Immunogenicity of Insulins in Biosimilar Development

European Immunogenicity Platform

Feb 25-27, 2019

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Disclaimer

Views expressed in this presentation are personal in nature and do not necessarily represent the views of Biocon

Biocon – Pioneer in *Affordable Access* to Biotech Medicines

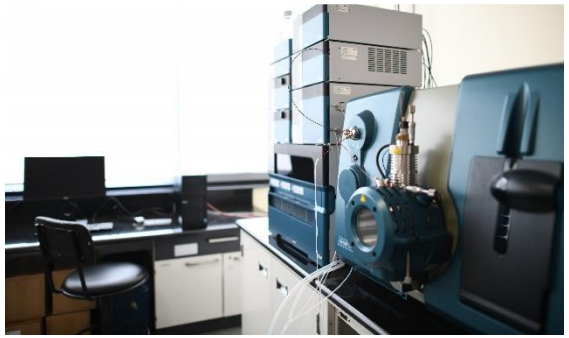
- 40 years in Biotechnology
- Expertise in *all* host systems (Yeast, *E.coli*, CHO, SP2/0)

FDA APPROVED

✓First Biosimilar Trastuzumab
✓First Biosimilar Peg-Filgrastim

- Insulins inc. Analogs approved in EU, Japan, Australia and in 40+ countries globally

State of the art Technology





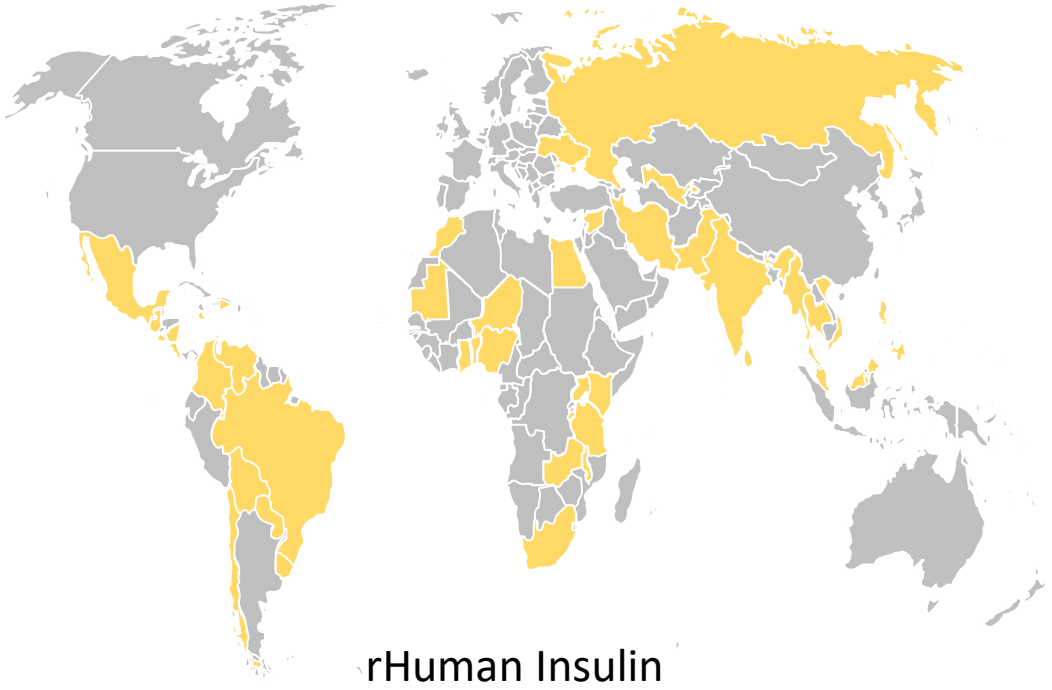


Asia's Largest Insulins Manufacturer

Affordable Access with Global Quality

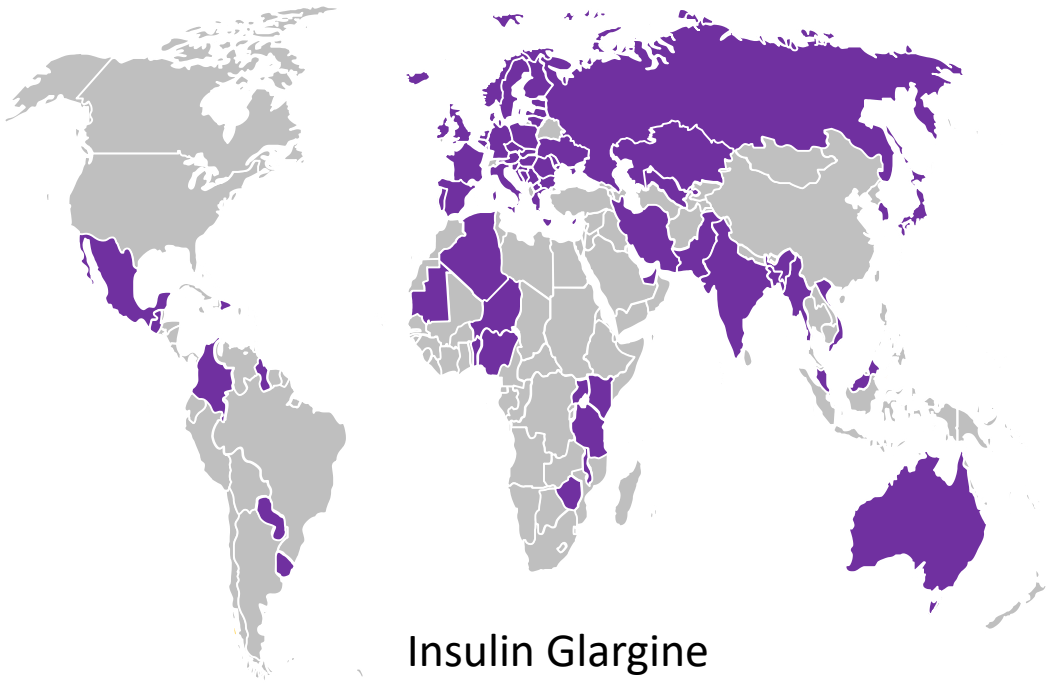
Expertise in Insulins: > 15 years of Manufacturing

One of the Largest Insulin Suppliers by Volume



rHuman Insulin

Pharmacopeial grade Insulin: 43 countries*



Insulin Glargine

Insulin Glargine: 68 countries*

Biocon has the Science, Scale, Technology, and Years of Patient Experience

*List of countries on file.

https://wayback.archive-it.org/7993/20170405222944/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM431118.pdf

Public Health Crisis

The New York Times

June 22, 2018

Diabetes Patients at Risk From Rising Insulin Prices

A Yale study found that one in four patients admitted to cutting back on insulin use because of cost. The consequences can be deadly.

Statement from FDA Commissioner Scott Gottlieb, M.D., on new actions advancing the agency's biosimilars policy framework

Dec 11, 2018

"limited competition in the insulin market has helped keep prices artificially high"

"Access to affordable insulin is literally a matter of life and death for these Americans"

BOSTON 25 NEWS: Spiking insulin costs causing dangerous behavior in diabetics

December 18, 2018

Christopher Noble is one of 7 million Americans who need insulin to manage their diabetes.

CBS NEWS: Woman says her son couldn't afford his insulin – now he's dead

January 4, 2019

When Nicole Smith-Holt's 26-year-old son died, he had just moved out of his parents' home and was starting a life of his own.

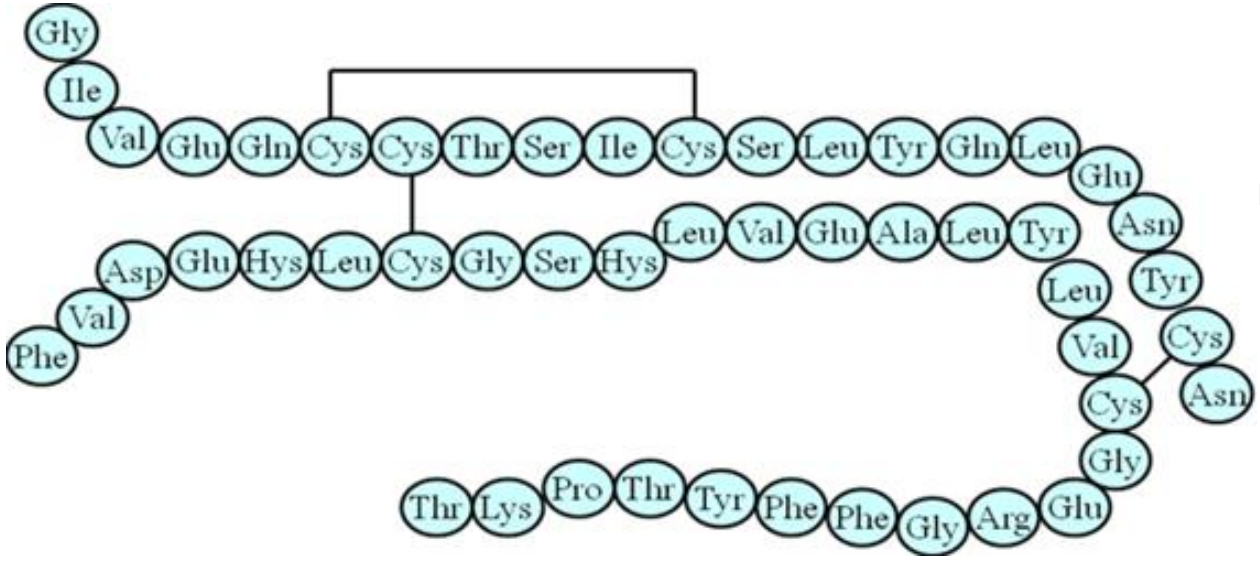
Patients urgently need high Quality Biosimilar Insulins

rInsulin – Simple and Well Characterized Polypeptide

STRUCTURE

Physicochemical characteristics

- **Amino acid sequence**
- **Secondary/HOS**
- **Impurities and Variants**



FUNCTION

Biological activity

Efficacy

Metabolic Activity

- **Insulin Receptor B Binding**
- **Insulin Receptor B Phosphorylation**
- **Glucose Uptake**
- **Adipogenesis**
- **Inhibition of stimulated lipolysis**

Safety

Mitogenic Activity

- **Insulin Receptor A Binding**
- **Insulin Receptor A Phosphorylation**
- **IGF-1 Receptor Binding**
- **Cellular Proliferation**

Small (51AA), Fully characterized Protein
Efficacy & Safety can be determined using Functional assays

Different Host Platforms: But all Safe

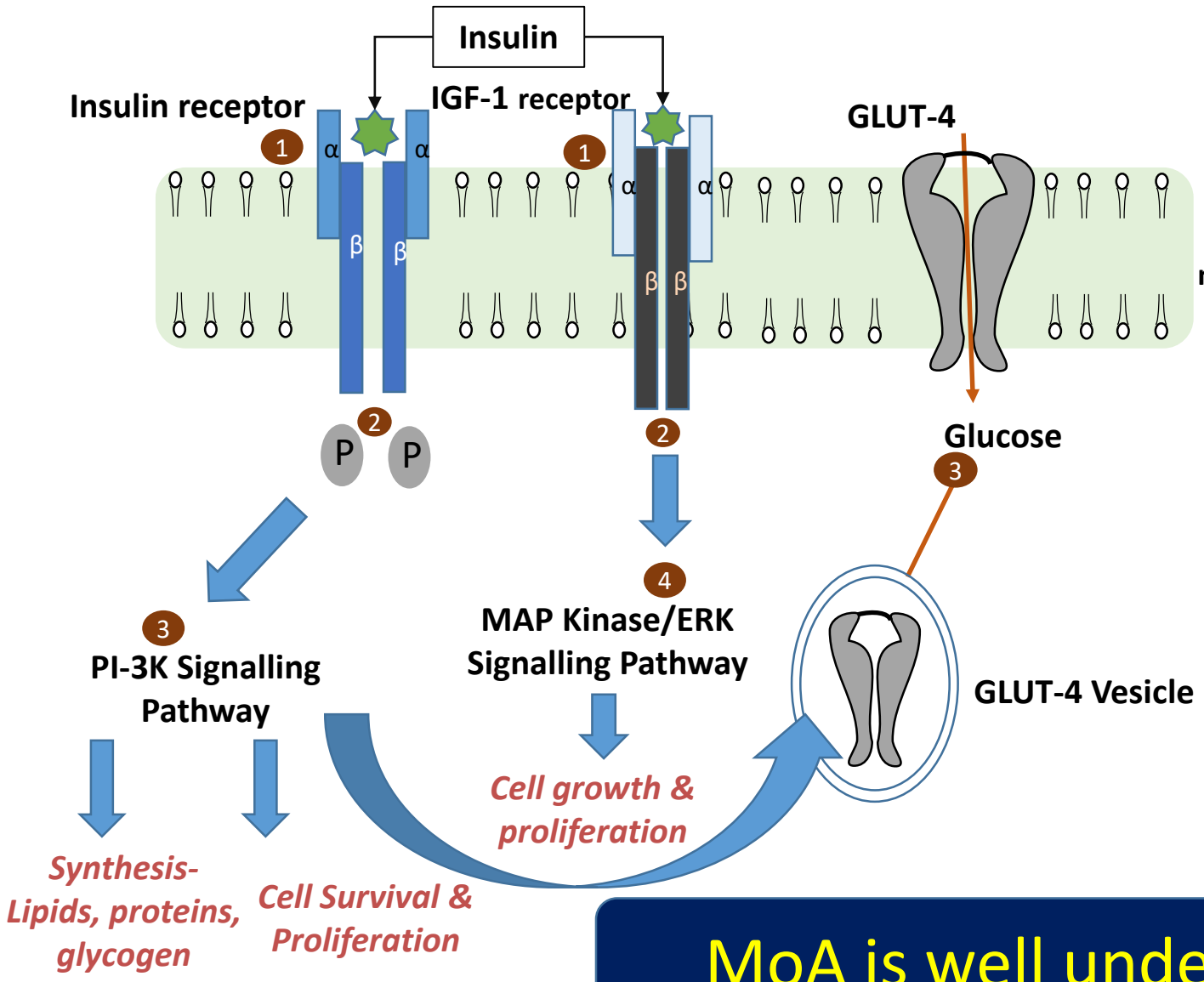
- Biocon's Insulin glargine manufactured in *Pichia Pastoris* is already approved in 68 countries including the EMA, PMDA and TGA
  - Note: Reference Drug Lantus® is made in E.Coli

- Humulin® (*E.coli*), Novolin® (*S.cerevisiae)*

- Glycosylated Species, Host Cell Proteins

No Clinical Impact on Safety, Effiacy and Immunogenicity

Insulin – Mechanism of Action



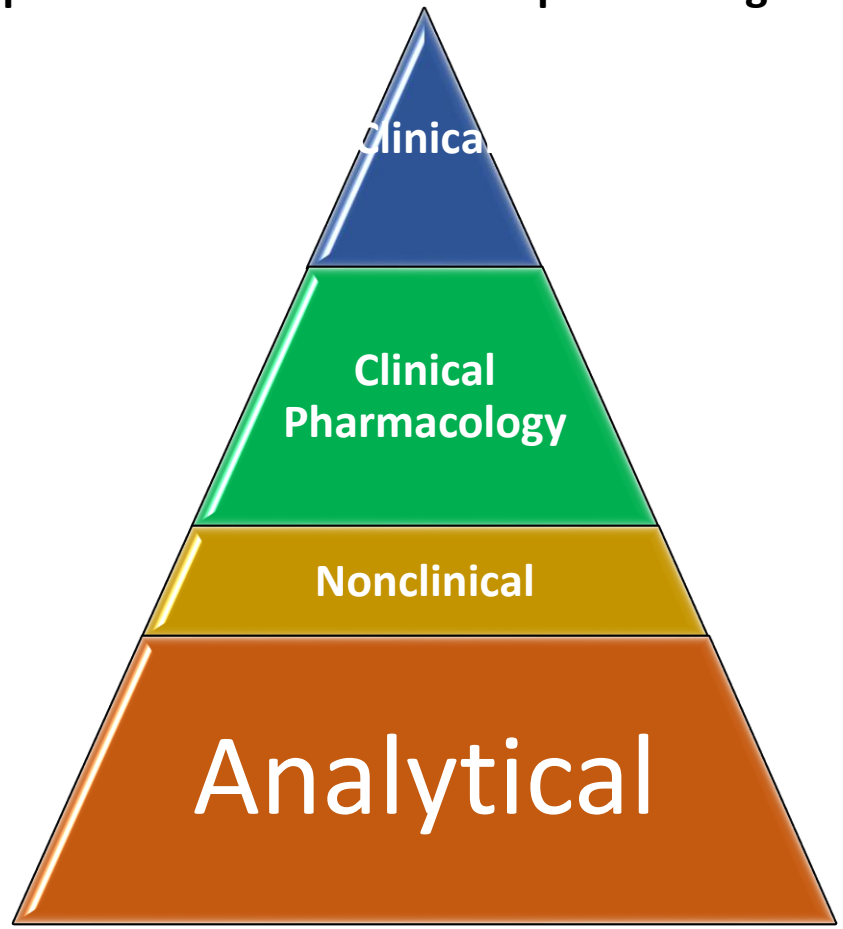
1. Receptor Binding
2. Receptor Activation
3. Metabolic Activity
4. Mitogenic Effect

MAPK/ERK: Mitogen-Activated Protein Kinases, originally called ERK, Extracellular Signal-Regulated
PI-3K/AKT: Phosphoinositol-4,5-bisphosphate 3-kinase. PI3K activation phosphorylates and activates AKT(Protein Kinase B)
GLUT-4: Glucose transporter type 4 is insulin-regulated glucose transporter

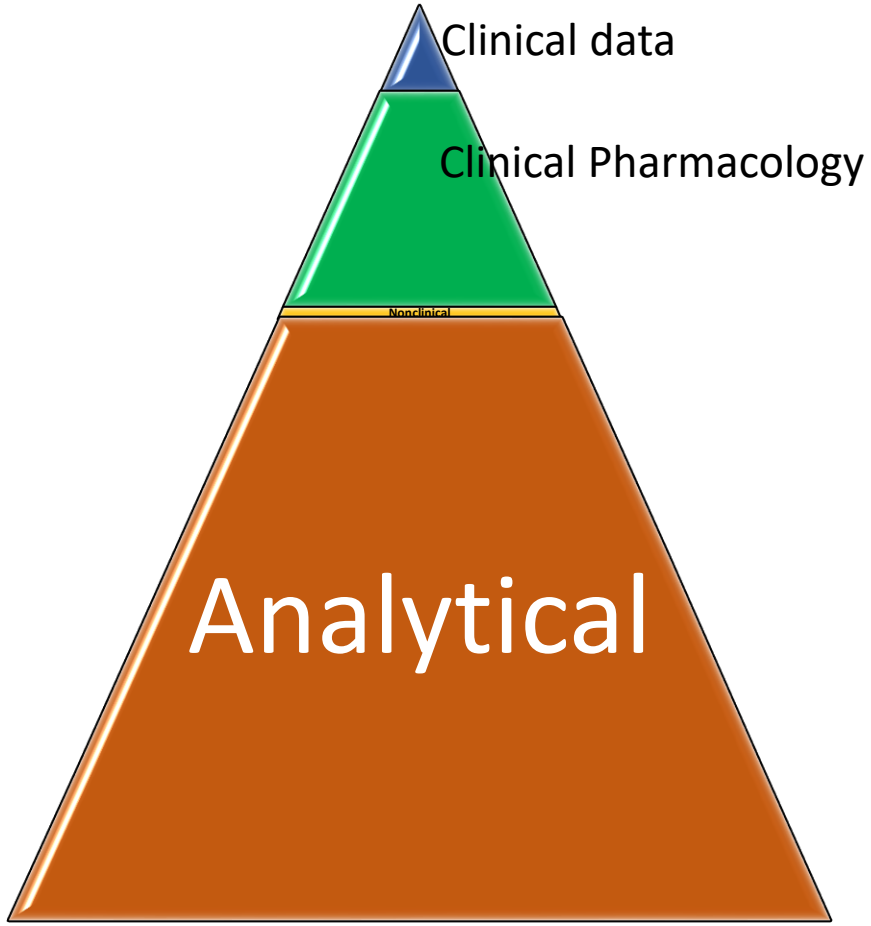
MoA is well understood

Biosimilar Development under EMA Biosimilar Pathway/ 351(k) pathway (US)

Typical "Abbreviated" Development Program



rHuman Insulin, small, simple Protein



CMC and PK/PD adequately addresses Biosimilarity requirements

https://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM587522.pdf

Proof of Analytical Similarity

	Structure	Proof of Analytical Similarity
1°	Intact mass	Identical
	Reduced mass	Identical
	Peptide map (R)	Identical
2° & 3°	Pep mass fingerprint (NR)	✓
	Far UV CD	✓
	FTIR Spectroscopy	✓
HOS	Intrinsic Fluorescence	✓
	X-ray comparability	✓
	NMR comparability	✓
Attributes	HPLC	✓
	Phase contrast microscopy	✓
	AA microscopy	✓

Function	Proof of Analytical Similarity
Mitogenic Assay (Potency)	✓
Adipogenesis (Potency)	✓

Impurities	Proof of Analytical Similarity
HMWP	✓
Other Related Proteins (ORP)	✓
A21 Deamidated impurity	✓

Crystal Morphology	Proof of Analytical Similarity
Crystal Length	✓
Crystal Breadth	✓

Structure, Impurities & Function by multiple, sensitive, orthogonal methods
Needs to be Highly Similar

Clinical Pharmacology (PK/PD)

- Clinical Pharmacology studies in the most sensitive population
  - Normal Healthy Volunteers
  - Cross-Over, Euglycemic, Hyperinsulinemic clamp technique is the state-of-the art method for the measurement of insulin action and PK

- Efficacy claim is supported by PD marker (for Insulin)
  - Glucose-infusion rate (GIR) over time describes the time-action profile of insulins
  - GIR is a well-known PD endpoint for insulins which directly correlate with efficacy in patients



Bioequivalence in PK/PD supports high similarity for Efficacy

FDA, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Dec 2016
FDA, Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, 2008
EMEA/CHMP/BMWP/32775/2005_Rev. 1, Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant Human Insulin and Insulin analogues

Residual Uncertainty of Immunogenicity Risk

- EMA and FDA both require 24 wk study for immunogenicity in T1DM patients, sufficient enough to see comparable immunogenicity and if its clinically meaningful.
  - EMA can consider waiver of pre-registration study if sufficient proof of similarity is demonstrated
- What would be sufficient?
  - Concept of TEAR rate

TEAR at week 24:

- Baseline –ve who became positive at week 24, and
- Baseline +ve who had 4 fold increase in titers at week 24

Anytime TEAR:

- Baseline –ve who became positive anytime in 24 weeks, and
- Baseline +ve who had 4 fold increase in titers anytime within 24 weeks

Persistent TEAR:

- Baseline –ve who became positive at 2 or more timepoints in 24 weeks, and
- Baseline +ve who had 4 fold increase in titers at 2 or more time points in 24 weeks

Treatment
Emergent
Antibody
Response

TEAR Rate: Clinical Relevance

- Studies for approved biosimilars: Basaglar, Lusduna and Humalog have conclusively demonstrated no clinical risk or relevance of AIA across a range of TEAR rates.
- Assay sensitivity differences are observed

Product	Indication	Patients evaluated	TEAR Rate Observed %	Safety	Efficacy	Dose
Basaglar (Lantus)	T1DM, T2DM	1262	1.9 - 10.9	✓	✓	✓
Lusduna (Lantus)	T1DM, T2DM	1025	14.9 - 40.6	✓	✓	✓
Admelog (Humalog)	T1DM, T2DM	992	14.4 – 24.2	✓	✓	✓

Publicly available information

What did we learn?

CLINICAL PARAMETER OF INTEREST	Correlation with POSITIVE AIA response post baseline including TITERS
HbA1c	✗
ISI, Hypersensitivity reactions	✗
Increase in required insulin dose	✗

In addition, transient nAbs are common, no definite correlationship with increasing titers or clinical parameters

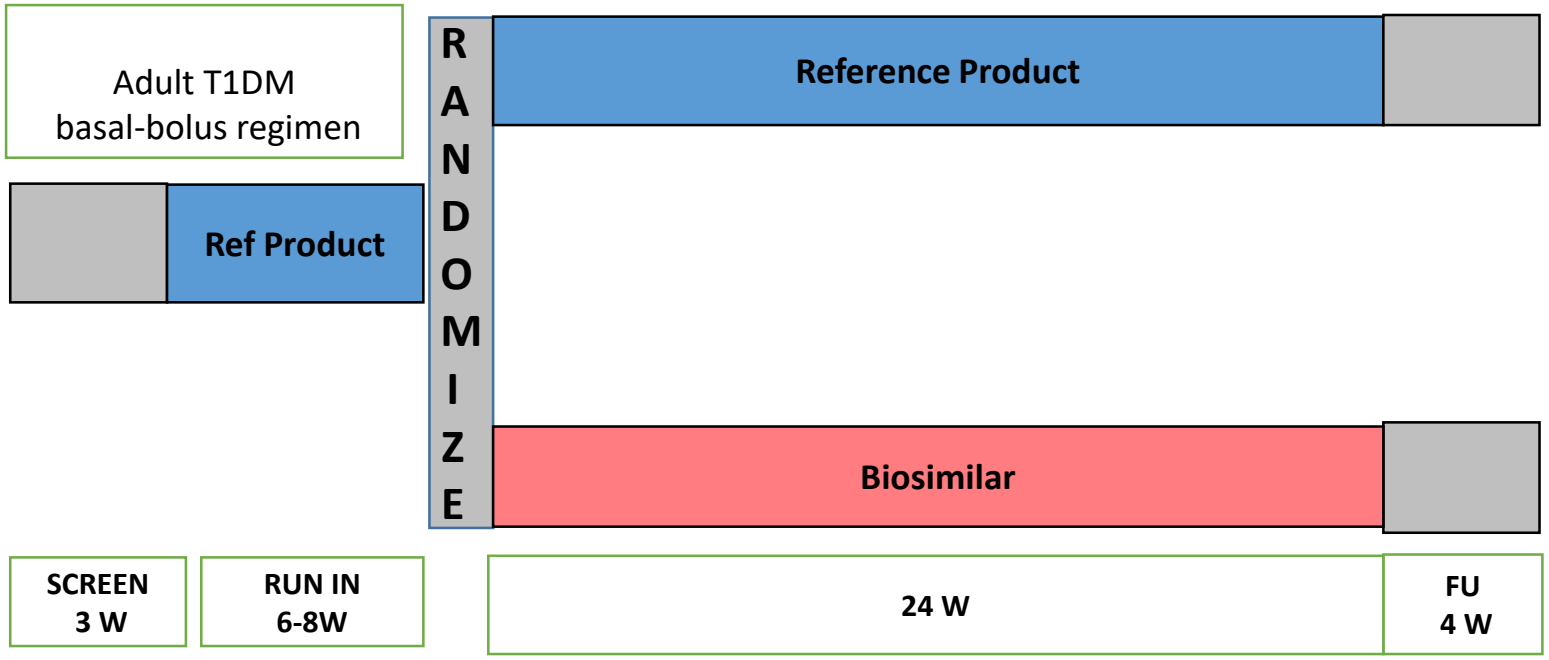
Should one set margins for statistical powering of trials?

Event Rate for Reference Product (%)	Margin with N=500 (5.7-13%)	Total N	Margin with N=300 (7.4-16.9%)	Total N	Margin with N=200 (9-20.7%)	Total N
5	5.7%	500	7.4%	300	9%	200
10	7.9%	500	10.1%	300	12.4%	200
15	9.3%	500	12.1%	300	14.8%	200
20	10.5%	500	13.5%	300	16.6%	200
25	11.3%	500	14.6%	300	17.9%	200
30	12%	500	15.5%	300	19%	200
35	12.5%	500	16.1%	300	19.7%	200
40	12.8%	500	16.6%	300	20.3%	200
45	13%	500	16.8%	300	20.6%	200
50	13.1%	500	16.9%	300	20.7%	200
55	13%	500	16.8%	300	20.6%	200
60	12.8%	500	16.6%	300	20.3%	200
65	12.5%	500	16.1%	300	19.7%	200
70	12%	500	15.5%	300	19%	200
75	11.3%	500	14.6%	300	17.9%	200
80	10.5%	500	13.5%	300	16.6%	200
85	9.3%	500	12.1%	300	14.8%	200
90	7.9%	500	10.1%	300	12.4%	200
95	5.7%	500	7.4%	300	9%	200

Assumptions:
Power of 80% , Type 1 error of 0.05
90% CI of TEAR (test product) to lie within Margin specified for observed TEAR of reference product.

Margins not relevant in light of clinical relevance of immunogenicity

Should one use PK as a surrogate for Immunogenicity?



PK and AIA sampling may be done at Baseline, 2, 6, 12, 18 and 24 weeks

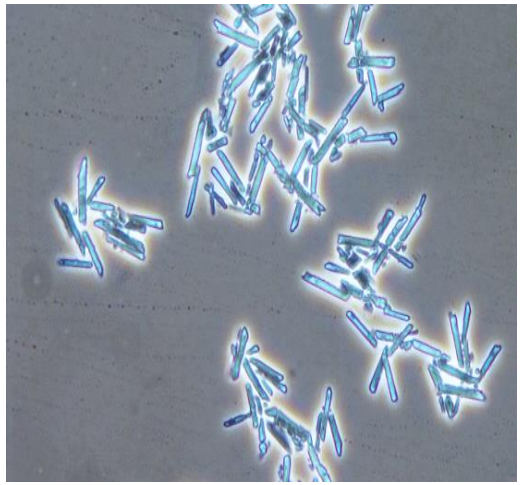
1. T1DM patient titrates dose to their daily need
2. Cmin levels may be done- although logistical issues (evening versus morning dose)

PK endpoint is not useful in the context of above issues

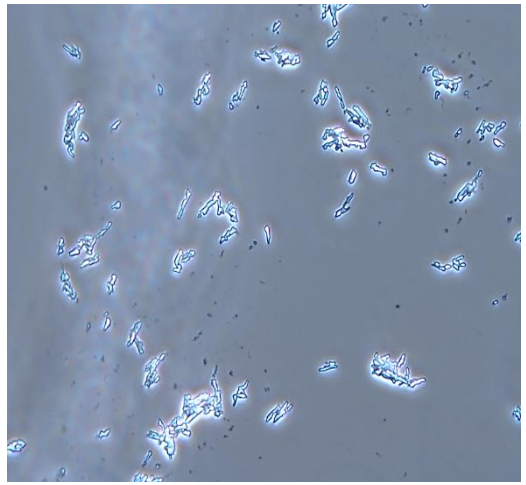
rHuman Insulin – OTC Product in the US

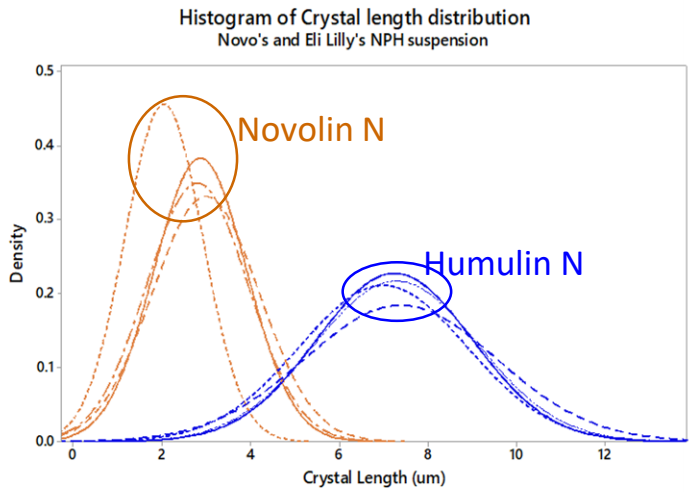
Differences that could impact PD, Immunogenicity do not result in any clinically meaningful difference

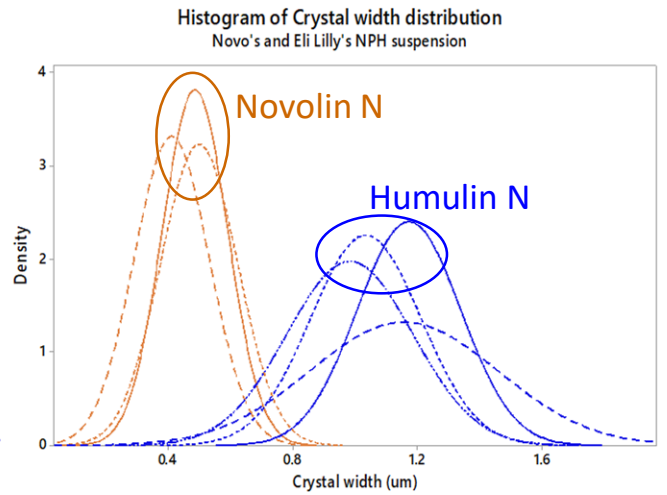
Humulin N®



Novolin N®







Pharmacodynamics[1]	Humulin R	Novolin R
Onset	30 min	30 min
Peak	3 hr	1.5 - 3.5 hr
Duration of Action	NA	NA

Humulin N	Novolin N
NA	1-2 hr
6.5 hr	NA
NA	24 hr

Humulin 70/30	Novolin 70/30
50 min	30 min
3.5 hr	NA
23 hr	up to 24 hr

Despite large differences in the Product Characteristics

- Under emergency situations the FDA allows rHI to be switched between manufacturers[2]
- Effective Therapeutic Range is the Same & Wide (dosage is Identical, unit-per-unit basis)

1. Data from the respective RLD US PI
2. https://www.fda.gov/Drugs/EmergencyPreparedness/ucm085213.htm

In Conclusion

- Immunogenicity risk needs to be looked in light of learning from past programs and data, Insulins do not pose a clinically meaningful safety or efficacy risk due to immunogenicity, while we will see AIA responses in trials.
- If pre-registration trials are needed, they need to be assessed based on pragmatic risk based approach. Large clinical trials for immunogenicity are unwarranted.
- High sensitivity of AIA assays facilitates comparative immunogenicity data in a smaller sample size.
- Totality of evidence approach is most pragmatic way of evaluating immunogenicity.
- A white paper on Insulins and Immunogenicity would help in shaping regulatory policy for biosimilars in the future.

Discussion/Questions

