EUROPEAN BIOANALYSIS FORUM PARALLEL SESSION 2: BIOSIMILARS

The use of PK, PD and ADA bioanalysis for evaluation of the overall Immunogenicity of biosimilars and the bioanalytical challenges for determining if there are equivalent safety risks

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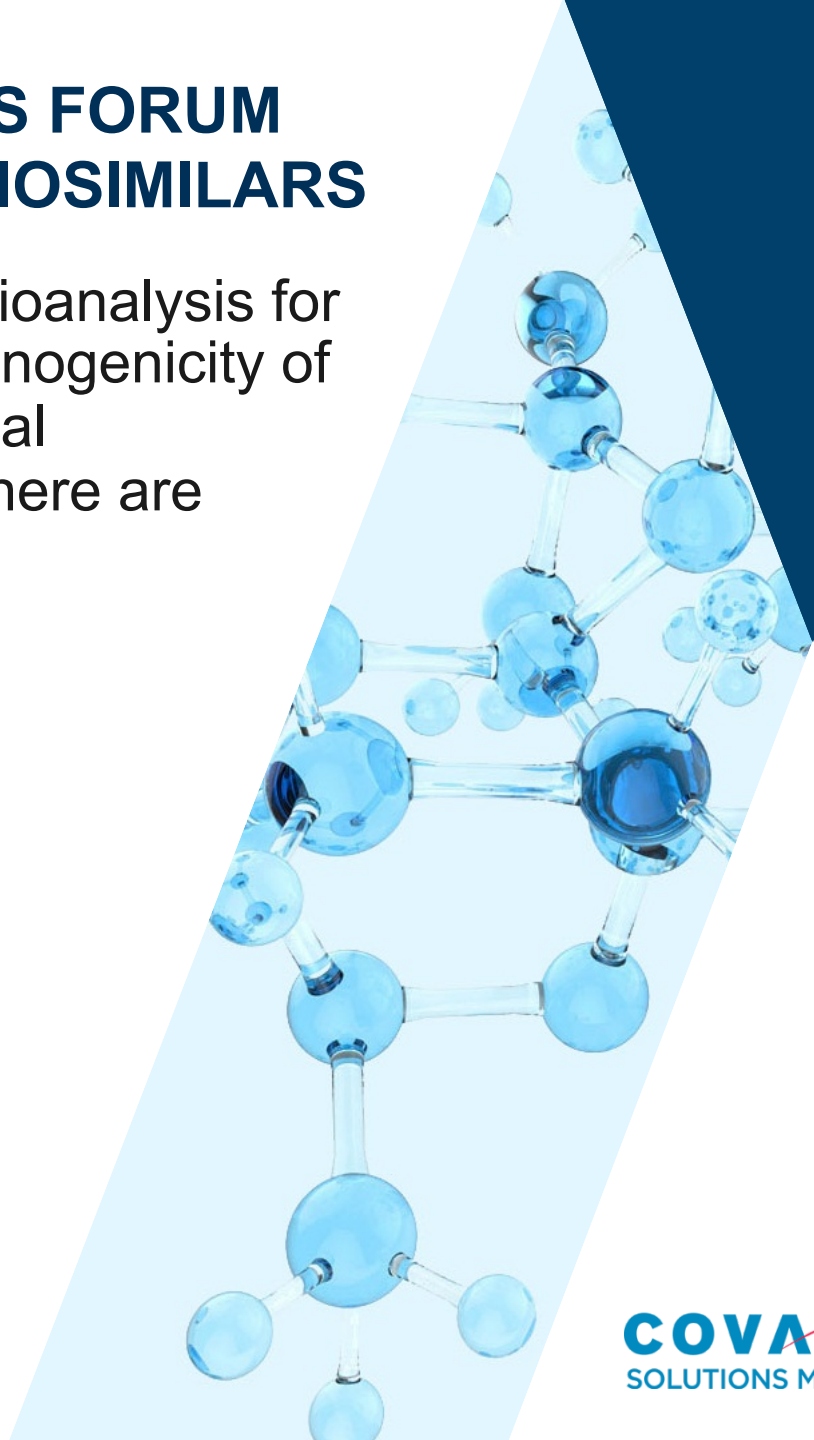
20th November 2014



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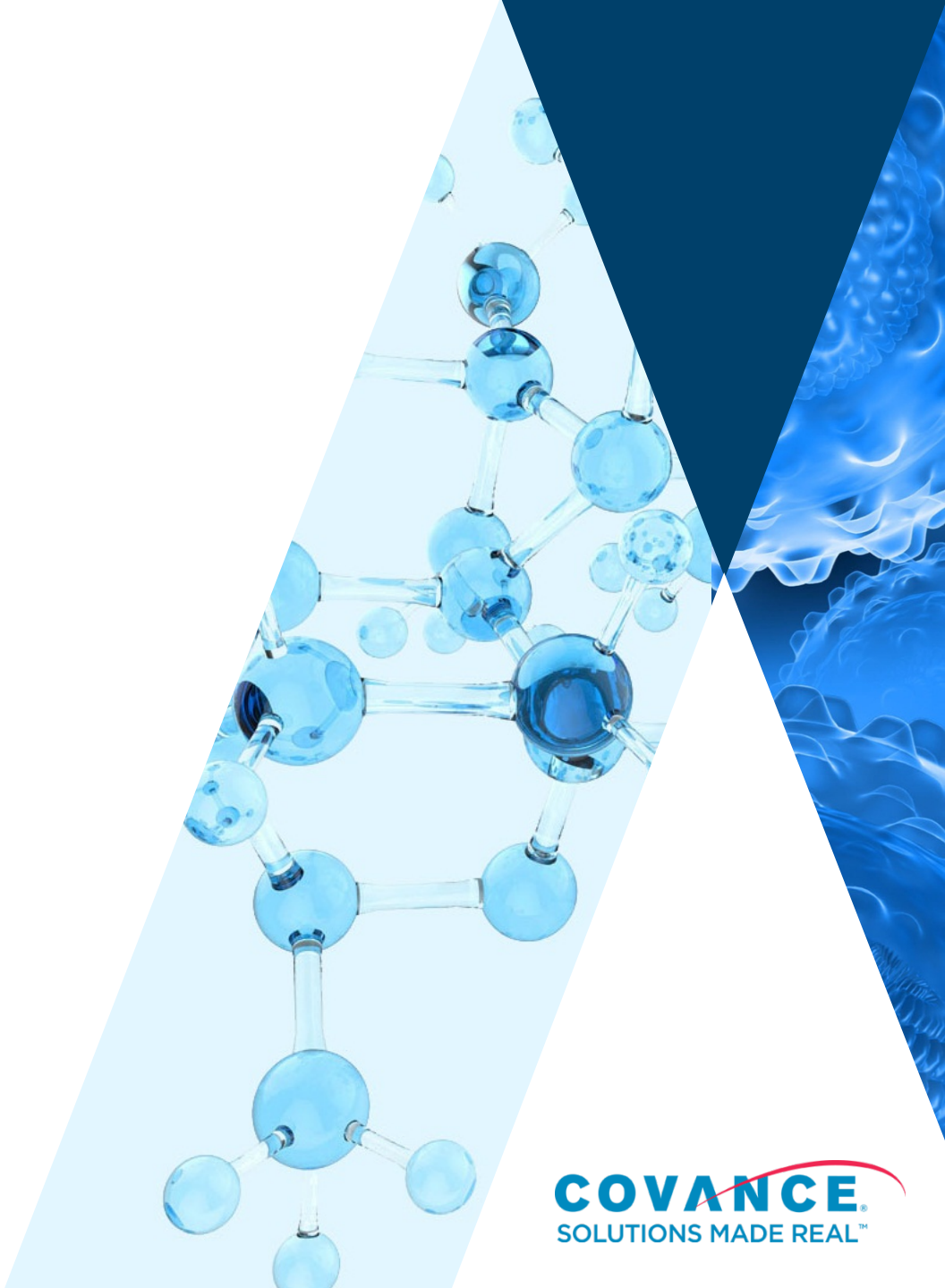
Agenda

- Introduction
  - The global regulatory landscape for biosimilars
  - Factors that influence immunogenicity
  - Biosimilar immunogenicity safety considerations
  - What does ADA, PK and PD (NAb) data tell us about the complex safety questions?

- Building assays to generate comparable bioanalytical data
  - PK
  - ADA
  - PD (Nab)

- How do you evaluate if you have comparable immunogenicity between the innovator and biosimilar materials?

Introduction



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What is the global regulatory landscape for biosimilars?

EMA

- Established EMA approval pathway
- 20 approved within the following product classes:
  - Human Growth Hormone, G-CSF, EPO, Insulin and Anti-TNFa

FDA

- Biologics Price and Innovation Act passed in 2010
- FDA 2012 draft guidance
  - Risk-based “totality-of-the-evidence” approach
- FDA 2014 draft guidance
  - Reinforces the main points from the 2012 Guidance, but provides some additional detail about how they will define proposed product as "highly similar, similar or not similar."
- 1 approved product under the biosimilar guidelines (G-CSF)

WHO

- Guideline came out in 2009

ROW

- Argentina, Australia, Brazil, Canada, Japan, Jordon, Korea, Malaysia, Saudi Arabia, Singapore, Taiwan, Turkey, Venezuela – Guidance available
- Colombia, Cuba, India, Mexico, South Africa and Thailand – Draft guidance available
- China – No specific guidance for biosimilars

No specific guidance on using PK, PD and ADA bioanalytical data to show comparable immunogenicity between the Innovator and Biosimilar

Factors that influence biosimilar immunogenicity

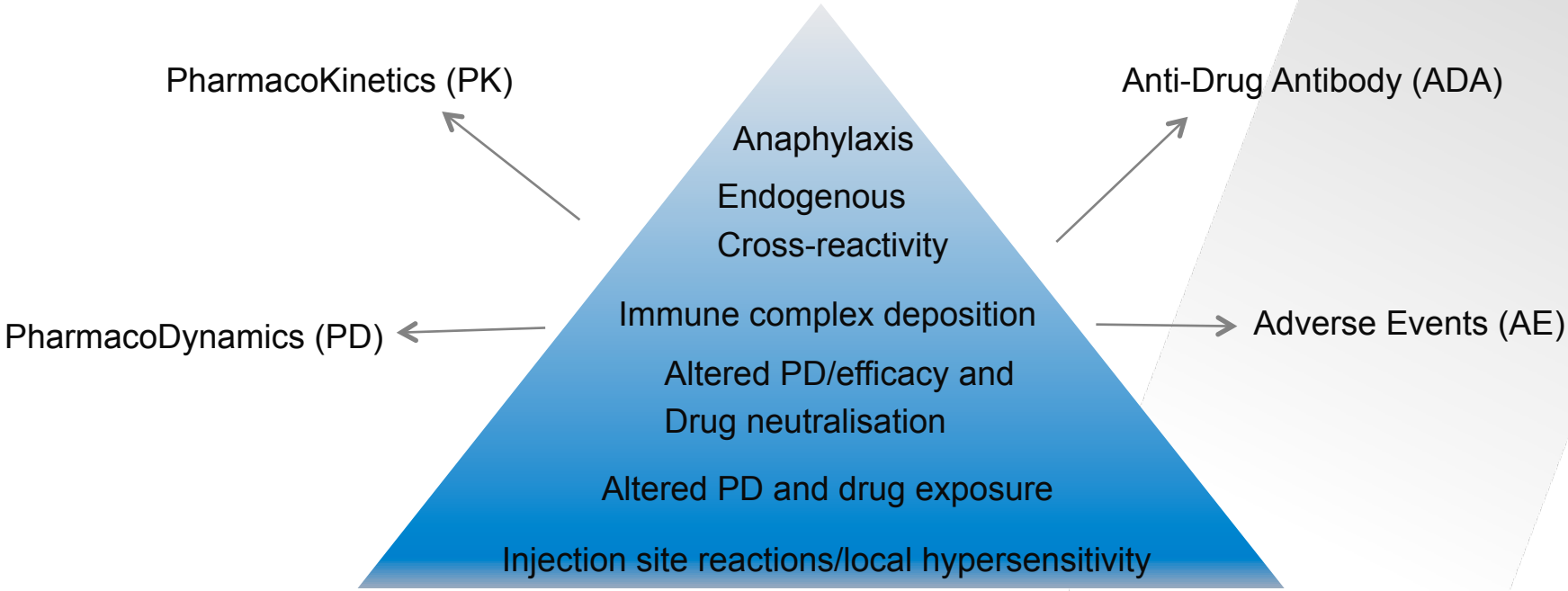
- New glycosylation pattern?
- Correctly folded?
- Aggregation?
- Truncated?
- Oxidation
- Phosphorylation
- New disulfide bonds?
- Formulation
- Route of Administration
- Dose and length of treatment
- Patient factors: health status, comedications, etc…

All of these factors can result in unwanted immunogenicity

Erythropoietin > Antibody mediated pure red cell aplasia (PRCA)

Biosimilar Hexal (HX575) - Tungsten exposure in pre-filled syringes precipitated immunogenic reactions.

Biosimilar Immunogenicity safety considerations



ADA + PK + PD + AE = Immunogenicity Assessment

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What does ADA, PK and PD (NAb) data tell us about these complex safety questions?

ADA…onset of immune response & kinetics

PK….pharmacokinetics (drug exposure)

PD….pharmacodynamics (drug activity/efficacy)

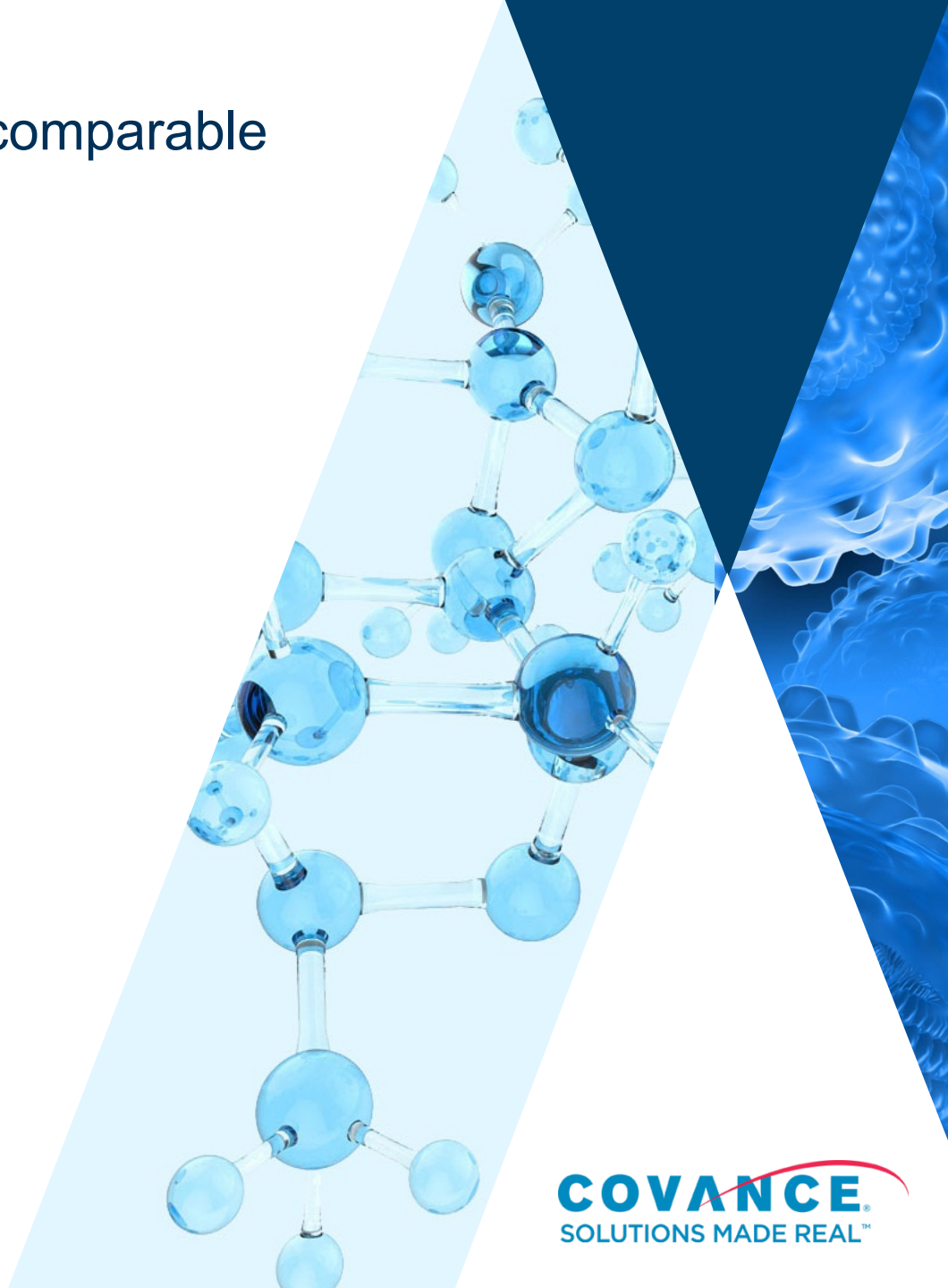
….all are important when interpreting study results!

….and to demonstrate equivalent immunogenicity all bioanalysis needs to be performed with assay formats that are comparable for the biosimilar and innovator materials

….currently no specific bioanalysis guidance exists on how to achieve this

Building assays to provide comparable bioanalytical data

- Comparable PK assay
- Comparable ADA assay
- Comparable PD assay



Comparable PK assays

Recommendation – Single ligand binding assay to support PK assessment of both Biosimilar and innovator materials

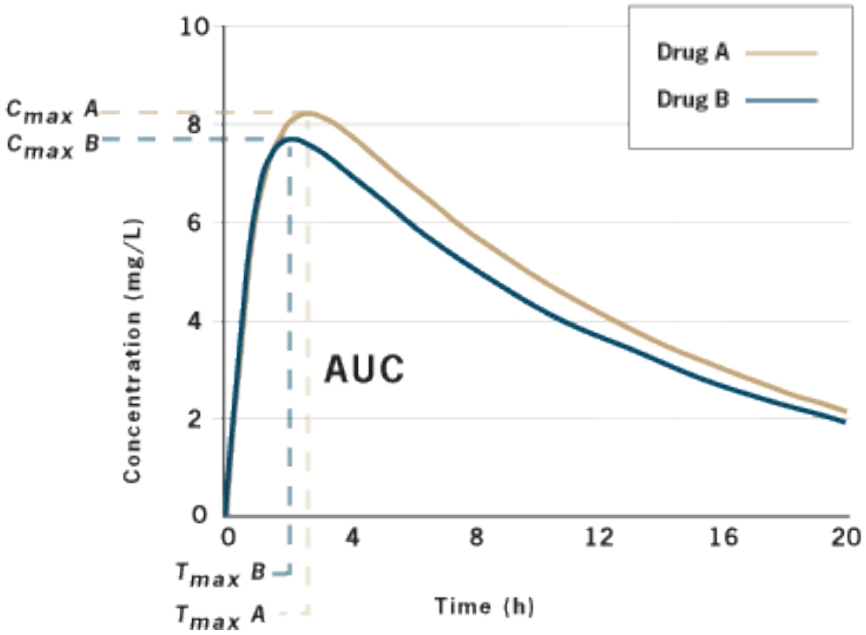
- Joseph Marini later today

Preferred approach for assay generation:

- Single assay in which during assay development it has been shown that biosimilar and Innovator standard curves are comparable.
- Single assay (preferably with biosimilar standard curve) in which during assay validation Biosimilar and Innovator QCs are comparable
- Single assay sample analysis

Demonstrating PK data is comparable

Adapted from Birkett D, 2003



Two versions of a drug are generally said to be biosimilar if the 90% confidence intervals for the ratios of the geometric means (innovator vs. biosimilar) of the AUC and Cmax fall within 80% and 125%. The Tmax (innovator vs. biosimilar) must also be comparable — and there should not be any significant differences between different patients

However, need to consider this in the context of ADA data.

Comparable ADA assays

One assay or two?

- Still a lot of debate within the industry about what approach is best
- Main concern for one assay approach using a bridging assay format is the potential to miss novel immunogenic epitopes between the Innovator and Biosimilar
- Comparability of Innovator vs Biosimilar results is easier to define with one assay and one cut point
- Sample analysis can be conducted blinded using one assay

How do you demonstrate a comparable assay with a qualitative assay format?

Case study examples

- Assay sensitivity approach with 2 assays
- Drug tolerance approach with one assay

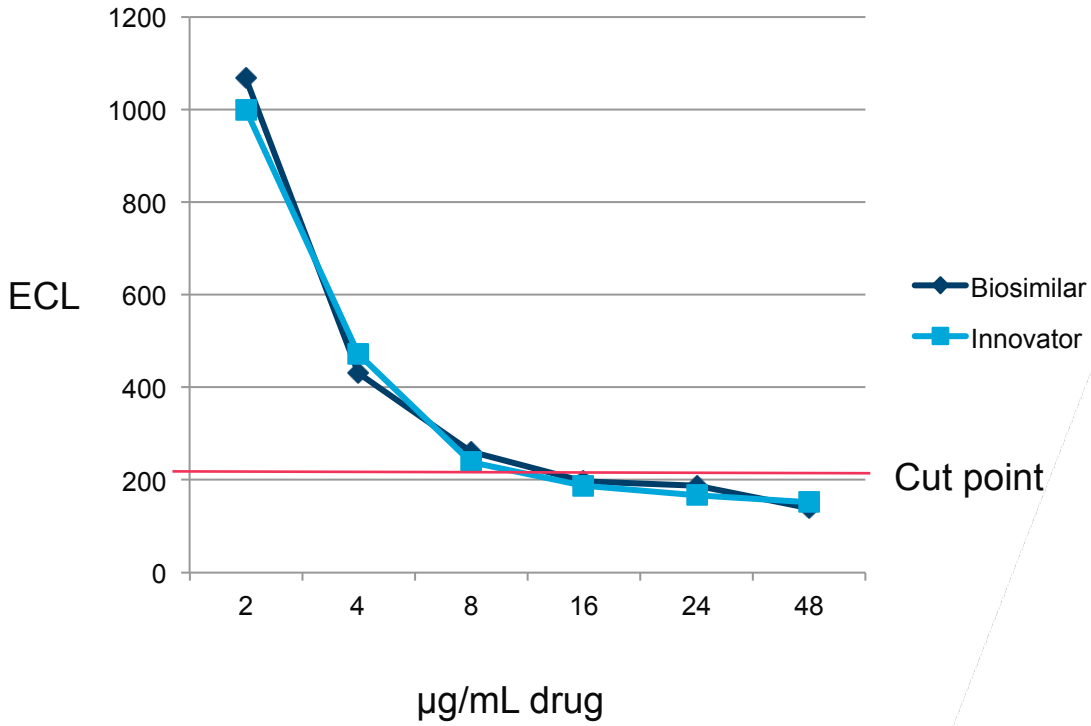
Defining comparability of two ADA assays based on titre of a single reference material in both assays

PC (ng/mL)	Assay 1 (S/N)	Assay 2 (S/N)	% Difference
1000	99	105	-5.88
500	51	45	12.50
250	24	25	-4.08
125	14	12	15.38
62.5	7	6	15.38

% Difference of less that 20 % indicates assays are comparable across the range of detection

Defining comparability of one assay by determining drug tolerance with Innovator and Biosimilar

500 ng/mL of reference material in the presence of increasing concentrations of Biosimilar or Innovator material



The same drug tolerance of each drug indicates comparability of the single assay approach

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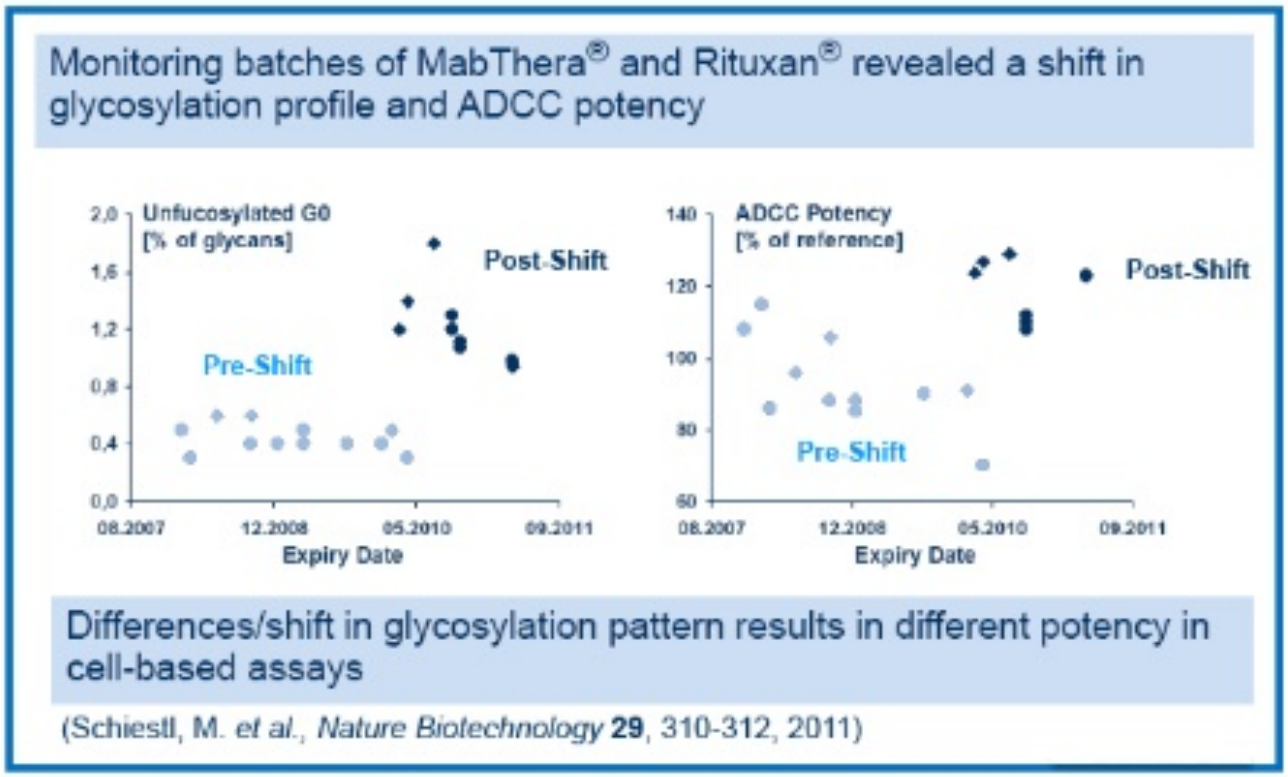
Comparable PD assays

Critical to asses the biological efficacy of the biosimilar is comparable to the Innovator material



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PD Assays

High variance of certain assay formats may mask real differences that occur between the innovator and biosimilar materials

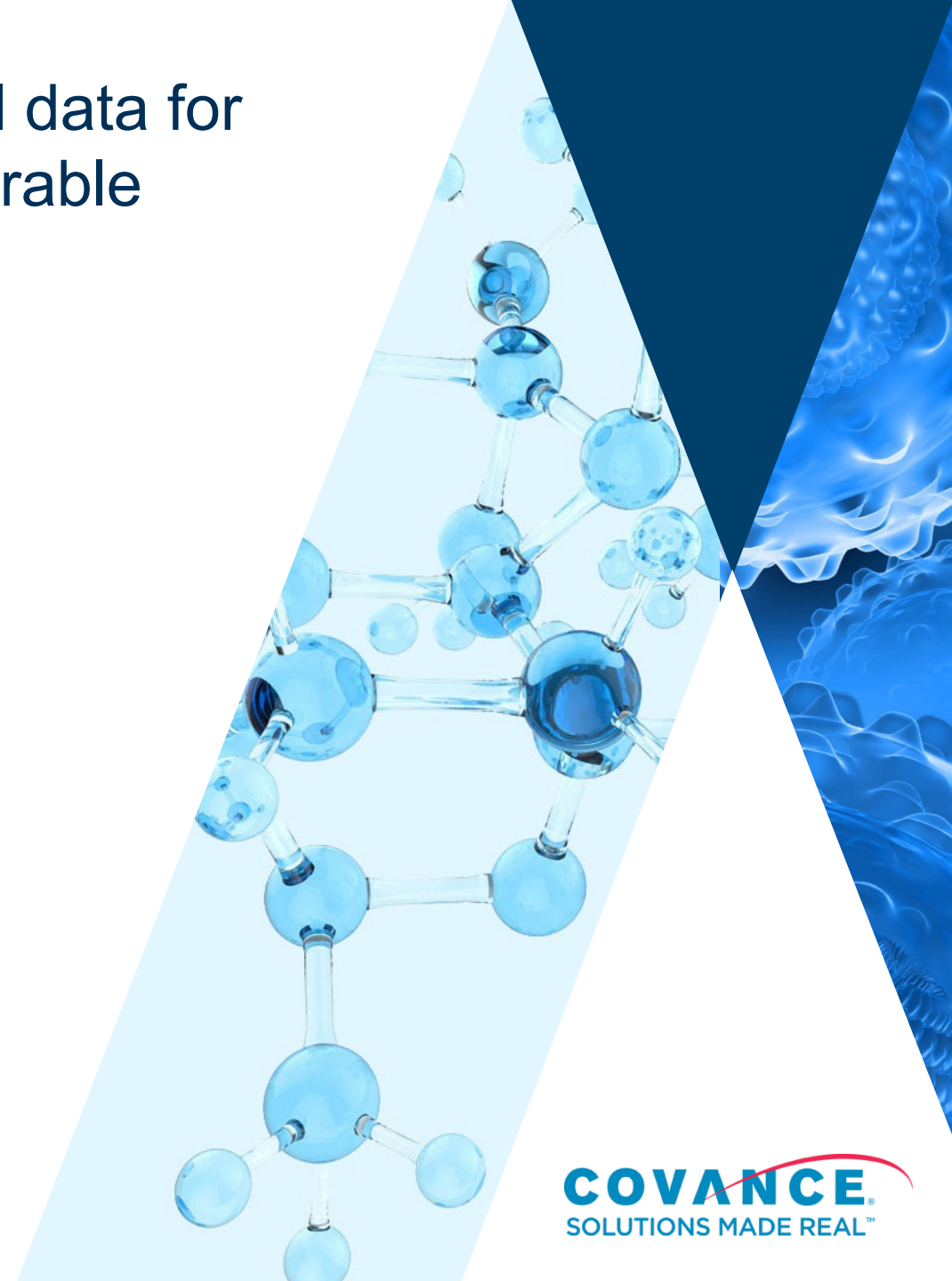
Functional activities to monitor:

- Target binding
- Pharmacological effect e.g. proliferation or inhibition
- MAb effector function (ADCC, CDC or Fc binding)

It may be possible to use the PD assay as a basis for a neutralising antibody assay

PD results need to be interpreted in the context of ADA results

Interpreting bioanalytical data for demonstration of comparable immunogenicity



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What does PK, ADA and PD bioanalytical data tell you about Immunogenicity?

ADA	PK	PD (NAb)	Category	Immunogenic effect
Positive	Normal	Normal	Binding	Antibody is binding to none effector region of drug
Positive	Increased	Increased	Sustaining	Antibody binding to drug and increasing exposure
Positive	Decreased	Decreased	Clearing	Antibody binding to drug and decreasing exposure
Positive	Decreased	Decreased	Neutralising	Antibody binding to drug and neutralising activity

Need to interpret results in the context of all bioanalytical data generated and relate these to any adverse events seen in the study population

Conclusions

- True Comparable assay formats for ADA, PK and PD are required
- Good scientific practice needs to be followed to define assays are capable of demonstrating comparable data analysis
- Guidance on the approaches to be followed are evolving
- The overall Immunogenicity assessment can only be defined in the context ADA, PK, PD and Adverse Events

Comparable ADA assay + Comparable PK assay + Comparable PD assay = True comparability of Immunogenicity assessment