Immunogenicity Risk Assessment of Therapeutic Proteins: A Guide to Risk Assessment for Therapeutic Peptides and Generic Peptides

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Disclosure and Disclaimer

Unless specified as FDA Guidance or Regulations, this speech reflects the views of the author and should not be construed to represent FDA's views or policies. I have no financial relationships to disclose.

"Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products"

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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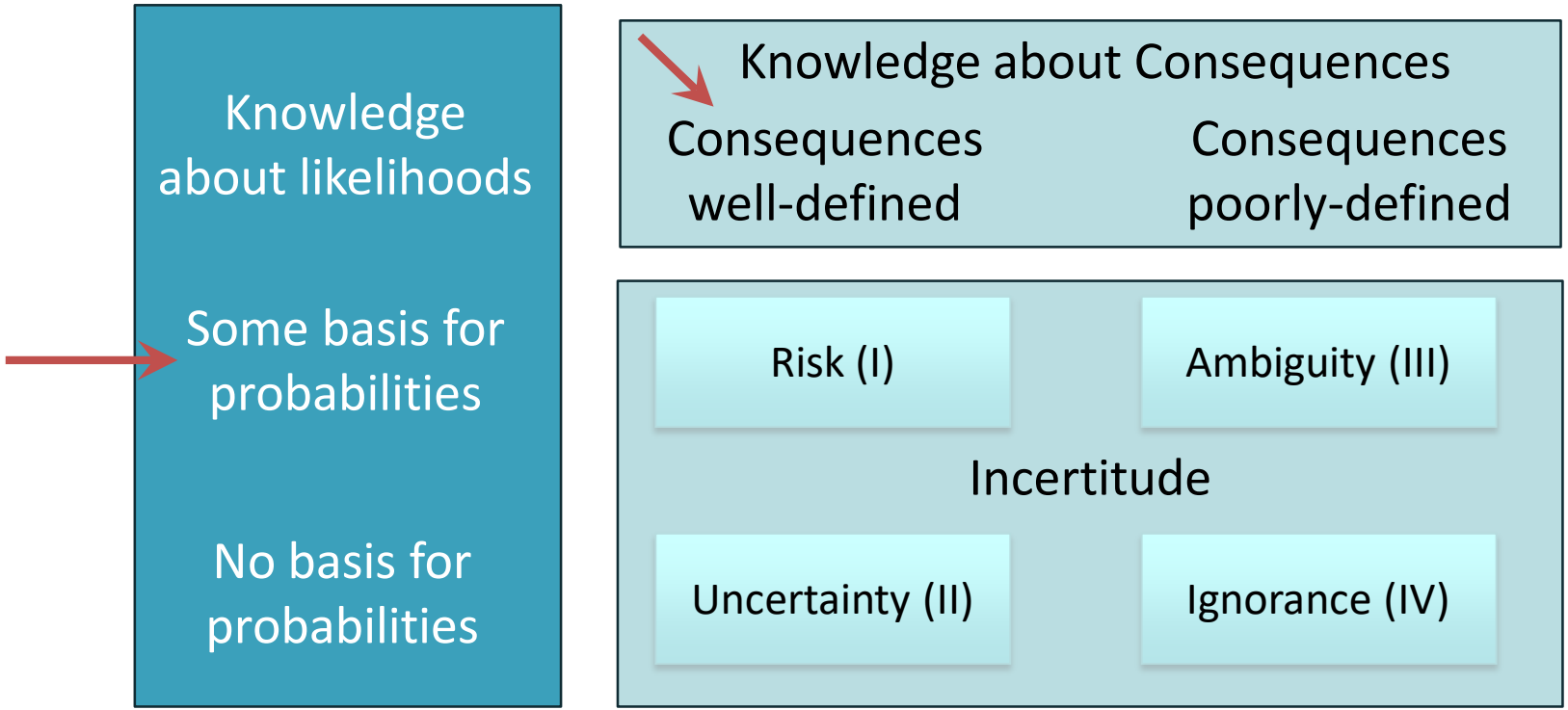
Clinical/Medical

"Immunogenicity is defined as the propensity of the therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically related adverse clinical events"

Immunogenicity Risk Assessment for Therapeutic Proteins and Peptides Requires Knowledge of Consequences and Probabilities

(modified from Stirling and Ghee 2002)



Immune Responses to Therapeutic Proteins and Peptides: *Consequences for Safety*

Fatality/Severe Morbidity

- Anaphylaxis-clinically defined, does not imply mechanism

- ***Neutralization of endogenous protein with non-redundant function generated by antibodies to the therapeutic homolog:***

  Endogenous factor with non-redundant function resulting in a deficiency syndrome e.g., Pure Red Cell Aplasia from Anti-Drug Antibodies (ADA) to erythropoietin;

- ***Neutralizing Antibodies to Life Saving Therapeutics***

  Enzyme replacement therapy for lysosomal storage diseases
  Coagulation factors for hemophilias

- Immune Complex Mediated Disease: delayed hypersensitivity

  serum sickness, nephropathy: observed in the context of administration of high doses of therapeutic protein in setting of robust antibody response; “dosing over”

Immunogenicity of Therapeutic Proteins and Peptides Risk Assessment: *Consequences for Efficacy*

Diminished efficacy of highly effective therapeutics

mAbs: e.g. TNF blockers

Alterations in PK

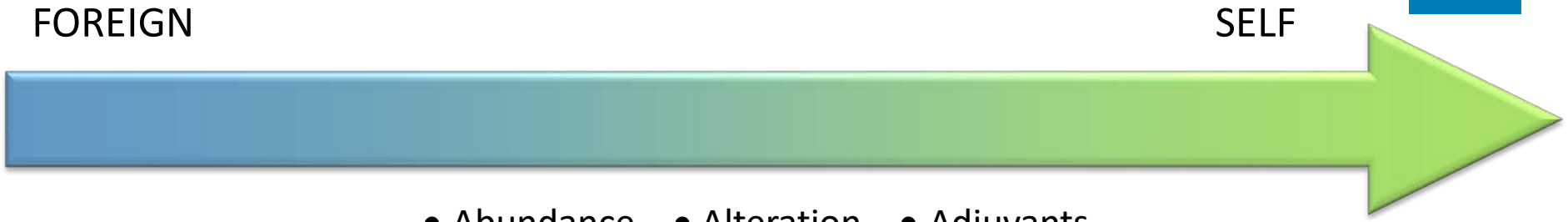
Antibodies to protein therapeutics may diminish or enhance PK/PD

Changes in dosing level to exceed antibody level, “dosing over,” may lead to worsened infusion reactions, epitope spread, generation of neutralizing antibodies, and circulating immune complex mediated hypersensitivity responses

No apparent effect

But sustained response may lead to epitope spread and generation of neutralizing responses, e.g. IL-2

Immunogenicity of Self Proteins Not Dichotomous



Expect Immunogenicity
No tolerance
Neutralize Product
Hypersensitivity

Potential Immunogenicity
Incomplete tolerance
Altered structure/
Antigen Present
Epitope spreading

Rare Immunogenicity
Robust tolerance
Novel Route of
Administration Adjuvants
HLA Haplotype Specific

Immunogenicity Risk Assessment: Consequences Based on Biological Function and Redundancy of Activity

Modified by Barry Cherney and Amy Rosenberg from Holly W. Smith, Eli Lilly

Immunogenicity Risk Assessment: Probabilities Based on Patient and Protocol Factors

Clinical/Protocol Factors

Dosing Frequency	Single		Chronic	Intermittent
Dose Concentration	Very High			Low-Average
Route of Administration	Oral	i.v.	s.c.	Inhaled
Patient Immune Status	Suppressed		Healthy	Activated
Immunomodulatory Action	Immunosuppressant			Immunostimulant
Endogenous Protein Level	High			Low

PROBABILITY =	**LOW**	**UNKNOWN**	**HIGH**

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Multiple Changes in Approved rhu Erythropoietin (Eprex) Associated with Increased Incidence of PRCA

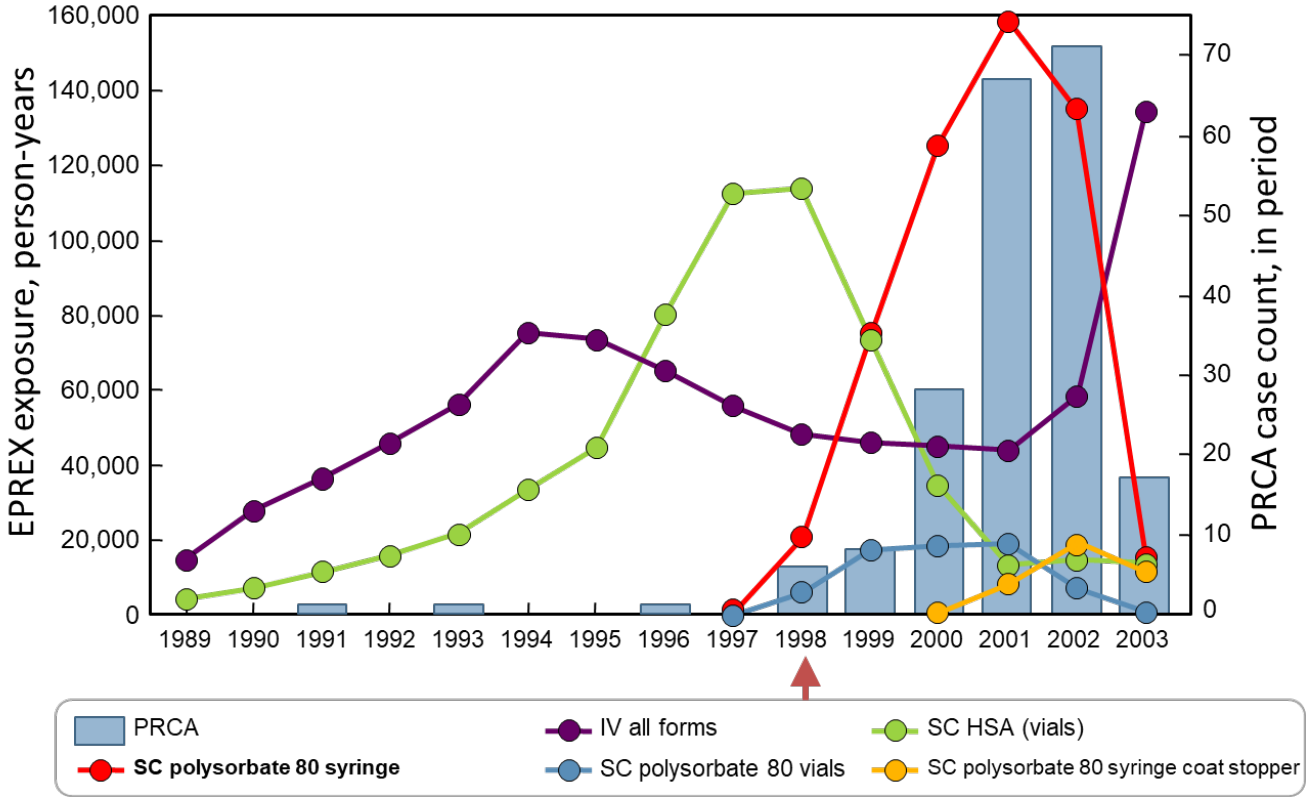
Endogenous Erythropoietin:
Sole factor mediating red blood cell production
Low abundance protein; levels in nanomolar range (sea level); spikes in levels due to changes in oxygen levels: altitude changes, anemia.

Tolerance to therapeutic, widely used in chronic kidney disease, relatively robust:
Few cases of PRCA related to Epo usage prior to 1998: associated with autoimmune disease

Increased incidence in PRCA following changes in formulation, container closure and administration route in 1998

Dramatic Increase in PRCA Cases Associated with Changes to Eprex: Formulation, Container Closure, Route of Administration

(Boven K et al 2005)



PRCA in Development of *Biosimilar* Epo: Suspect Lineup in the Search for the Smoking Gun

- Three cases of NABs and one case of PRCA in development of a biosimilar Epo: ***two implicated batches*** thoroughly analyzed for suspect PQAs
  - Aggregates of Epo arising from:
    - Micelles of erythropoietin: polysorbate generated micelles
    - ***Tungsten leachates*** from tungsten used in needle hub formation in the form of reactive tungsten oxides caused Epo aggregation; shown previously to aggregate other therapeutic proteins
  - adjuvant material leaching from rubber stopper:
    - ***vultac*** responsible for cross linking of rubber protein; but cannot cross link other proteins; vultac has adjuvant properties (Sharma et al 2004)

What if?

Lessons from high risk therapeutic proteins as applicable to peptide/generic peptide therapeutics

Approved peptide based on activity of a non-redundant endogenous protein-> Generic Peptide ANDA

Approved Peptide based on activity of a life saving Enzyme Replacement Therapy → Generic Peptide ANDA

Approved Peptide based on activity of a mAb to TNF-a with high efficacy in autoimmune disease → Generic Peptide ANDA

No room for significant differences in immunogenicity of approved peptide products with established clinical safety profile vs. generic peptides not tested clinically

Case Example of a High Risk Approved Peptide Therapeutic: Teriparatide as Replacement for Parathyroid Hormone a Non-Redundant Endogenous Hormone

- Parathyroid hormone: Endogenous non-redundant 84-amino acid hormone; primary regulator of calcium and phosphate metabolism in bone and kidney
- Teriparatide: approved peptide therapeutic derived from the N-terminal 34 amino acids of human parathyroid hormone as replacement therapy for PTH to treat osteoporosis
- Teriparatide relatively non-immunogenic per clinical study: 2.8% of treated patients developed anti-drug antibodies after twelve months of treatment

Generic versions of Teriparatide must not have significant differences in immunogenicity or patients risk loss of calcium homeostasis

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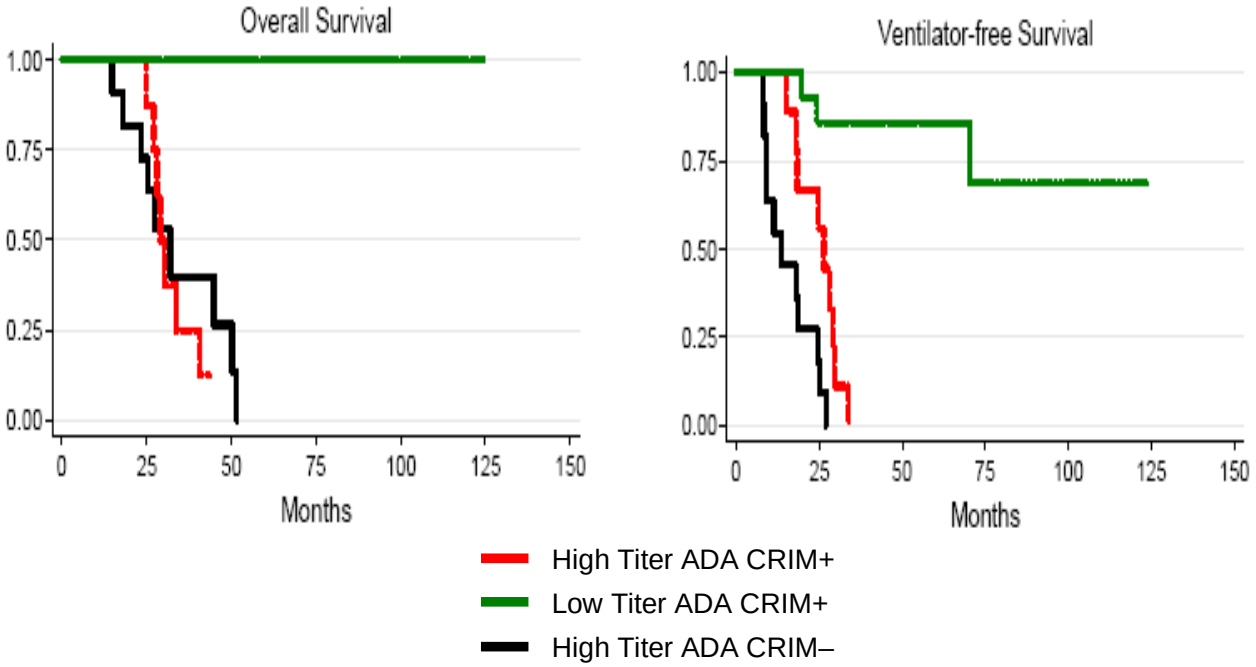
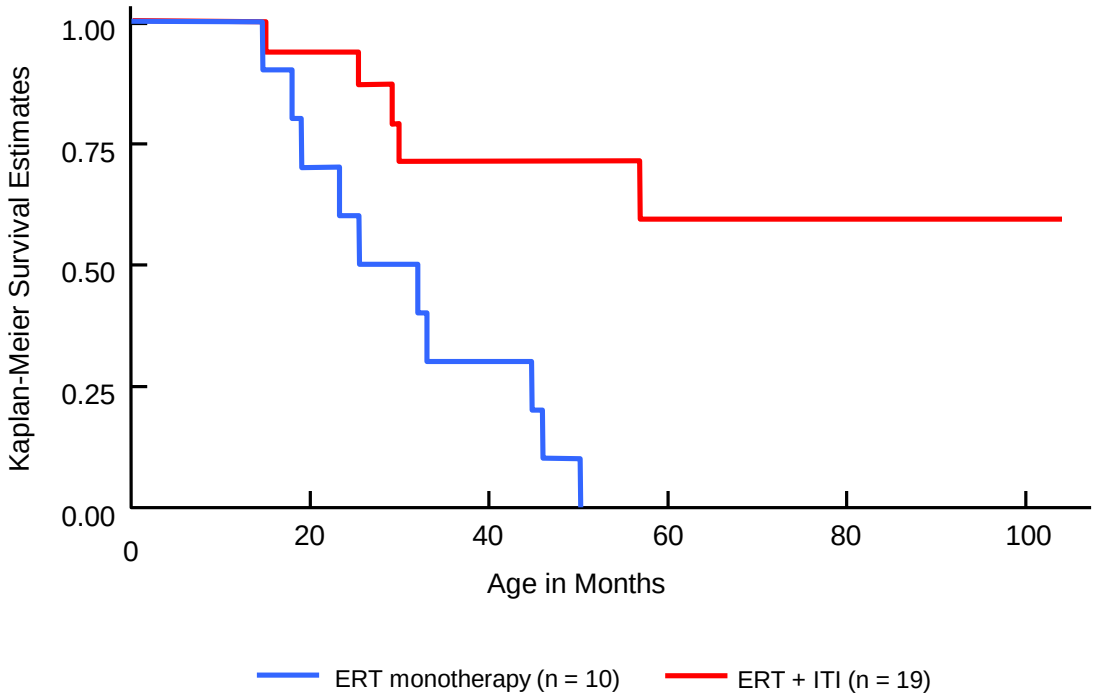
Neutralizing Antibodies to Life Saving Enzyme Replacement Therapy (Myozyme) in Infantile Pompe Disease (IPD) Patients Leads to Respiratory Failure and Death



(Kishnani PS et al 2011)

ERT Tolerant Pompe Patients Experience Prolonged Survival

(Kazi ZB et al JCI Insight 2017)



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Immunogenicity Assessment for High Risk Peptide Generics

- Differences in impurities, formulation components and aggregates may have a profound effect on immunogenicity with the additional caveat that peptides are generally more prone to aggregation than full length proteins
- Robust non-clinical evaluations of proposed peptide generics must be performed for generic peptides in general but are especially critical for generic peptides that are life saving or therapeutic counterparts of non-redundant endogenous proteins/peptides; animal studies may be informative especially for evolutionarily conserved proteins (eg thrombopoietin)
- Residual uncertainty as regards potential for immunogenicity following comprehensive evaluation of a proposed high risk generic peptide should prompt consideration of whether the ANDA route is appropriate for the proposed generic product.

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- Daniela Verthelyi, Ph.D., M.D, OBP, CDER
- Zuben Sauna, Ph.D., OTAT, CBER
- Steven Kozlowski, M.D., OBP, CDER

Speakers

Valerie Quarmby

Valerie Quarmby has contributed to IND, BLA and related filings for many approved medicines at Genentech.

She has presented and published extensively in the areas of bioanalysis and biopharmaceutical development, and she has extensive knowledge of the strategies and methods than can be used in risk based assessments of immunogenicity for protein therapeutics.

Vibha Jawa

Vibha brings more than 20+ years of experience in supporting biologics, vaccine development and gene therapy with contributions to multiple IND, BLA and MAA filings. She is a recognized leader in the area of Bioanalysis and Immunogenicity with more than 50 peer reviewed publications. In her current role as an Executive Director for Biotherapeutics Bioanalysis at Bristol Myers Squibb, Vibha is responsible for leading biotherapeutic and cell therapy bioanalytical (BA) function.

Her research interest has focused on streamlining preclinical immunogenicity assessments by using algorithms and invitro human derived assays and use those outputs to drive a risk based clinical strategy. She is an active member of multiple industry groups like AAPS and Industry Innovation and Quality (IQ) Consortium for Cell/Viral/Gene therapies.

Sophie Tourdot

Sophie has over 20 years of experience in vaccine and immunotherapy pre-clinical development for infectious diseases, oncology and allergy in positions held in academia and industry.

Prior to joining Pfizer, Sophie was a key member of the leadership team of the IMI-funded ABIRISK project, a consortium program focused on the analysis of underlying biological mechanisms, measurement and clinical relevance of unwanted immunogenicity of therapeutic proteins.

In her current role, Sophie leads the Immunogenicity Sciences group in charge of immunogenicity risk assessment of Pfizer biologics portfolio at all stages of development. A major activity of her group is the use of pre-clinical immunogenicity screening tools for therapeutic protein drugs, molecular design, and lead selection. She is also Director of Scientific Affairs for the European Immunogenicity Platform.

Tim Hickling

Dr Tim Hickling, D.Phil., Immunosafety Science Lead, Roche, Switzerland

Tim leads the Immunosafety group in Roche that includes responsibility for immunogenicity risk assessments and developing predictive methods for immune responses. Tim joined Roche in 2020 after leading Pfizer's Immunogenicity Sciences group, where he developed mathematical models of immune responses to vaccines and therapeutic proteins. He had previously obtained his Biochemistry degree and Immunology Doctorate from the University of Oxford, U.K. and was an Assistant Professor in Virology at the University of Nottingham, U.K.