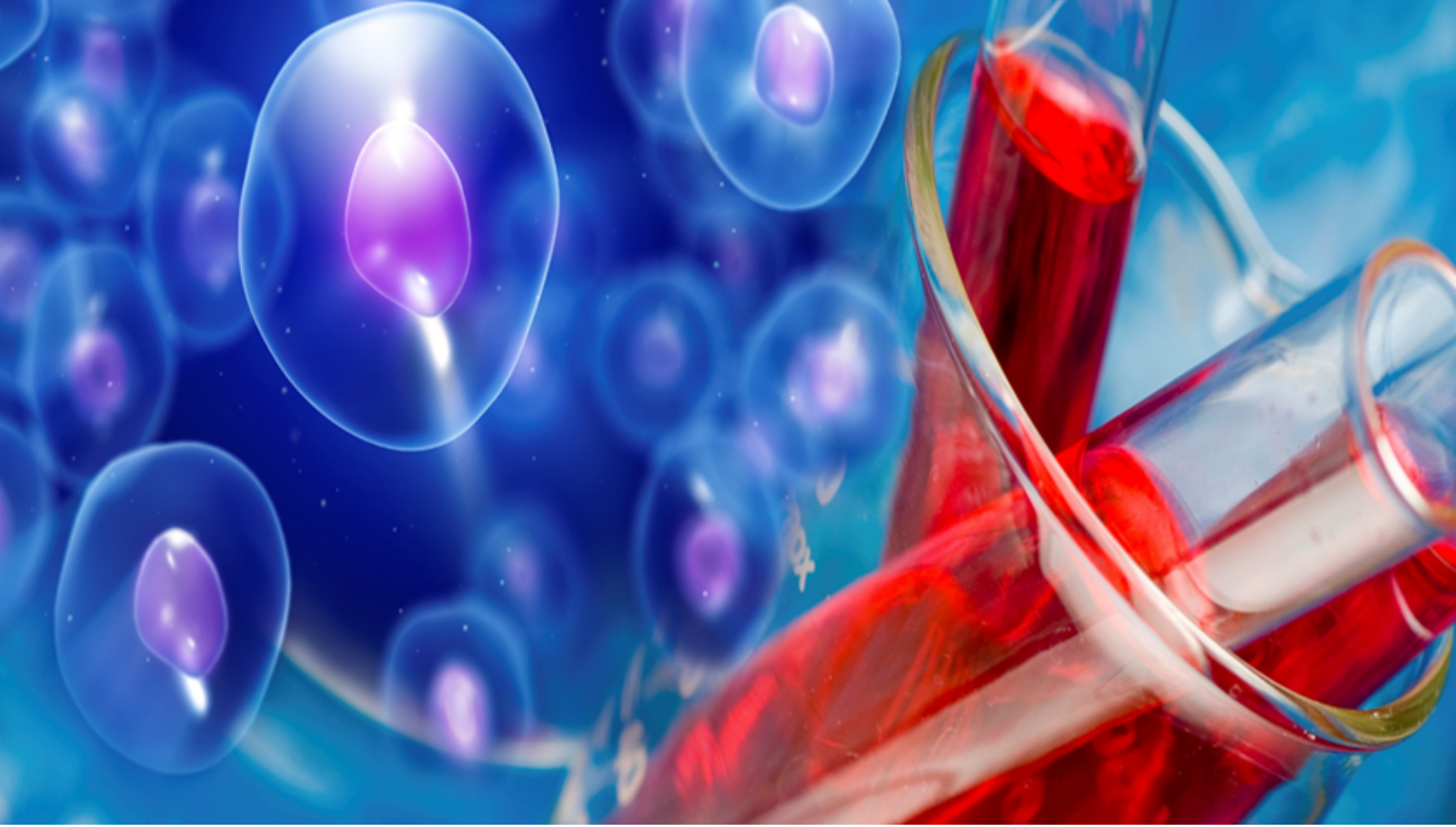


SANOFI

After 20 Years of immunogenicity testing, where do we stand today?

Daniel Kramer
Sanofi R&D, Translational Medicine & Early Development

20 Years of Immunogenicity Testing

Milestones

EPO PRCA

Mire-Sluis White Paper

EIP Foundation

EMA Guideline

Shankar et al. ADA Validation White Paper

Draft FDA Assay Guideline

ICHS6 R1

NAb Validation WhitePaper

ABIRISK

Shankar et al. Terminology WhitePaper

Draft FDA Assay Guideline Rev1

NAb Assay Formats WhitePaper

EMA Guideline Rev1

1998 2004 2007 2008 2009 2011 2012 2014 2016 2017….

Prehistory

Gold Rush Era

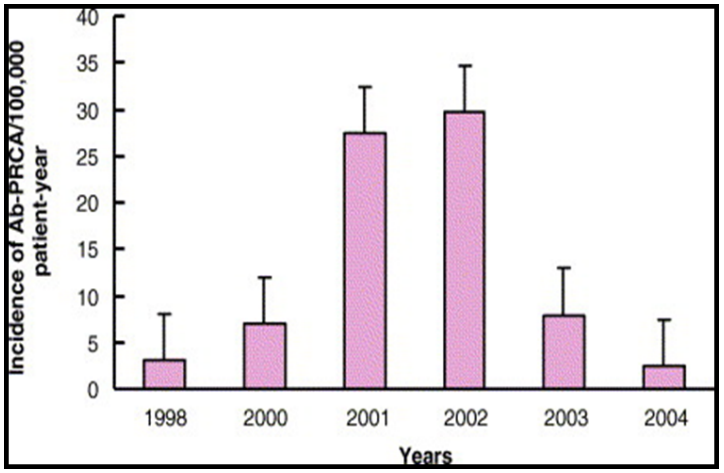
Consolidation Era

SANOFI

Immunogenicity

Booster Detonation

- **Recombinant human EPO was marketed 1988 for chronic kidney disease**
- **Since 1998, a sudden and large increase in the number of cases of EPO induced pure red cell aplasia (PRCA) was observed**
  - EPO induced PRCA is caused by ADAs against rhEPO cross-neutralizing endogenous EPO
    - Majority of PRCA cases occurred in patients treated with EPO marketed outside the United States
    - Increase in PRCA coincides with changes in EPO formulation in 1998 (removal of HSA)
      - New formulation seem to be more prone to aggregation => Immunogenicity



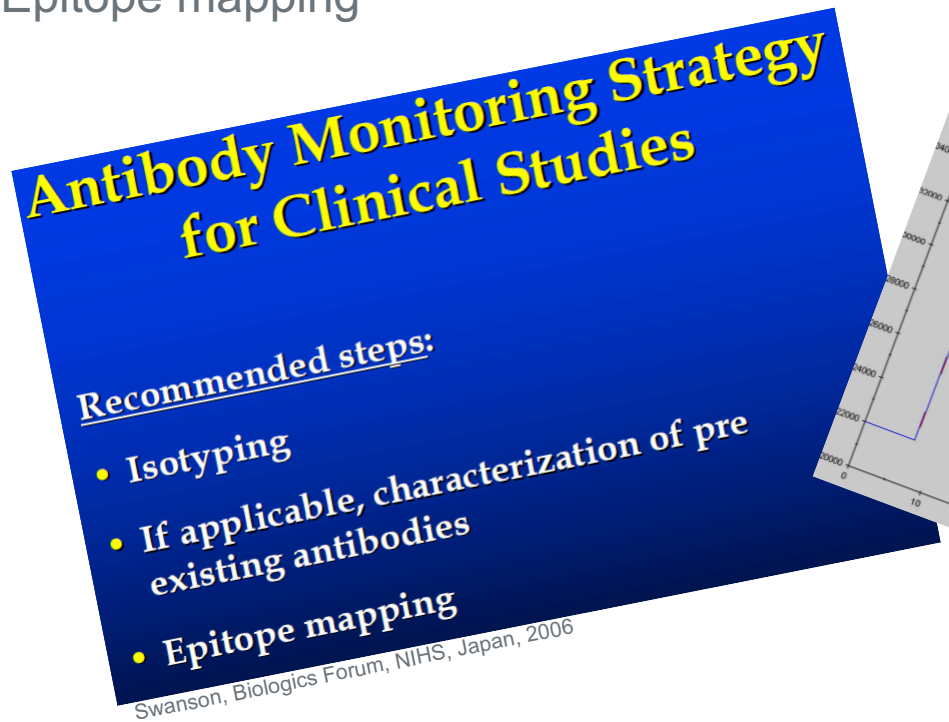
Ross, EIP pre-conference workshop, 2012

Immunogenicity

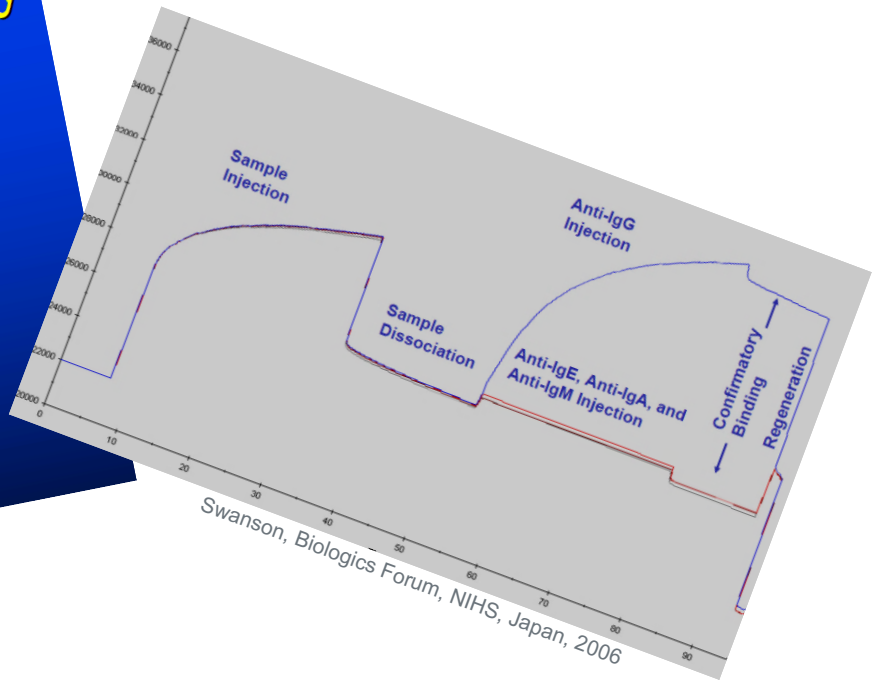
Gold Rush Era

- **After the EPO shock many companies introduced a whole battery of ADA assays**
  - SPR to detect low affinity antibodies
  - Isotyping (IgG, IgM, IgE) and subtyping (IgG1, IgG2, IgG4)
  - Epitope mapping

Clinical Relevance ????



Swanson, Biologics Forum, NIHS, Japan, 2006



Swanson, Biologics Forum, NIHS, Japan, 2006

Immunogenicity – Lessons Learned

Preclinics

- **Historically significant efforts were invested for ADA testing during toxicity studies for biologics**
- **Over the years it became obvious that antibody formation in animals (even NHPs) is not predictive of the situation in humans**
- **In 2011 ICHS6 R1 clarified that:**
  - ADA samples in repeated dose toxicity studies should be drawn but only analyzed in the following cases:
    - Evidence of altered PD activity
    - Unexpected changes in exposure in the absence of a PD marker
    - Evidence of immune-mediated reactions (e.g. immune complex disease, vasculitis, anaphylaxis)

mAbs 5:5, 810–816; September/October 2013; © 2013 Landes Bioscience

Immunogenicity of mAbs in non-human primates during nonclinical safety assessment

Peter J.K. van Meer,[1,*] Marlous Kooijman,[2] Vera Brinks,[1] Christine C. Gispen-de Wied,[3] Beatriz Silva-Lima,[4] Ellen H.M. Moors[2] and Huub Schellekens[1,2]

[1]Utrecht Institute of Pharmaceutical Sciences; Department of Pharmaceutics; Utrecht University; Utrecht, the Netherlands; [2]Copernicus Institute of Sustainable Development; Innovation studies; Utrecht University; Utrecht, the Netherlands; [3]Medicines Evaluation Board; Utrecht, the Netherlands; [4]IMED-UL; Department of Pharmacological Sciences; University of Lisbon; Lisbon, Portugal

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

June 2011
EMA/CHMP/ICH/731268/1998
Committee for medicinal products for human use (CHMP)

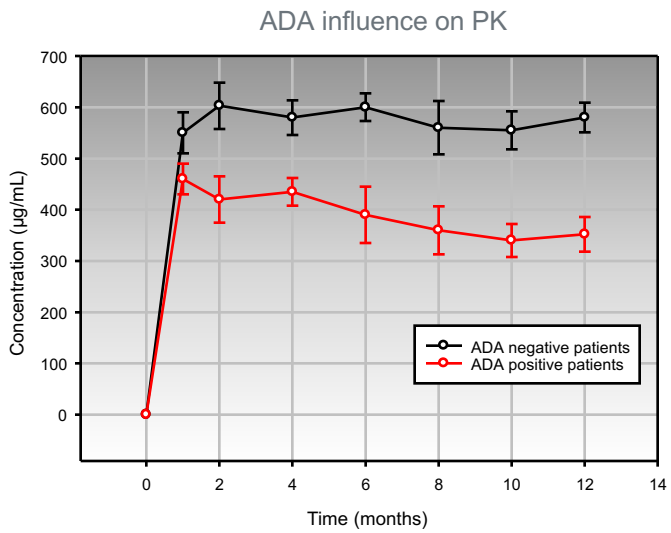
ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals

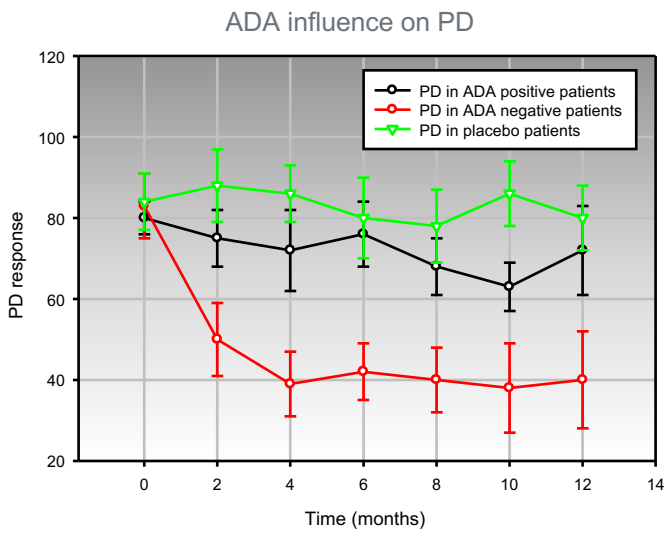
Step 5

Immunogenicity – Lessons Learned

Clinical Relevance

- **Immunogenicity as stand alone information is not helpful**
- **Immunogenicity needs to be put into context with clinical consequences ("holistic picture")**
  - Impact on PK/PD
    - ADAs enhancing the clearance (with or without impact on PD)
    - ADAs decreasing the clearance (with and without impact on PD)
  - Impact on safety
    - Hypersensitivity reaction (type II; type IV)
    - Deficiency syndrome (cross-neutralization of non-redundant endogenous counterparts)
- **EMA immunogenicity guideline (2017): "*The purpose of investigating immunogenicity of therapeutic proteins is to understand the clinical consequences; i.e. consequences for PK, PD, efficacy and safety*"**

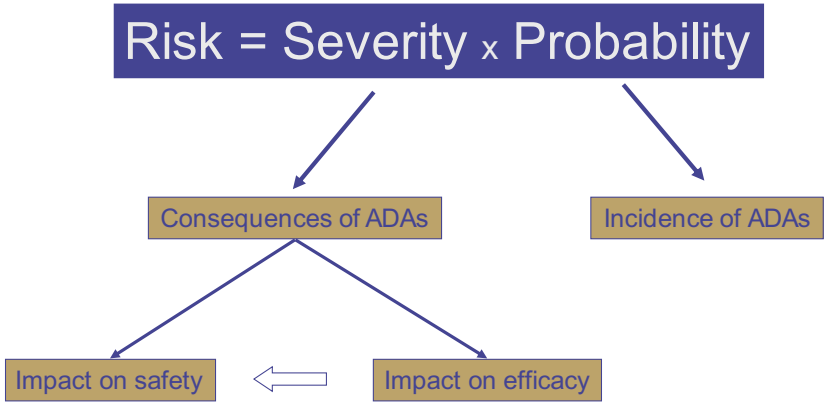




Immunogenicity – Lessons Learned

Immunogenicity Risk Assessment (I)

- **Regulatory agencies recommend a risk-based approach for evaluating the immunogenicity of therapeutic proteins**
- **An immunogenicity risk assessment approach enables:**
  - Identification of potential clinical consequences even in the absence of clinical data
  - Ranking of biologics according to their immunogenicity risk class
  - A tailored immunogenicity sampling and testing strategy based on the immunogenicity risk class



Immunogenicity – Lessons Learned

Immunogenicity Risk Assessment (II)

- **Immunogenicity risk factors form the basis for immunogenicity risk assessment**
  - They include patient-, disease-, posology- and product-related risk factors
  - They influence the incidence/clinical sequelae of an ADA response
- **The risk to safety is considered of prime importance**
  - A few subjects with severe ADA-related clinical consequences are of more concern than many ADA-positive individuals without apparent clinical impact
- **Risk factors are used to classify biotherapeutics into risk categories**
  - The extent of clinical immunogenicity sampling/testing is based on the risk category

Risk Assessment

IMMUNOGENICITY RISK FACTOR	Lower Risk → Higher Risk				
Similarity to endogenous counterpart(s)	No similarity	Partial similarity	Complete similarity		
Primary Sequence	Fully human	Partially human	Non-human		
Glycosylation pattern	Fully human	Partially human	Non-human		
Dosing regimen	Short term exposure	Long term exposure	Intermittent treatment		
Route of administration	IV	IM	IP	SC	Inhaled
Mode of action	Antagonistic	Agonistic			
Immune status of patients	Immune-compromised	Normal immune system	Activated immune system		
Concomitant medication	Immunosuppressive co-medication	Immunostimulatory co-medication			

Risk-based sampling/testing strategy

Testing strategy for lower / medium risk proteins	Testing strategy for higher risk proteins
Frequency of sampling within study: • More frequently early in the drug program and less frequently in phase 3 trials **Assessment of ADAs:** • Detection of ADAs using screening and confirmatory assays • Titration of confirmed positive samples • Assessment of the neutralizing capacity of ADA positives should be explored for phase 3 the latest **Validation status:** • "Fit for purpose" assays for non-pivotal trials • Validated assays for pivotal trials **Sample testing:** • Retrospective analysis at the end of a trial might be sufficient	**Frequency of sampling within study:** • More frequently throughout all phases of clinical development **Assessment of ADAs:** • Detection of ADAs using screening and confirmatory assays • Titration of confirmed positive samples • Assessment of the neutralizing capacity of ADA positives from phase 1 onwards **Validation status:** • Fully validated assays from phase 1 onwards **Sample testing:** • Consider real time analysis of ADA samples and post-study follow-up of positive subjects

Immunogenicity – Lessons Learned

Reporting of Immunogenicity (I)

- **For years there was a lack of standardization in the terminology used for the collection, analysis, and presentation of immunogenicity results in clinical trial reports, regulatory documents (IND, IMPD) and product labels**
  - This lack of sufficient and consistent description was one major reason that physicians and patients felt inadequately informed of the true benefit/risk of the treatment
- **AAPS and ABIRISK issued white papers to foster a harmonized approach for the reporting of clinical immunogenicity data**

The AAPS Journal (© 2014)
DOI: 10.1208/s12248-014-9599-2

White Paper

Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations

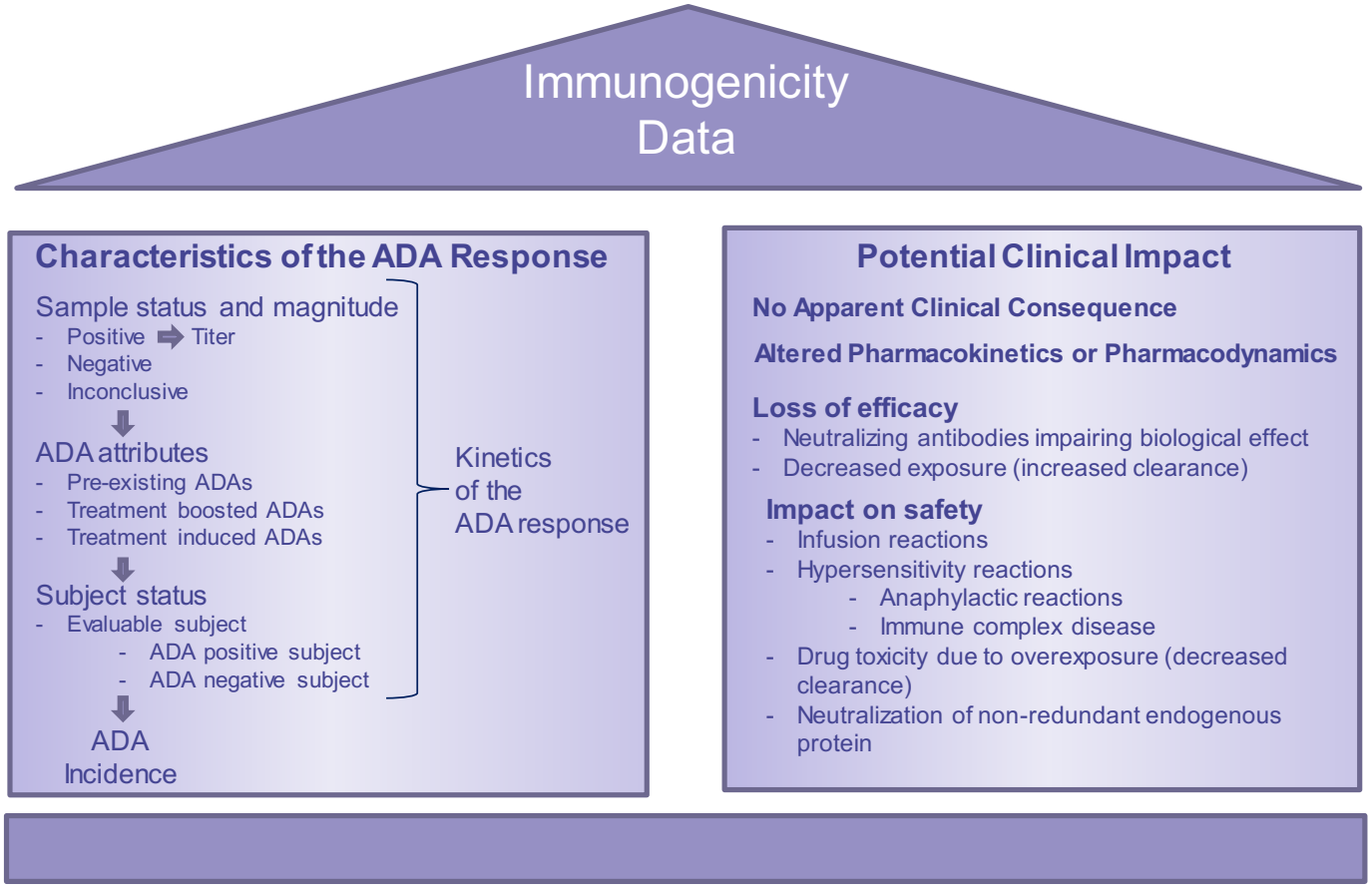
G. Shankar,[1,14] S. Arkin,[2] L. Cocea,[3] V. Devanarayan,[4] S. Kirshner,[5] A. Kromminga,[6] V. Quarmby,[7] S. Richards,[8] C. K. Schneider,[9,10] M. Subramanyam,[11] S. Swanson,[12] D. Verthelyi,[5] and S. Yim[13]

Clinical & Experimental Immunology
The Journal of Translational Immunology
immunology
Clinical and Experimental Immunology REVIEW ARTICLE doi:10.1111/cei.12652

Standardizing terms, definitions and concepts for describing and interpreting unwanted immunogenicity of biopharmaceuticals: recommendations of the Innovative Medicines Initiative ABIRISK consortium

Immunogenicity - Lessons Learned

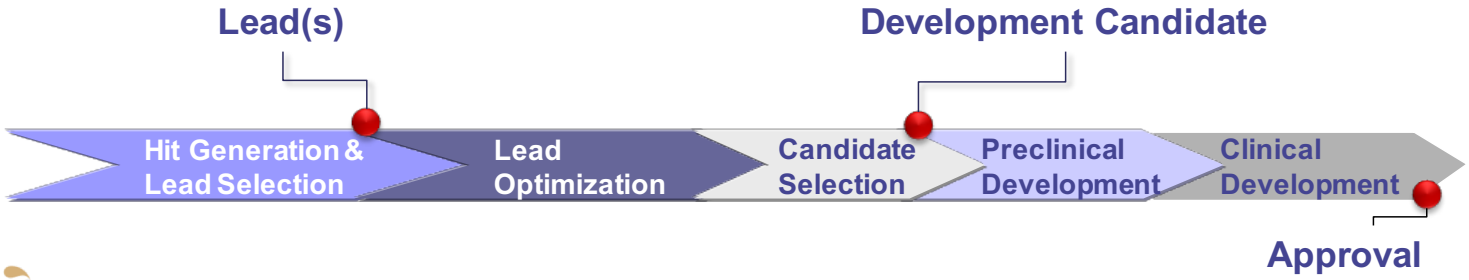
Reporting of Immunogenicity (II)



Immunogenicity – Lessons Learned

Prediction of Immunogenicity

- **Currently biopharmaceutical industry is blind in respect to human immunogenicity until a biologic enters repeated dose clinical trials**
  - Therefore leading biopharmaceutical companies are investing huge efforts into various approaches to predict immunogenicity
  - Most companies focus on in-silico and in-vitro prediction tools
- **There is now a common understanding that these tools cannot predict the ADA incidence in a clinical setting**
  - However, they are useful to assess "relative immunogenicity"
    - Ranking of leads for selection of the least immunogenic development candidates
      - Mainly done by "in-silico"
    - Assessment of the relative immunogenicity of a biosimilar vs the originator or of a post-change to a pre-change material in a comparability exercise
      - Done with "in-vitro" T-cell assays



Immunogenicity – Room for Improvement

- **Pharmaceutical industry is rather conservative and still tends to "overshoot" in respect to immunogenicity (to minimize the risk of getting issues during filing)**
  - An even stronger focus on clinical relevance when designing the ADA sampling/testing strategy would help providing meaningful information to agencies, physicians and patients
- **Frequent exchange of positions between industry consortia (AAPS, EIP, EBF,…) and agencies would build mutual understanding and trust**
- **A better understanding of the contribution of extrinsic factors (e.g. aggregates) on immunogenicity is needed**
  - Interdisciplinary discussions between immunogenicity folks and CMC colleagues are important

20 Years of Immunogenicity

Summary

- **We have come a long way since the EPO case**
  - Harmonized approach for ADA and NAb assay validation
  - Focus on relevance of ADAs
    - ICHS6R1 for the preclinical space
    - Risk based immunogenicity sampling/testing strategies for clinical studies (EMA, FDA guidelines)
    - Correlation of immunogenicity with clinical consequences (EMA, FDA guidelines)
  - Harmonized approach for the reporting of immunogenicity data
  - Common understanding of the best use of immunogenicity prediction tools

- **But there is still a long way to go**
  - In spite of all harmonization efforts in respect to immunogenicity we are still doing things rather different in pharmaceutical industry
    - Assay validations
    - Immunogenicity risk assessment
    - Focus on clinical relevance of immunogenicity
  - Lot of efforts were put in understanding of intrinsic factors but much less into extrinsic ones (e.g. aggregates, post-translöational modifications)

THANKS!!!!!!