacies: Cross-sectional Study

Benjamin Penley[1], PharmD; Lana Minshew[2], PhD; Hui-Han Chen[1], MHS; Stephen Eckel[1], MHA, PharmD; Sachiko Ozawa[1,3], MHS, PhD

- "The ease of access to low-cost insulin through illegitimate internet pharmacies calls for urgent attention. Illegitimate internet pharmacies place patients at risk of poor-quality medications and subpar pharmacy services, resulting in adverse events."

Biosimilar Insulin Analogs: Role of Devices

Feature	Explanation
Reusable or disposable	Possible implications in terms of patient preference and, potentially, costs
Unique color coding and tactile identifiers	Important for ease of identification to prevent confusion between different devices/insulin
Dose range and deliverable dose	Larger maximum doses may be preferable in patients who take large insulin doses, whereas children may benefit from the ability to select half-unit increments
Dose capacity/volume (i.e., number of units available per device)	Most currently available models are either prefilled with 3 mL (300 U) of insulin or are designed for use with 3-mL cartridges, which may be less convenient for patients requiring higher doses
Dose accuracy	Required accuracy of delivering the dose that is set to be administered
Dial back	Allows readjustment if dose is dialed incorrectly
End-of-content feature	Prevents dosing errors by not allowing a dose to be dialed which is greater than the remaining insulin in the device
Low injection force; reduced button extension; autoinjection (spring assisted) delivery	Impact on comfort and ease of use, and may be of particular importance to patients with impaired hand function
Auditory/tactile feedback (e.g., confirmatory click on full delivery)	May be of particular importance for patients with visual impairment
Robustness against environmental impact	The device should meet requirements during or after different use scenarios (e.g., temperature, humidity, after free fall)
Electronic memory function	May be particularly useful for patients prone to omitting or forgetting their insulin injections

Heinemann L et al Diabetes Technol Ther 2017;19:79=84

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"As people with diabetes become familiar with a particular pen device, changing the pen might be more of a concern for them than the change in the insulin analog product."

Heinemann L et al Diabetes Technol Ther 2017;19:79=84

Summary: Biosimilar insulin concepts

- Rationale for encouraging biosimilar insulin development

- Issues with stressing interchangeability as criterion

- Effectiveness of existing biosimilar insulin preparations

- Immunogenicity as potential biosimilar insulin safety issue

- Other biosimilar insulin safety issues