17th Open Scientific EIP Symposium on Immunogenicity of Biopharmaceuticals

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Peptide Drug Products
Aligning Immunogenicity evaluations with Regulatory Expectations

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Immunogenicity Integrated

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Peptide products

1. EMA & FDA Regulatory framework
2. Abbreviated versus NME pathways
3. Implications to immunogenicity evaluation
4. Conclusions and future questions

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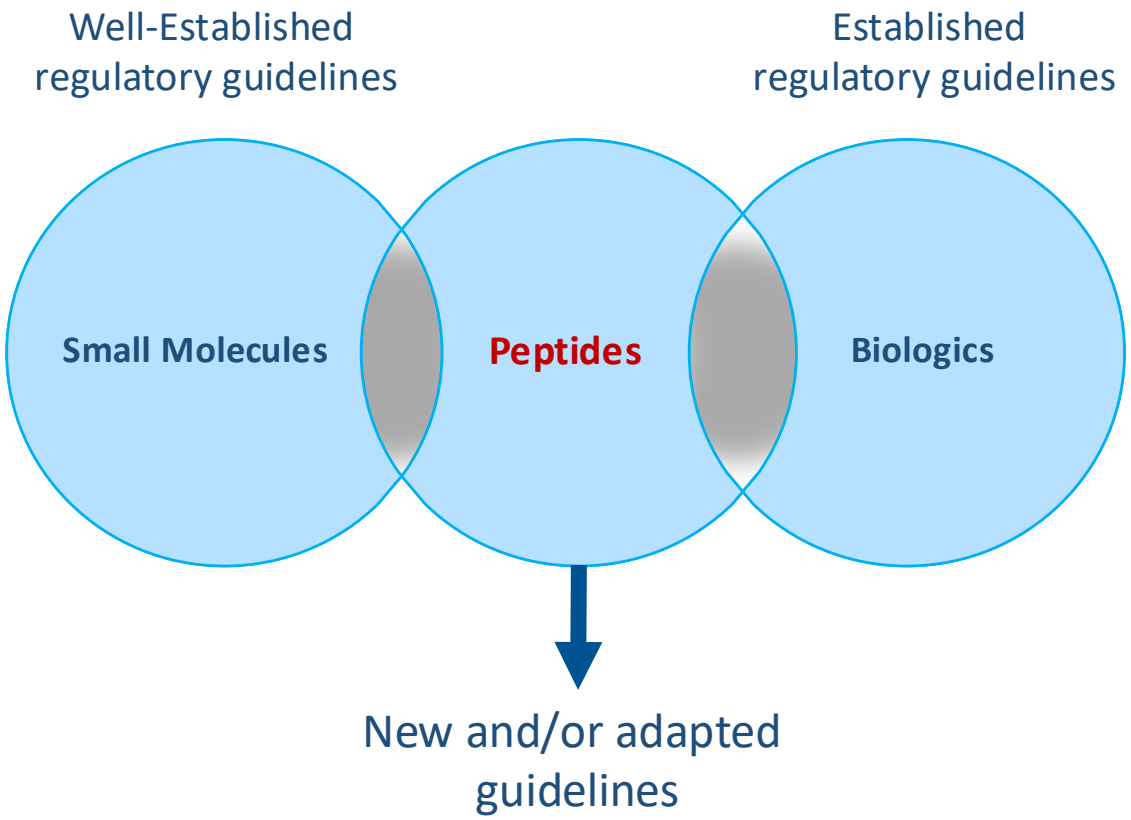
Peptide products “conundrum”



Adapted from Dr. René Thürmer | European Quality Guidelines for Synthetic Peptides and Oligonucleotides - 09.04.2024 USP Workshop on Peptide and Oligonucleotide Therapeutics

- **Any polymer consisting of 40 or fewer amino acids** (*FD&C Act, USA FDA*)
- “**Short chain of amino acids**”, but regulatory distinction with biologicals relies on the **manufacturing process** (EMA/454576/2016; EMA/CHMP/CVMP/QWP/367182/2025)
- Peptides are at **the interface between small molecules and biologics** therefore specific considerations apply to this class of therapeutics

Implications to immunogenicity

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Generic/Abbreviated Pathways

Generic products

EMA: "a **generic medicinal product** is a product which has the **same qualitative and quantitative composition in active substances and the same pharmaceutical form** as the reference medicinal product, and whose **bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies**" (Directive 2001/83/EC, Article 10(2)(b))

FDA: GDUFA requires **generic drugs** to meet strict FDA standards for **quality and bioequivalence**, ensuring they are the **same as brand-name drugs in dosage, safety, strength, and intended use** (GDUFA 2012)

How does immunogenicity address residual uncertainty for sameness demonstration?

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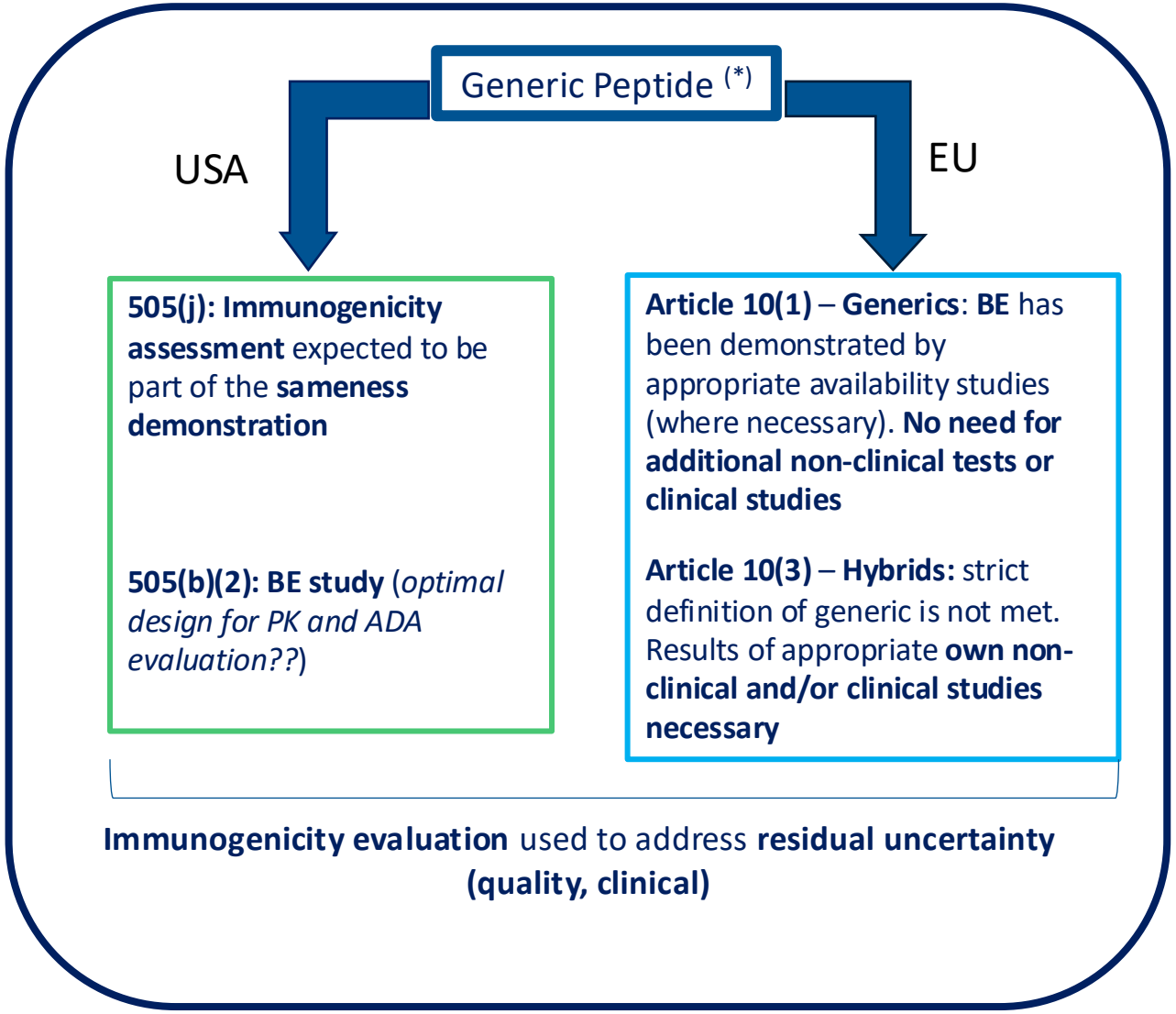
Immunogenicity strategy to be defined by regulatory pathway



Sameness demonstration to support 505(j) and Article 10(1) Generic applications

Abbreviated clinical study to support 505(b)(2) and Article10(3) Hybrid applications

(*) New guidance expected for March 2026 (BE and quality)

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Synthetic peptides referencing a recombinant RLD/RMP

(505(j))/Article 10(1))

- The biosimilar regulatory pathway **is not possible** for **chemically synthesized peptides** because they **fall outside the definition of a biological substance**

- But some **basic quality aspects of biologics** use to demonstrate **biosimilarity** should be considered to demonstrate **sameness**:

    - **Impurity characterization**: peptide and process-derived
    - **Manufacturing consistency**

Assessing the immunogenicity risk of impurities is crucial to support 505(j)/Article 10(1)

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Impurities in generics

Impurities	Peptide-related [a]	Defining acceptable thresholds [b, c]		Process-related	Acceptable thresholds
Chemical synthesis	Stereoisomers Deletions Insertions Truncations	> 0.1% report **> 0.5 % identify** > 1.0% qualify	≤ RLD **New Impurities** at **0.1-0.5%** characterized, identified, and justified	Elemental impurities Residual solvents	ICH Q3C, ICH Q3D
Biological manufacturing	Truncated forms HMW species Aggregates			HCP hDNA Endotoxin	ICH Q6B

[a] ICH Q3A(R2), ICH Q3B(R2)
[b] Ph. Eur. Monograph "Substances for Pharmaceutical Use" for peptide-related impurities
[c] FDA Guidance 2021

Impurity thresholds are relevant to:

1) Demonstrate **manufacturing consistency**
2) Define **acceptable impurity levels (safety thresholds)** in **daily dose**
3) Inform **concentration range** for **"in vitro" immunogenicity assays** (translability)

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“Non-clinical methods” to support sameness demonstration

Orthogonal methods are recommended:

1) Prediction of new CD4 T cell epitopes using “in silico” tools (peptide-related impurities)
2) “In vitro” assays (MAPPS, DC:T cells, PBMC, indicator cell lines) (peptide- and process- related impurities)

Relevant aspects to communicate in the immunogenicity risk assessment:

1) Description of the prediction algorithm (unnatural amino acids and primary sequence modifications)
2) Clear description of experimental design for “in vitro” assays, including cell viability, and rationale for selection of product concentration and method suitability controls
3) If indicator cell lines are selected, provide rationale for representativeness of the readouts to primary cells
4) Justification of selected readout (cytokine, proliferation)

Lee JK et al., AAPS J. 2026; FDA, May 2021

Teriparatide generics

Teriparatide: recombinant human 34 amino acid long peptide (*E. coli*). Active fragment human parathyroid hormone (PTH)
Indication: Osteroporosis
Dosage: daily s.c.
Immunogenicity: 3% of cross-reactive ADA (12 months). No apparent clinical consequences (FORTEO USPI, 2024).

RLD/RMP	USA (FORTEO®)	EU (FORSTEO®)
Teriparatide	2 505(j) 1 505(b)(2)	Article 10(4) CP Article 10(1) DCP Article 10(3) DCP

Therapeutic Equivalents Teriparatide ; Klein et al., Front. Med., 2024

Implications of DCP/CP in PV and interchangeability in EU

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Liraglutide generics

Liraglutide: human recombinant GLP-1 analog (97% homology). Expression system: *S. cerevisae*
Indication: Chronic weight management
Dosage: daily s.c.
Immunogenicity: Only a subset of all treated subjects (44% of total) were tested for ADA at the end of treatment (26 weeks or longer). 9% TE-ADA with ~50% cross-reactivity to endogenous GLP-1% incidence. NAb ~ 1% (to analog). No identified clinically significant consequences (VICTOZA USPI, 2025).

RLD/RMP	USA (VICTOZA®)	EU (VICTOZA®)
Liraglutide	505(j)	Article 10(1) DCP - Rejected
	USA (SAXENDA®)	**EU (SAXENDA®)**
	505(j)	Article 10(1) DCP (pre-filled pen)

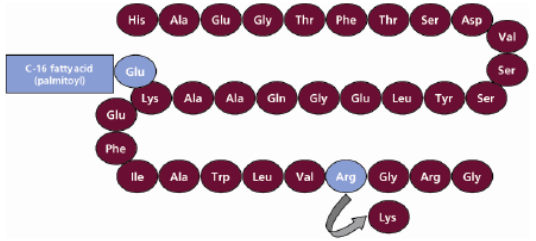
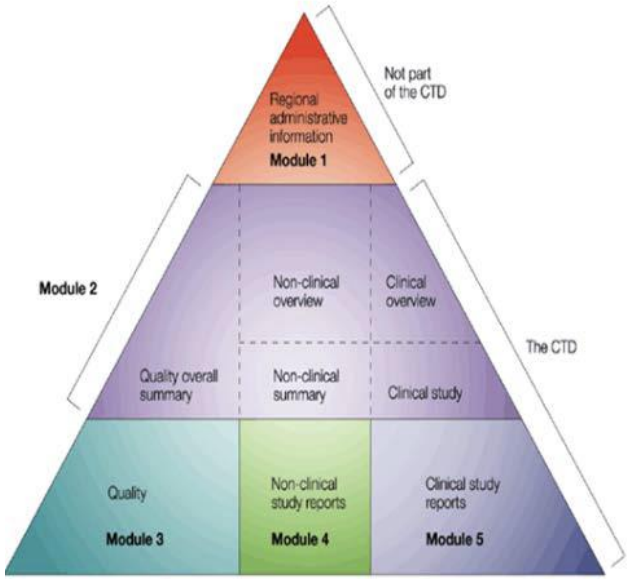


Figure 1. Structural Formula of liraglutide

ANDA / Generic application documentation

- Prepare an **immunogenicity risk assessment (IRA)** describing:

1. Previous clinical experience with RLD/RMP (immunogenicity aspects)
2. Summary of manufacturing process (i.e. rDNA → chemical synthesis)
3. Impurity characterization in DS and DP
    1. Results from “in silico” analysis (new peptide-related impurities)
    2. Results from “in vitro” cell studies (new peptide-impurities and process-related impurities)
    3. If available, submit reports, as IRA document appendices
4. Conclusion to support no incremental risk of immunogenicity



Chamberlain, P., Bioanalysis, 2019
ICH M4E(R2)
EMA, 2017
FDA, 2019

- The **IRA** can be submitted as:

1. Independent report under eCTD Module 5.3.5.3
2. Cross-referenced under eCTD Module 2.7.2.4 Special studies (OPTIONAL: Include synopsis)

New Drug Application

USA market

Peptide particularities

Immunogenicity Risk Assessment

- **Primary amino acid sequence modifications** and chain length limit accuracy of current “in silico” tools (unnatural amino acids, acylation)
- **Sequence modifications** may challenge development of critical reagents (reduced antigen presentation of acylated peptides)
- **DP formulation**

Bioanalytical considerations

- **Domain specificity** characterization should be leveraged for **chimeric peptides**
- **Cross-reactivity and NAb** to **native peptide**

Clinical outcomes

- **Extended half-life** may have consequences in the **long-term tolerance to endogenous counterpart**
- **Pharmacokinetics evaluations** need to be adapted to **product dosing and drug disposition**
- **Evaluation of PD markers** may be more informative to interpret risk of **neutralizing activity** (titer and cross-reactivity)
- Consistent reporting of **Injection site reactions** (**ISR**) by clinical sites

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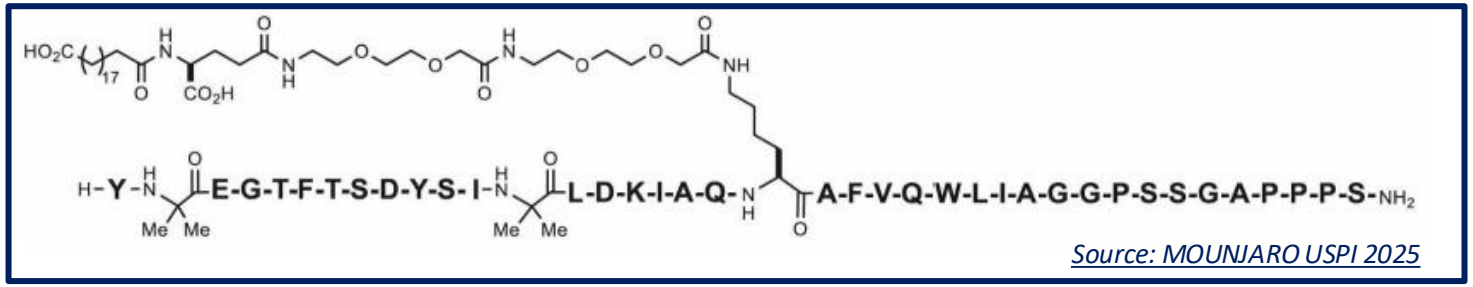
Tirzepatide (MOUNJARO ®)



Source: MOUNJARO USPI 2025

Immunogenicity

ADA incidence: 51%

Cross-reactivity to native GIP: 34%

Cross-reactivity to native GLP-1: 14%

NAb to each tirzepatide domain:

GIP : 2% ; nGIP: 0.9%

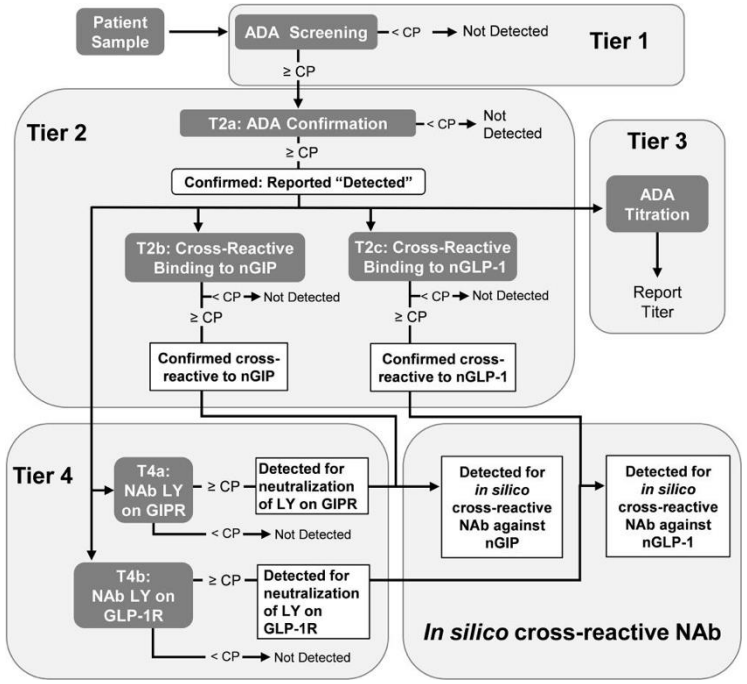
GLP-1: 2%; nGLP-1: 0.4%

Clin Pharm conclusions:

No clinically significant effect in exposure (CL/F) or effectiveness (%HbA1c)

Clinical experience:

Increased ISR frequency



Sources:

Mounjaro NDA drug approval package; Mullins et al. 2023

- ✓ Sequence homology analysis and side-by-side "in silico" analysis of CD4 T cell epitope frequency/affinity predicts high likelihood of cross-reactivity of ADA to endogenous GLP-1 and GIP 1
- ✓ Clinical consequences of neutralizing activity to native peptides are likely to overlap with those of anti-tirzepatide NAb

These are some of the relevant risks that need to be identified early in development

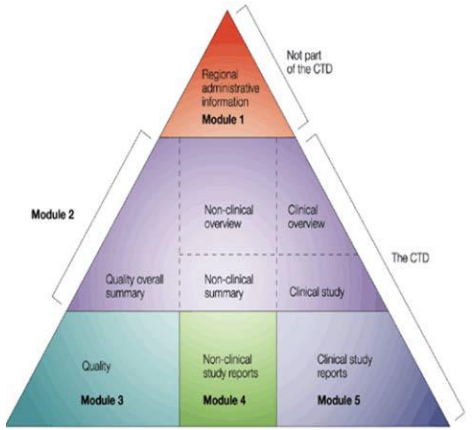
IRA supports early safety assessment

Early development
(**Safety**)

NCE
((505(b)(1); Art.8(3))

IND/CTA
Immunogenicity Risk Assessment (IRA)

- Intrinsic immunogenicity (impact of modifications in prediction and Ag processing)
- Product variants and non-peptide impurities and by-products (i.e. enantiomers, neo- epitopes, rDNA, rHCP, aggregates)
- DP formulation
- Systems biology and/or MoA (Off-target/on-target immune toxicities)
- "In vitro" assays used to derisk immune toxicities
- Inferred fit-for-purpose bioanalytical strategy
- Clinical sampling plan



Chamberlain, P., Bioanalysis, 2019
ICH M4E(R2)
EMA, 2017
FDA, 2019

Effect of ADA/NAb in Tirzepatide pharmacokinetics

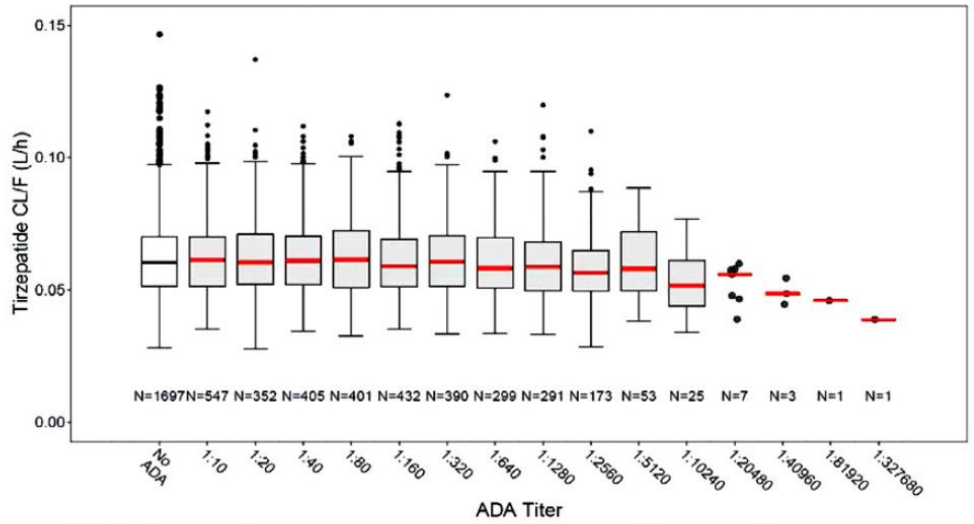


Figure ISI.4.5. Tirzepatide apparent clearance (CL/F) across ADA titer in Phase 3 studies.

Mounjaro NDA drug approval package; Mullins et al, 2023

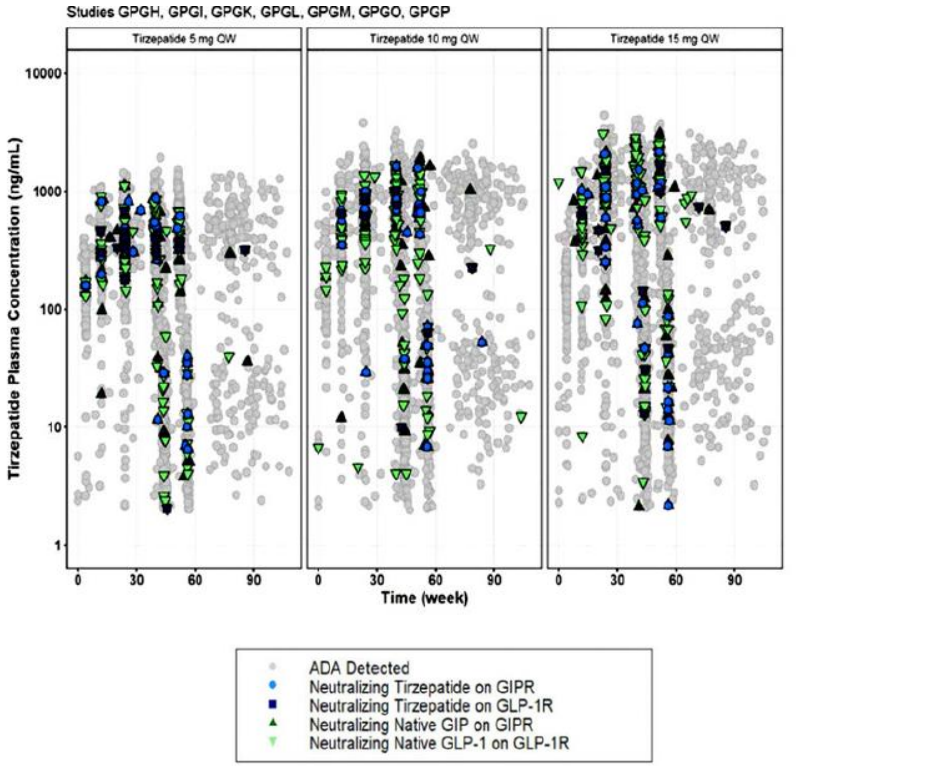
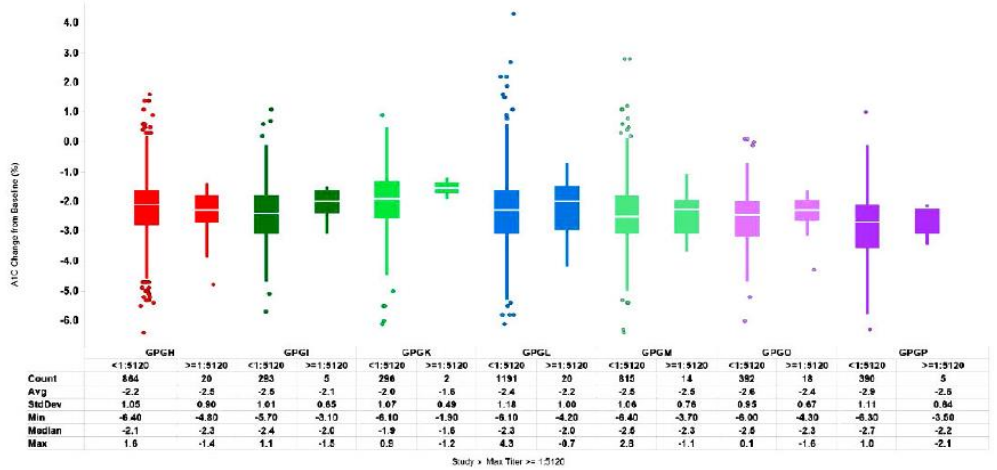


Figure ISI.4.6. Comparison of observed tirzepatide concentrations from patients with detected tirzepatide neutralizing antibodies in Phase 3 studies.

No clinically significant changes in pharmacology readouts when analyzed by ADA titer groups or NAb specificity

Immunogenicity and tirzepatide efficacy (safety)

A1C change from baseline (%) vs max titer (on treat) (1:5120): TZP Only



	GPGH		GPGI		GPGK		GPGL		GPGM		GPGO		GPGP	
	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120
Count	884	20	283	5	296	2	1191	20	815	14	392	18	396	5
Avg	-2.2	-2.5	-2.5	-2.1	-2.0	-1.5	-2.4	-2.2	-2.5	-2.5	-2.5	-2.4	-2.9	-2.5
StdDev	1.05	0.90	1.01	0.65	1.07	0.49	1.18	1.00	1.06	0.76	0.95	0.67	1.11	0.84
Min	-6.40	-4.80	-5.70	-3.10	-6.10	-1.90	-6.10	-4.20	-6.40	-3.70	-6.00	-4.30	-6.30	-3.60
Median	-2.1	-2.3	-2.4	-2.0	-1.9	-1.6	-2.3	-2.0	-2.6	-2.3	-2.5	-2.3	-2.7	-2.2
Max	1.6	-1.4	1.1	-1.5	0.6	-1.2	4.3	-0.7	2.8	-1.1	0.1	-1.6	1.0	-2.1

Study > Max Titer >= 1:5120

Abbreviations: ADA = antidrug antibody; Avg = average; A1C = glycated hemoglobin (HbA1c); Max = maximum; Min = minimum; StdDev = standard deviation; TZP = tirzepatide.

Figure ISI.4.8. **Change from baseline in HbA1c for tirzepatide-treated patients with ADA titer <1:5120 vs ≥1:5120.**

Table ISI.4.25. **Change from Baseline in HbA1c for Tirzepatide-Treated Patients with or without NAb+ against Tirzepatide Activity to GIPR and/or GLP-1R**

Statistic	GPGH			GPGI			GPGK			GPGL			GPGM			GPGO			GPGP		
	TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+	
		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R
N	398	12	11	129	2	5	134	4	1	551	21	20	461	16	26	106	23	25	151	9	11
Mean	-2.1	-2.3	-2.4	-2.5	-2.2	-3.2	-2.0	-1.4	-1.9	-2.3	-2.5	-2.1	-2.4	-2.4	-2.2	-2.6	-2.7	-2.6	-2.8	-3.8	-2.9
SD	1.08	0.58	0.67	1.10	0.28	1.17	1.24	0.98	-	1.28	1.48	0.89	1.16	0.74	0.87	0.97	0.90	0.82	1.05	0.62	1.42
Min	-6.40	-3.30	-3.50	-5.70	-2.40	-4.50	-6.10	-2.70	-1.90	-6.10	-4.60	-3.60	-6.40	-4.00	-4.70	-4.50	-4.70	-4.70	-5.80	-5.00	-5.70
Median	-2.0	-2.3	-2.2	-2.4	-2.2	-3.6	-1.8	-1.3	-1.9	-2.2	-2.9	-2.2	-2.4	-2.3	-2.1	-2.6	-2.5	-2.4	-2.7	-3.5	-2.2
Max	1.4	-1.2	-1.5	0.6	-2.0	-1.4	0.9	-0.4	-1.9	4.3	1.9	-0.4	2.8	-1.1	-0.6	0.1	-1.5	-1.5	-0.1	-3.1	-1.0

Abbreviations: GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor; HbA1c = glycated hemoglobin; Max = maximum; Mean = arithmetic mean; Min = minimum; N = number of patients; NAb = neutralizing antibody; SD = standard deviation; TE ADA = treatment-emergent antidrug antibody; TZP = tirzepatide.

- ✓ ADA titers ranged from 1:20 to 1:327860 (median 1:160)
- ✓ About 45.4% patients had a titer > median titer (1:160)

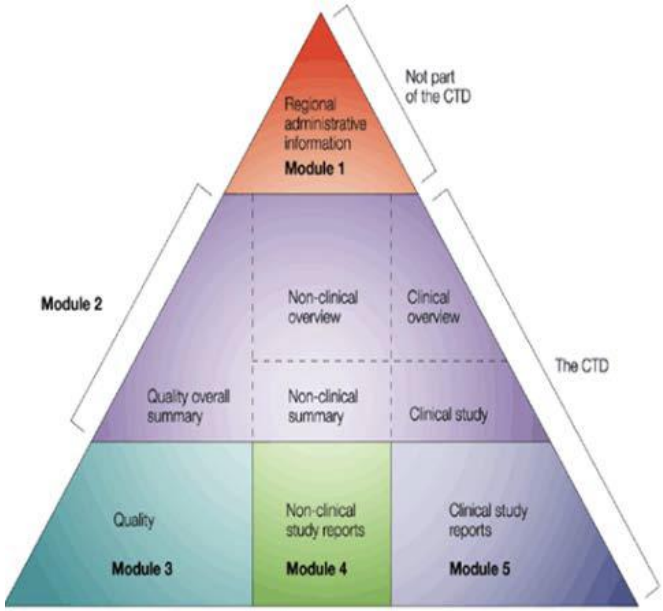
✓ No impact of NAb specificity on Hb1AC change

Market Application

IND/CTA → → → → → NDA/NCE ((505(b)(1); Art.8(3))

EOP2 and PreNDA meetings as optimal windows to discuss final dataset and immunogenicity analysis based on results from Phase 1b/2 studies

Market application **(Safety, exposure and efficacy)**



NDA/MAA

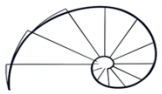
Integrated Summary of Immunogenicity (ISI)

- IRA (historical of the program)
- Justification of bioanalytical strategy (i.e. 3-tier approach)
- Adequacy and genealogy of analytical methods used in supportive clinical studies
- Immunogenicity results from supportive clinical studies
- Interpretation of relevant clinical outcomes (safety, exposure, and efficacy) in an ADA positive and negative background
- Clinical management

Chamberlain, P., Bioanalysis, 2019
ICH M4E(R2)
EMA, 2017
FDA, 2019

Conclusions

- Tailored risk assessments are expected
  - “In silico” and “in vivo” methodologies expected to be “fit-for-purpose” so they can support demonstration of sameness (505(j) and generics)
  - Clear rationale to connect quality aspects to potential immunogenicity risks (impurities characterization and safety thresholds) (505 (j) and generics)
- “Fit-for-purpose” bioanalytical strategy (NME)
- Preparation of IRA and ISI, like for therapeutic proteins, helps internal decision making and regulatory understanding
- Agency meetings to define final testing strategy and immunogenicity dataset analysis are recommended
  - Use of initial clinical immunogenicity data from Phase 1/1b and Phase 2 when available
- Regulatory expectation to present immunogenicity in an ISI for market applications



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Open questions

How to define an optimal **bioequivalence (BE) study design** to address **residual immunogenicity concerns** to support generics and hybrid applications?

Can some commonalities from biosimilars development (Phase 1 PK/ADA study) be identified and leveraged?

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THANK YOU!

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https://immunogenicityintegrated.com/

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