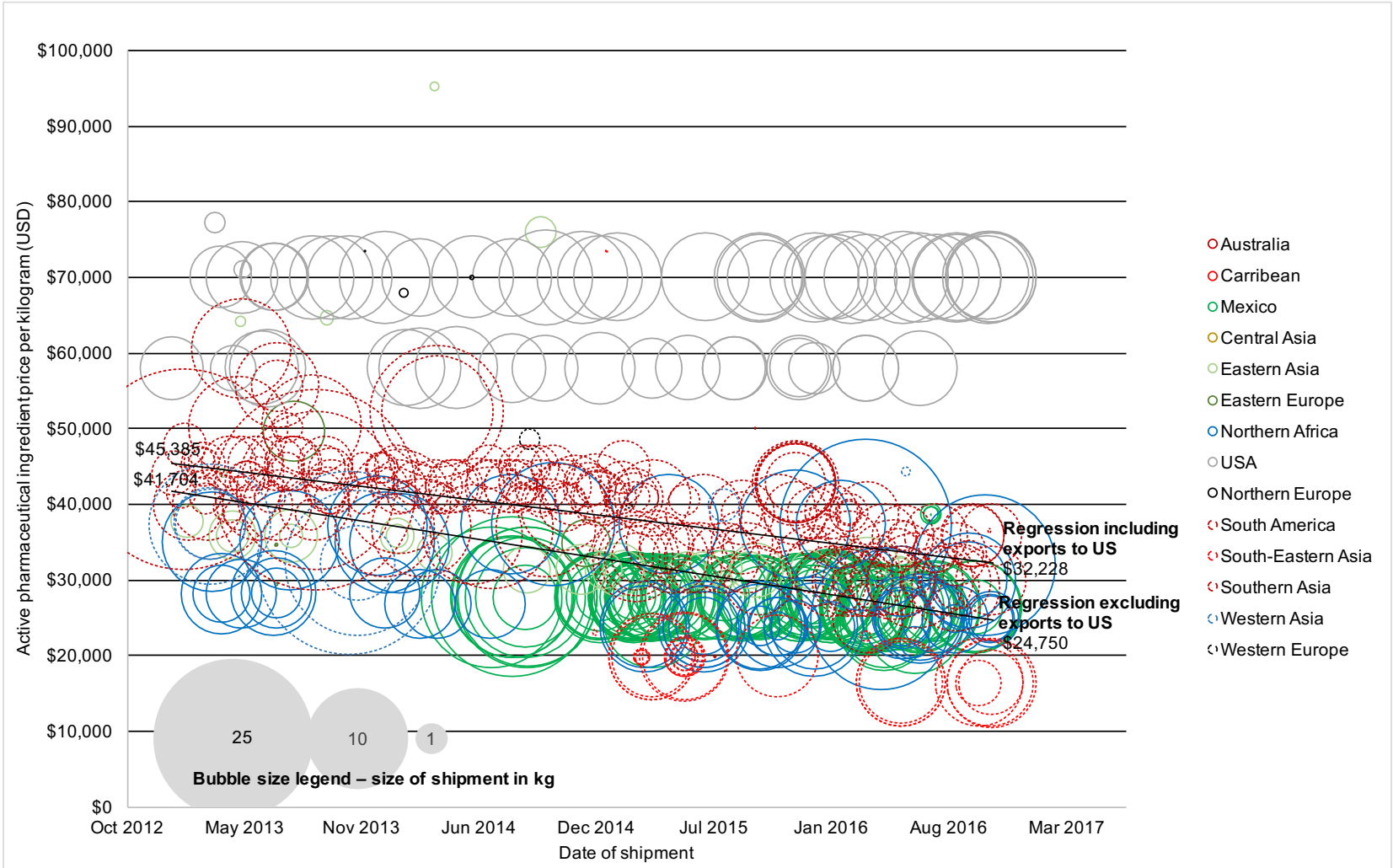
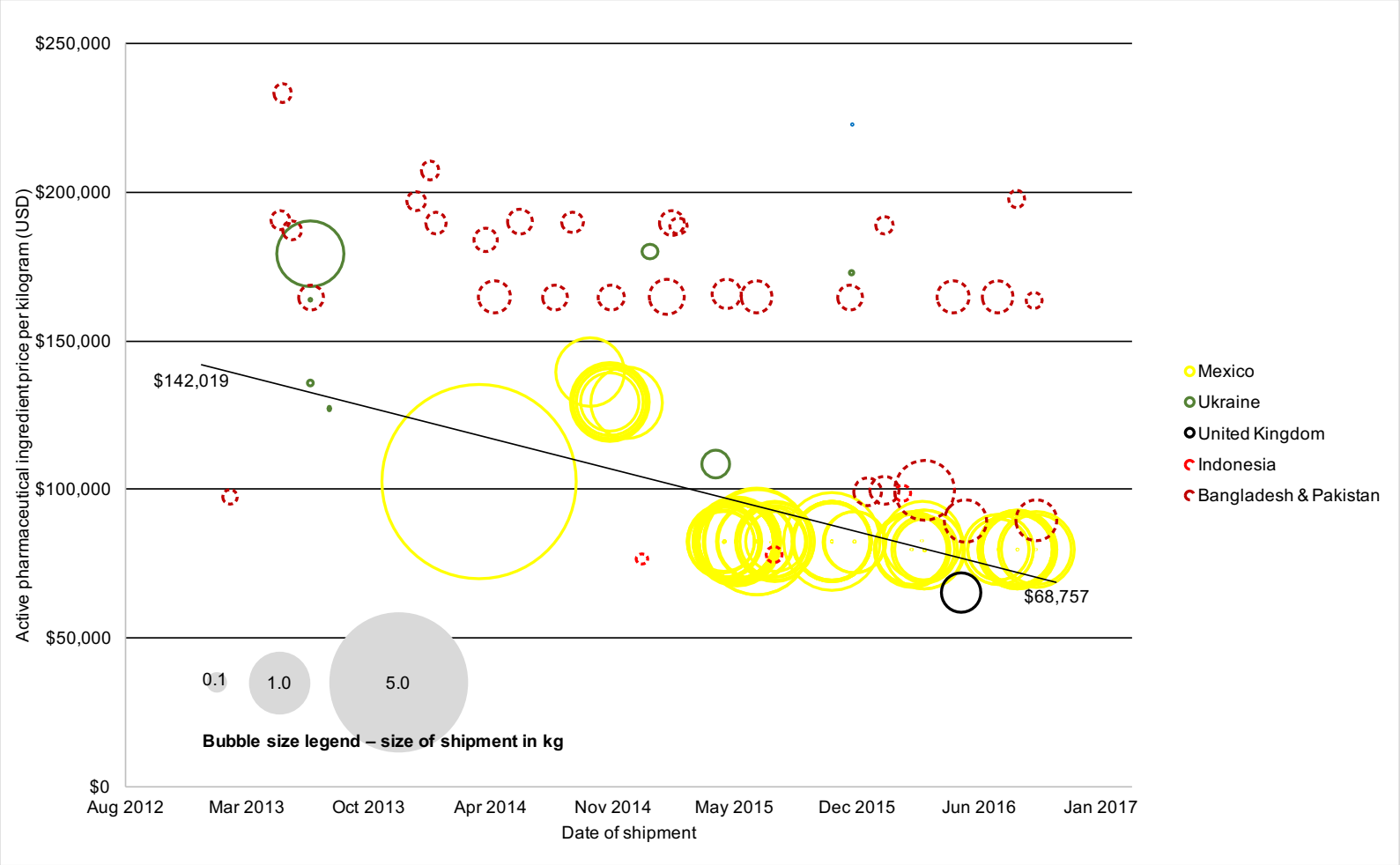
Supplementary material

Supplementary figure 1. Cost per kilogram (USD) and linear regression of regular human insulin API exported from India 1 Jan 2013 to 1 Nov 2016.



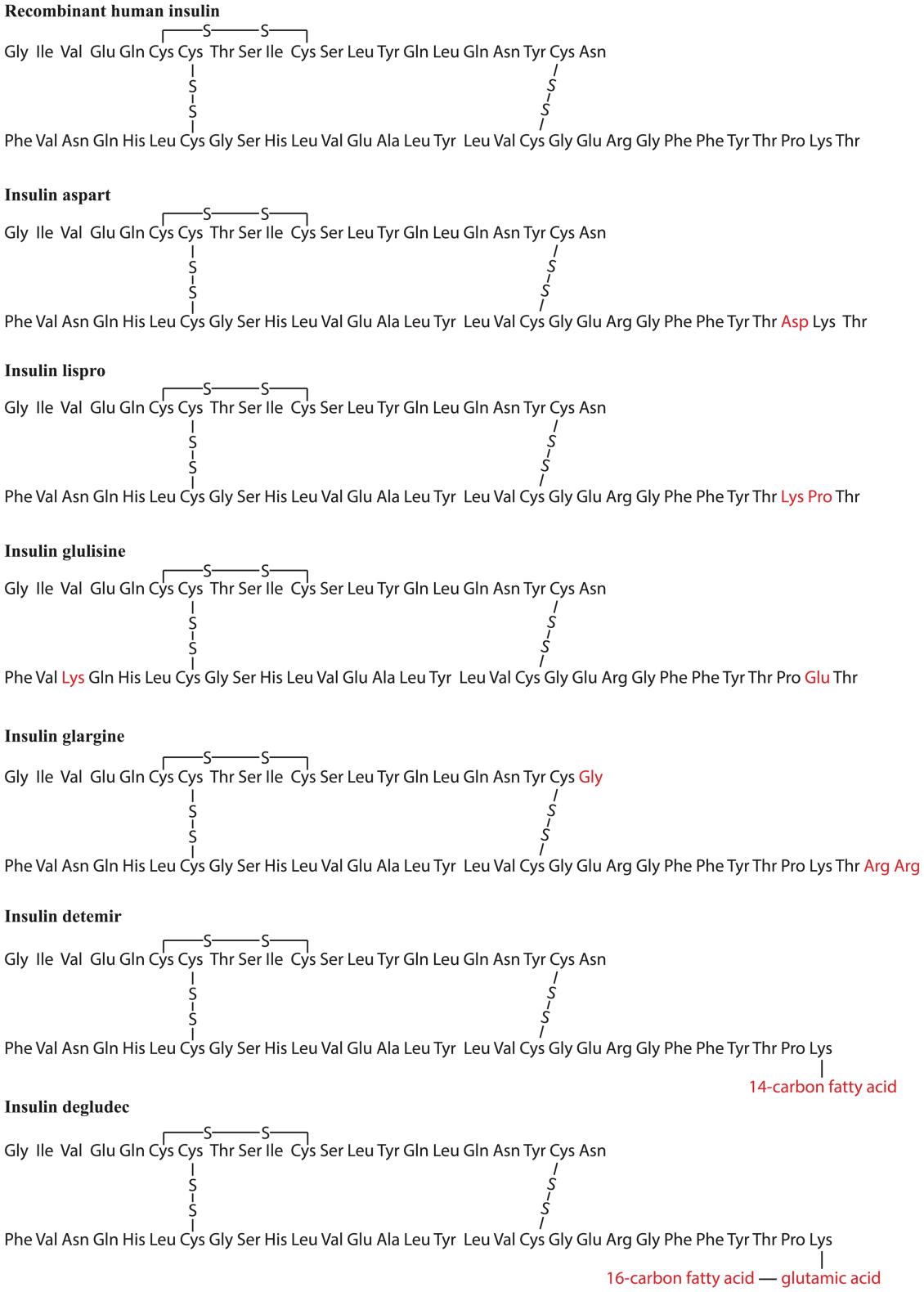
Over the period of 3 year and 10 months, the top export destinations by volume were Mexico (826kg), followed by the US (356kg), Iran (254kg), Bangladesh (249kg), Morocco (218kg), and Pakistan (199kg).

Supplementary figure 2. Cost per kilogram (USD) and linear regression of insulin glargine API exported from India 1 Jan 2013 to 1 Nov 2016.



Over the period of 3 year and 10 months, the top export destinations by volume were Mexico (113kg), followed by Bangladesh (6kg), Ukraine (2kg), United Kingdom (1kg), and Pakistan (1kg).

Supplementary figure 3. Comparison of molecular structures of human insulin and insulin analogues.



Dosage of insulins in milligrams

Regular human insulin 100 units = 3.50mg
Insulin NPH 100 units = 3.91mg
Lispro 100 units = 3.50mg
Aspart 100 units = 3.50mg
Glulisine 100 units = 3.49mg
Glargine 100 units = 3.64mg
Detemir 100 units = 14.20mg
Degludec 100 units = 3.66mg

Source: Summary of Product Characteristics available from www.medicines.org.uk.

Excipient cost

Item	Price (USD/kg)	Reference
M-Cresol	57.47	http://www.emdmillipore.com/US/en/product/m-Cresol,MDA_CHEM-809691
Phenol	133.00	http://www.emdmillipore.com/US/en/product/Phenol,MDA_CHEM-822296
Zinc oxide	133.00	http://www.sigmaaldrich.com/catalog/product/sigald/14439?lang=en&region=US
Glycerin	47.82	http://www.sigmaaldrich.com/catalog/product/sial/g2289?lang=en&region=US
Sodium phosphate dibasic dehydrate	73.20	http://www.sigmaaldrich.com/catalog/product/sigald/30435?lang=en&region=US
Sodium choloride	15.52	http://www.sigmaaldrich.com/catalog/product/mm/106400?lang=en&region=US
Water for injection	8.51	http://www.sigmaaldrich.com/catalog/product/mm/486505?lang=en&region=US
Polysorbate-20	507.00	http://www.sigmaaldrich.com/catalog/product/sial/44112?lang=en&region=US

All hyperlinks accessed June 15, 2017.
HCl and NaOH for buffering not included in excipient cost calculation.

Excipient content of vials

Except where indicated otherwise, composition of vials is from Niazi SK. Handbook of Pharmaceutical Manufacturing Formulations, Second Edition: Sterile Products. New York: Informa Healthcare USA, Inc.; 2009.

Insulin aspart

Component	Cost per kg (USD)	Amount per 1mL	Cost per 10mL vial (USD)
Glycerin	47.82	16mg	0.0076512
Phenol	133.00	1.5mg	0.001995
M-Cresol	57.47	1.72mg	0.000988484
Zinc oxide	133.00	19.6mg	0.026068
Disodium hydrogen phosphate dihydrate	73.20	1.25mg	0.000915
Sodium chloride	15.52	0.58mg	0.000090016
Water for injection	8.55	1g	0.08545
		Total:	0.1231577

Insulin glargine

Component	Cost per kg (USD)	Amount per 1mL	Cost per 10mL vial (USD)
Glycerol 85%	47.82	20mg	0.0076512
Phenol	133.00	1.5mg	0.001995
M-Cresol	57.47	2.7mg	0.00155169
Zinc oxide	133.00	30mg	0.0399
Water for injection	8.55	1g	0.08545
		Total:	0.13654789

Insulin NPH

Component	Cost per kg (USD)	Amount per 1mL	Cost per 10mL vial (USD)
Zinc oxide	133.00	0.012mg	0.00001596
Liquefied phenol	133.00	0.73mg	0.0009709
Metacresol	57.47	1.6mg	0.00091952
Glycerin	47.82	16mg	0.0076512
Sodium phosphate dibasic	73.20	3.78mg	0.00276696
Water for injection	8.55	1g	0.08545
		Total:	0.09777454

Insulin lispro

Component	Cost per kg (USD)	Amount per 1mL	Cost per 10mL vial (USD)
Protamine sulfate	10,800.00	0.28 mg	0.03024
Glycerin	47.82	16.00 mg	0.0076512
Sodium phosphate dibasic	73.20	3.78mg	0.00276696
M-Cresol	57.47	1.76mg	0.001011472
Zinc ion	133.00	0.025mg	0.00003325
Liquefied phenol	133.00	0.715mg	0.00095095
Water for injection	8.55	1.00g	0.08545
		Total:	0.128103832

Regular human insulin

Component	Cost per kg (USD)	Amount per 1mL	Cost per 10mL vial (USD)
Metacresol	57.47	2.5 mg	0.00143675
Glycerin	47.82	16 mg	0.0076512
Water for injection	8.55	1g	0.08545
		Total:	0.09453795

Insulin glulisine

From Niazi SK. Biosimilars and Interchangeable Biologics: Strategic Elements. CRC Press. 2016.

Component	Cost per kg (USD)	Amount per 1mL	Cost per 10mL vial (USD)
Metacresol	57.47	3.15 mg	0.001810305
Tromethamine	47.82	6 mg	0.0028692
Sodium chloride	15.52	5mg	0.000776
Polysorbate-20	507.00	0.01mg	0.0000507
Water for injection	8.55	1g	0.08545
		Total:	0.090956205

Insulin detemir and degludec

Excipients used in these formulations are the same as those used in the other analogues. Published information on the exact amounts of the excipients used in detemir and degludec could not be identified, so the excipient costs for these were conservatively assumed to be equal to the highest excipient cost across analogues – those for insulin glargine.

Conversion and packing cost norms published by the Indian National Pharmaceuticals Pricing Authority in November 2012, pursuant to the Drugs (Prices Control) Order 1995.

The norms are available from http://www.nppaindia.nic.in/wh-new-2012/wh-new-29-2012.html (accessed 28 Jul 2017).

Item	Cost per unit in 2012 Indian rupees	Cost per unit in 2017 US cents
Conversion cost		
Sterile liquid vial 5–15mL	1.55	2.96
Packing cost		
Liquid in vial >5mL	0.69	1.32
Packaging material cost		
Tubular glass vial 10mL	2.44	4.66
	Total:	8.94

2012 average exchange rate 1 USD = 55.911 INR
(source: https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates)

2012 to 2017 US inflation 6.7%
(source: http://www.usinflationcalculator.com/)

Adjustment for inflation was done by multiplying the 2012 value in Indian rupees by the 2012 average exchange rate, and then by the 2012-2017 US inflation factor.

Lowest-priced items formulated as ampoules.

Item	Price per unit in the UK (USD)
Ondansetron 4mg in 2mL ampoule	0.1092
Furosemide 20mg in 2mL ampoule	0.1196
Metoclopramide 10mg in 2mL ampoule	0.1508
Morphine 10mg in 2mL ampoule	0.1599
Adrenaline 1mg in 1mL ampoule	0.1989

Prices collected from the UK drugs and pharmaceutical electronic market information tool (eMit) in February 2017, available at https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

Lowest-price items formulated as vials.

Item	Price per unit in the UK (USD)
Ceftriaxone 1g in vial	0.6370
Dopamine 200mg in 5mL vial	0.6786
Vancomycin 250mg in vial	0.7215
Gentamicin 80mg in 2mL vial	0.7800
Phenytoin 250mg in 5mL vial	0.8476

Prices collected from the UK drugs and pharmaceutical electronic market information tool (eMit) in February 2017, available at https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

Broken down estimation of manufacturing costs and estimated biosimilar prices

Competitive formula								
Drug	**human insulin**	**neutral protamine Hagedorn**	**glargine**	**lispro**	**aspart**	**glulisine**	**detemir**	**degludec**
Cost of API (1 kg)	$19,800	$18,626	$55,006	$80,000	$80,000	$80,000	$80,000	$80,000
1000 units in mg	35	39.1	36.4	35	35	34.9	142	36.6
Cost of API for 1000 unit vial	$0.69	$0.73	$2.00	$2.80	$2.80	$2.79	$11.36	$2.93
Cost of excipients for 1000 unit vial	$0.09	$0.10	$0.14	$0.13	$0.12	$0.09	$0.14	$0.14
Cost of API + excipients	$0.79	$0.83	$2.14	$2.93	$2.92	$2.88	$11.50	$3.06
Adjust for 4.5% process loss of API and excipients	$0.82	$0.86	$2.23	$3.06	$3.05	$3.01	$12.01	$3.20
Add cost of formulation at $0.09/vial	$0.91	$0.95	$2.32	$3.15	$3.14	$3.10	$12.10	$3.29
Add cost of development	$2.28	$2.32	$3.69	$4.52	$4.51	$4.47	$13.47	$4.66
Total cost of production	**$2.28**	**$2.32**	**$3.69**	**$4.52**	**$4.51**	**$4.47**	**$13.47**	**$4.66**
Add costs of tranportation and customs at 20%	$2.74	$2.79	$4.43	$5.42	$5.42	$5.37	$16.17	$5.59
Add profit margin at 20%	$3.29	$3.35	$5.32	$6.51	$6.50	$6.44	$19.40	$6.71
Total estimated biosimilar price	**$3.29**	**$3.35**	**$5.32**	**$6.51**	**$6.50**	**$6.44**	**$19.40**	**$6.71**
Conservative formula								
Cost of API (1 kg)	$24,750	$23,282	$68,757	$100,000	$100,000	$100,000	$100,000	$100,000
1000 units in mg	35	39.1	36.4	35	35	34.9	142	36.6
Cost of API for 1000 unit vial	$0.87	$0.91	$2.50	$3.50	$3.50	$3.49	$14.20	$3.66
Cost of excipients for 1000 unit vial	$0.09	$0.10	$0.14	$0.13	$0.12	$0.09	$0.14	$0.14
Cost of API + excipients	$0.96	$1.01	$2.64	$3.63	$3.62	$3.58	$14.34	$3.80
Adjust for 4.5% process loss of API and excipients	$1.00	$1.05	$2.76	$3.79	$3.79	$3.74	$14.98	$3.97
Add cost of formulation at $1.00/vial	$2.00	$2.05	$3.76	$4.79	$4.79	$4.74	$15.98	$4.97
Add cost of development	$3.37	$3.42	$5.13	$6.16	$6.16	$6.11	$17.35	$6.34
Total cost of production	**$3.37**	**$3.42**	**$5.13**	**$6.16**	**$6.16**	**$6.11**	**$17.35**	**$6.34**
Add costs of tranportation and customs at 20%	$4.05	$4.11	$6.15	$7.39	$7.39	$7.33	$20.82	$7.60
Add profit margin at 20%	$4.86	$4.93	$7.38	$8.87	$8.86	$8.80	$24.99	$9.13
Total estimated biosimilar price	**$4.86**	**$4.93**	**$7.38**	**$8.87**	**$8.86**	**$8.80**	**$24.99**	**$9.13**

Estimation of per-unit cost of production based on companies' reports

As a point of comparison to our estimates of biosimilar price based in API cost, we sought to estimate the cost of production deriving from originator companies' reported cost of goods sold.

Novo Nordisk, Lilly, and Sanofi together control 96% of the global market for insulins by volume.[1] All three companies reports their 'cost of goods sold' (COGS; i.e. the costs of manufacturing their products) as a percentage of their total sales.[2–4] As they do not report the total number of items sold, or COGS broken down by product, this cannot be directly translated to a precise per-product cost of production.

In 2016 Novo Nordisk reported that "28 million patients use [their] diabetes care products".[2] We used this number to estimate the COGS per item. We were unable to identify similar numbers for Lilly or Sanofi that would allow an estimate of the number of items sold.

The cost of production per insulin item can be estimated by combining total sales figures with their reported percentage of sales spent on COGS and estimates for the number of insulin items sold per year (this must be estimated because Novo Nordisk does not report the exact number of items sold).

As Novo Nordisk produces some diabetes products that are not used in type 1 diabetes (liraglutide, semaglutide, repaglinide), we assumed that 80% of these 28 million patients are using Novo Nordisk insulins (22.4 million) rather than other products. The World Health Organization defines the Defined Daily Dose (DDD) for insulin as 40 units,[5] equivalent to 14,600 units per year. Depending on the size of the vial used – 300 units or 1000 units – this would be equivalent to about 15 or 50 vials, respectively, per year. Assuming 22.4 million people use between 15 and 50 vials/cartridges of insulin in a year, and assuming that between half and all of their yearly insulin use is with products sold by Novo Nordisk (7.5–15 vials/pens per year if all are 1000 units and 25–50 vials per year if all are 300 units), this is equivalent to 168–336 million items sold annually if all items contain 1000 unit and 560–1,120 million items sold annually if all items contain 300 units.

Total sales of insulin	**Reported COGS as percentage of sales**	**Total COGS for insulins**	**Estimated items sold**	**Estimated COGS per item**
US$10.1 billion*	16% (diabetes and obesity products)*	US$1.62 billion	*Assuming all items contain 1000 units of insulin:*	
			168-336 million	$4.82–$9.64
			Assuming all items contain 300 units of insulin:	
			560-1,120 million	$1.45–2.89

COGS – cost of good sold, i.e. production costs. Assumed 1 DKK = 0.16 USD
**Figures from Novo Nordisk's 2016 Annual Report.[2]*

1 Beran D, Ewen M, Laing R. Access to insulin - Current Challenges & Constraints. 2015. http://apps.who.int/medicinedocs/documents/s22269en/s22269en.pdf.
2 Novo Nordisk. Annual report. 2016. https://www.novonordisk.com/content/dam/Denmark/HQ/AnnualReport/2016/PDF/Novo-Nordisk-Annual-Report-2016.pdf (accessed Jan 25, 2018).
3 Eli Lilly and Company. 2016 Financial Report. 2016. http://files.shareholder.com/downloads/LLY/5382793911x0x933961/450B26F2-F56C-44B0-8AEB-3E15E98D24D8/English.PDF (accessed Oct 16, 2017).
4 Sanofi. Form 20-F. 2016. https://www.sanofi.com/media/Project/One-Sanofi-Web/sanofi-com/en/investors/docs/20-F_2016.pdf (accessed Feb 25, 2018).
5 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2018. https://www.whocc.no/atc_ddd_index/ (accessed Jan 25, 2018).