Medicines & Healthcare products Regulatory Agency

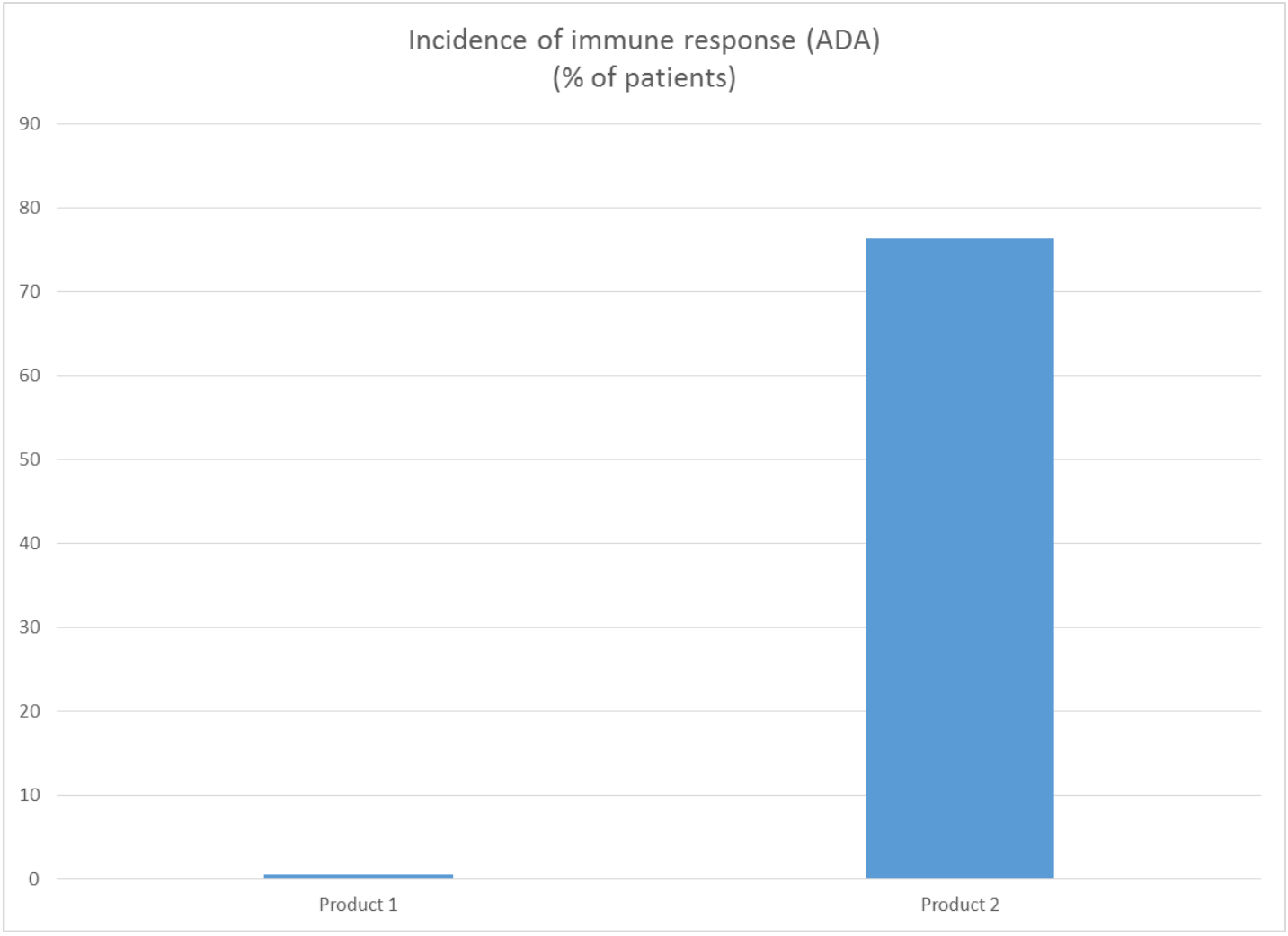
NIBSC
Confidence in Biological Medicines

How to integrate risk assessment and risk stratification into a risk-based approach for immunogenicity assessment ***General introduction on the topic***

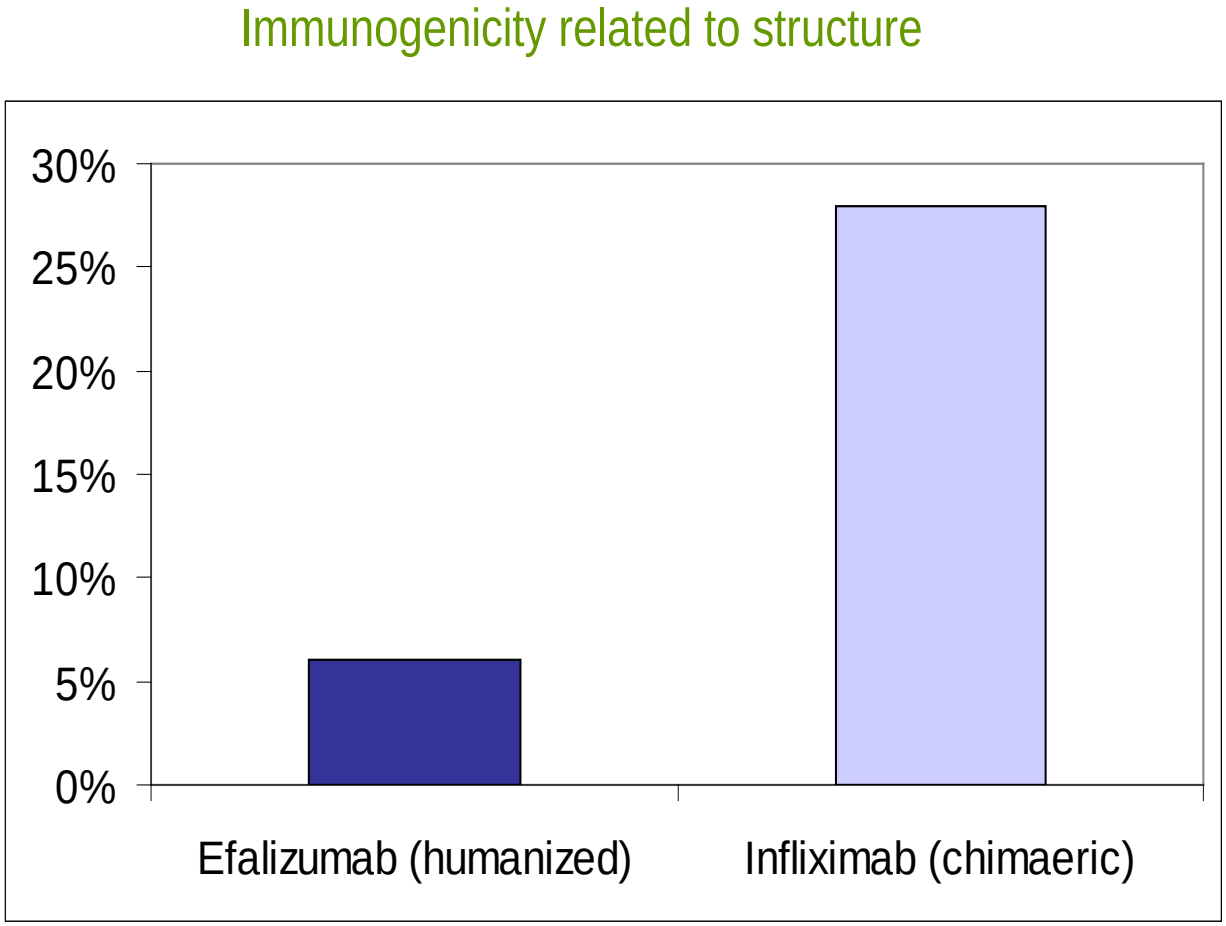
Workshop on immunogenicity assessment of biotechnology-derived therapeutic proteins – European Medicines Agency 9th March 2016

Presented by Christian K Schneider, MD

Low and high risk products

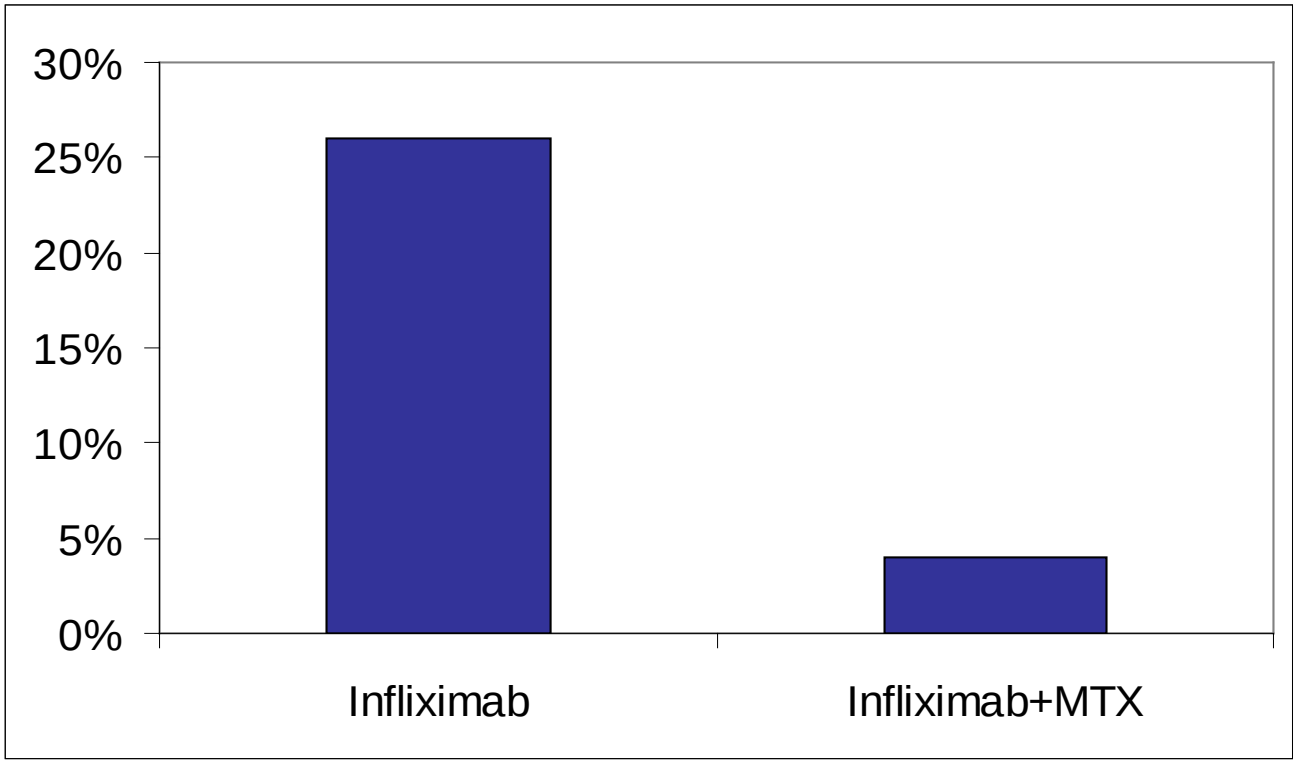


Impact of Immunogenicity on Efficacy and Safety mAbs as a paradigm



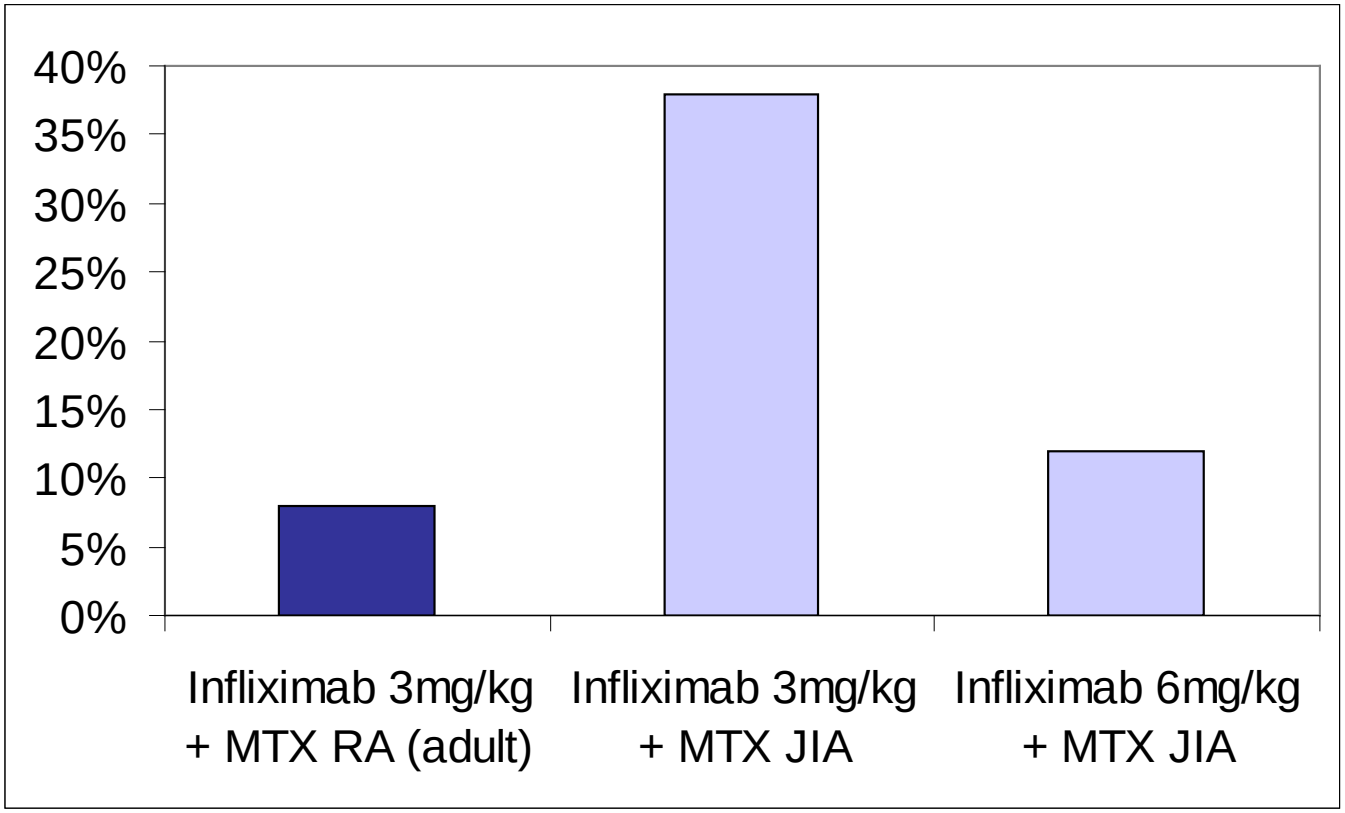
Impact of Immunogenicity on Efficacy and Safety mAbs as a paradigm

Influence of concomitant immunomodulators / immunosuppressives



Impact of Immunogenicity on Efficacy and Safety mAbs as a paradigm

Age, indication, dose, different sampling schedule, chance?



Clinical safety: Depends on the product

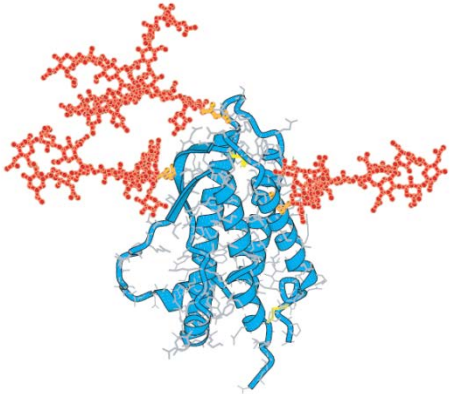
Erythropoietin: „High-risk“ product

The New England
Journal of Medicine

VOLUME 346 FEBRUARY 14, 2002 NUMBER 7

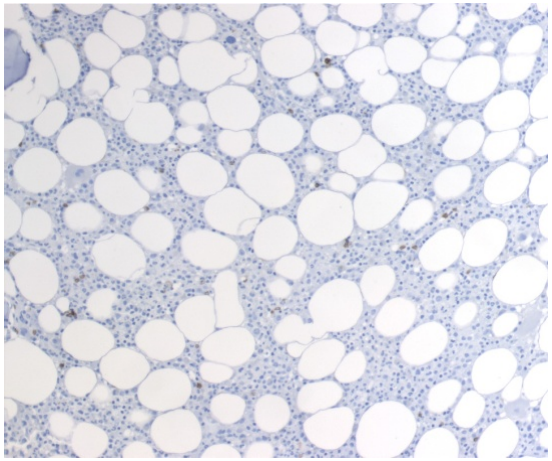
PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.



Molecular model of erythropoietin with complex N-linked glycans at sites N24, N38 and N83. The glycan-protein linkages are likely to exhibit considerable flexibility; the structure shown is just one possible conformation.

Courtesy of M.R. Wormald and R.A. Dwek, Oxford Glycobiology Institute, and P.M. Rudd, NIBRT



Clinical safety: Depends on the product

ORIGINAL RESEARCH

Managing Cetuximab Hypersensitivity-Infusion Reactions: Incidence, Risk Factors, Prevention, and Retreatment

Thomas J. George, Jr, MD, FACP, Kourtney D. LaPlant, PharmD, Edmund O. Walden, PharmD, BCOP, Arlene B. Davis, RN, MSN, AOCN, Charles E. Riggs, MD, Julia L. Close, MD, Sarah N. George, MA, and James W. Lynch, MD

THE JOURNAL OF SUPPORTIVE ONCOLOGY VOLUME 8, NUMBER 2 ■ MARCH/APRIL 2010

Tumori, 96: 473-477, 2010

Successful treatment with the fully human antibody panitumumab after a severe infusion reaction with cetuximab

Wolfram Brugger

Schwarzwald-Baar Clinic, Villingen-Schwenningen, Teaching Hospital, University of Freiburg, Germany

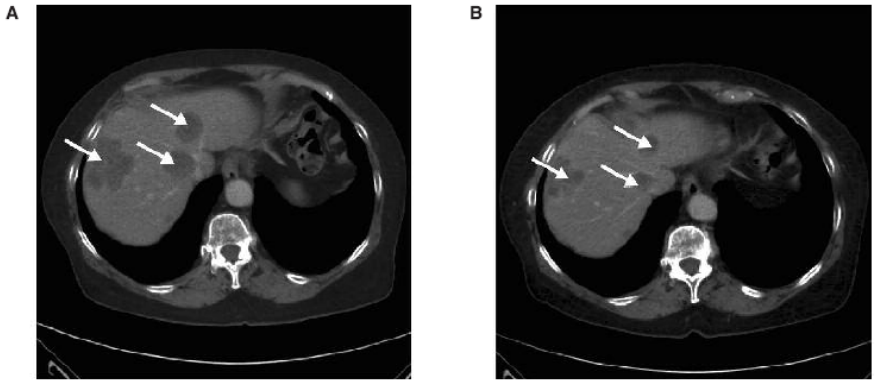


Figure 2 - Computed tomography scans of the patient's liver (A) before and (B) after 2 months of panitumumab therapy, showing response to treatment.

Monoclonal antibodies:
Low(er) risk?

„Fit-for-purpose“ recommendations?

Table 3 Bioanalytical strategy for evaluating immunogenicity in clinical studies

Bioanalytical scheme for lower-risk products	Bioanalytical scheme for medium-risk products	Bioanalytical scheme for higher-risk products
Frequency of sampling within study:	Frequency of sampling within study:	Frequency of sampling within study:
More frequently early in the drug program and less frequently (baseline, end of study, and possibly longer term follow-ups) in phase 3 trials	More frequently early in the drug program and less frequently (baseline, end of study, and possibly longer-term follow-ups) in phase 3 trials	More frequently throughout all phases of clinical development
Assessment of ADAs:	Assessment ADAs:	Assessment of ADAs:
Detection of ADAs through screen and confirmatory immunoassays	Detection of ADAs through screen and confirmatory immunoassays	Detection of ADAs through screen and confirmatory immunoassays
Characterization of titer/relative concentration of ADAs	Characterization of titer/relative concentration of ADAs	Characterization of titer/relative concentration of ADAs. Consider real-time IR bioanalysis for the program.
Consideration of value of mapping ADA reactivity to distinct parts of the drug molecule	Consideration of value of mapping ADA reactivity to distinct parts of the drug molecule	Consideration of value of mapping ADA reactivity to distinct parts of the drug molecule. In the absence of a validated neutralizing antibody assay, the antigenic reactivity data could indicate neutralizing potential and preclude (to be decided for each patient) further treatment.
Characterization of neutralizing activity of ADA positives may be explored as necessary.	Characterization of neutralizing activity of ADA positives using a target binding inhibition–based neutralizing antibody immunoassay or a cell-based neutralizing antibody bioassay	Characterization of neutralizing activity of ADA positives using cell-based neutralizing antibody bioassay, and a target binding inhibition–based neutralizing antibody immunoassay if one is also available
	Consider testing NAb against the endogenous protein using a cell-based NAb bioassay.	If a neutralizing antibody assay is more sensitive than the screening immunoassay, all samples should also be tested using the neutralizing antibody assay.
	Clinical protocol design:	Clinical protocol design:
	Include clinical monitoring of endogenous factor deficiency, particularly for sole-activity factors/ replacement therapies and life-threatening diseases.	Include clinical monitoring of endogenous factor deficiency, particularly for sole-activity factors/ replacement therapies and life-threatening diseases.
		Consider sequential patient dosing rather than classic cohort model for first-in-human studies.

ADA, anti-drug antibody; IR, immunoreactivity; NAb, neutralizing antibody.

e.g., anti-TNFalpha mAbs

e.g., beta-interferons

e.g., erythropoietins

Shankar, G., Pendley, C., Stein, K.E. (2007) *Nat Biotechnol*, 25(5): 555-561

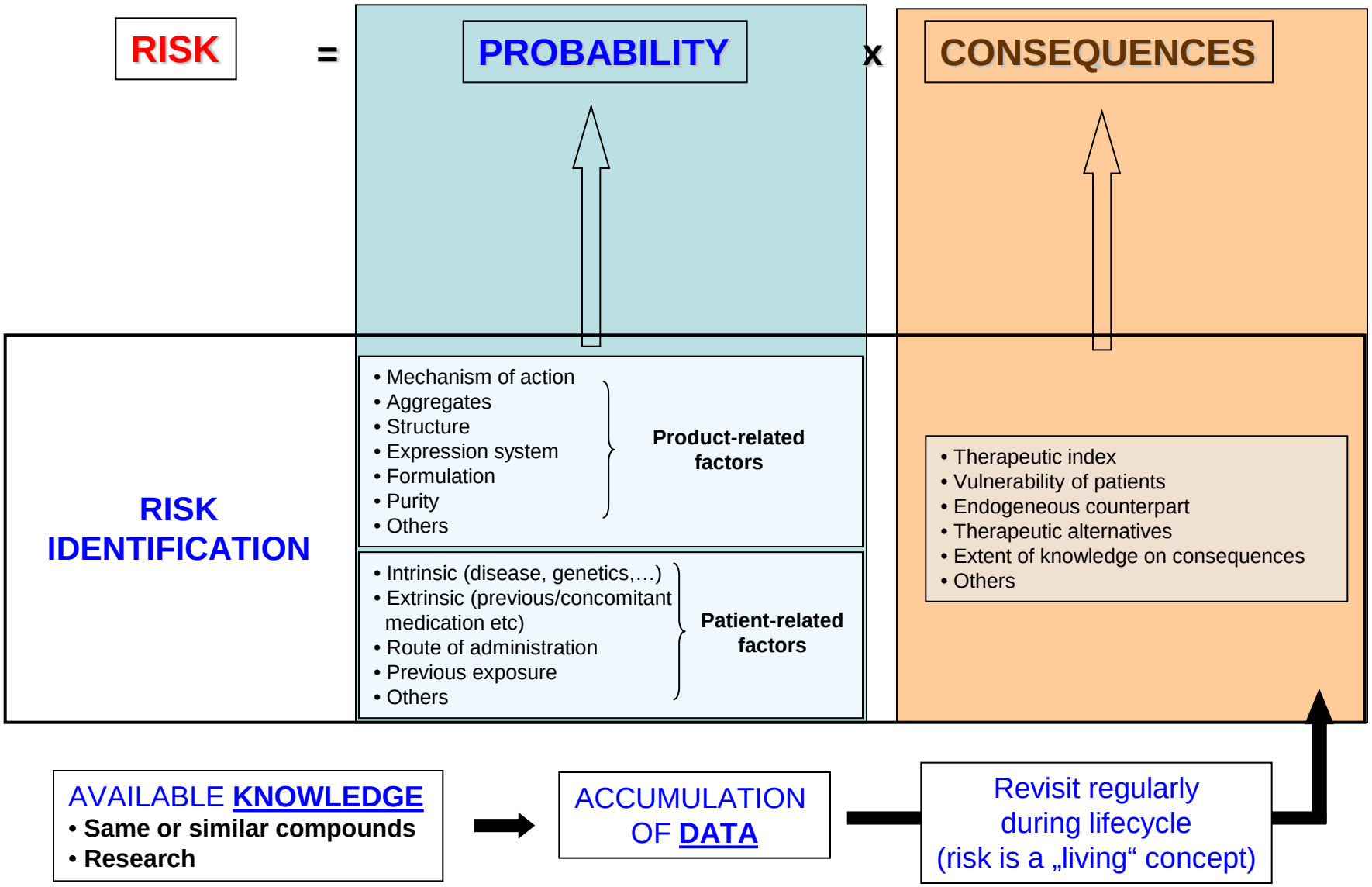
„Fit-for-purpose“ recommendations?

- Standard algorithms not useful, since:
  - Risk perception might change during development
  - Risk is not only a matter of structure of the active substance

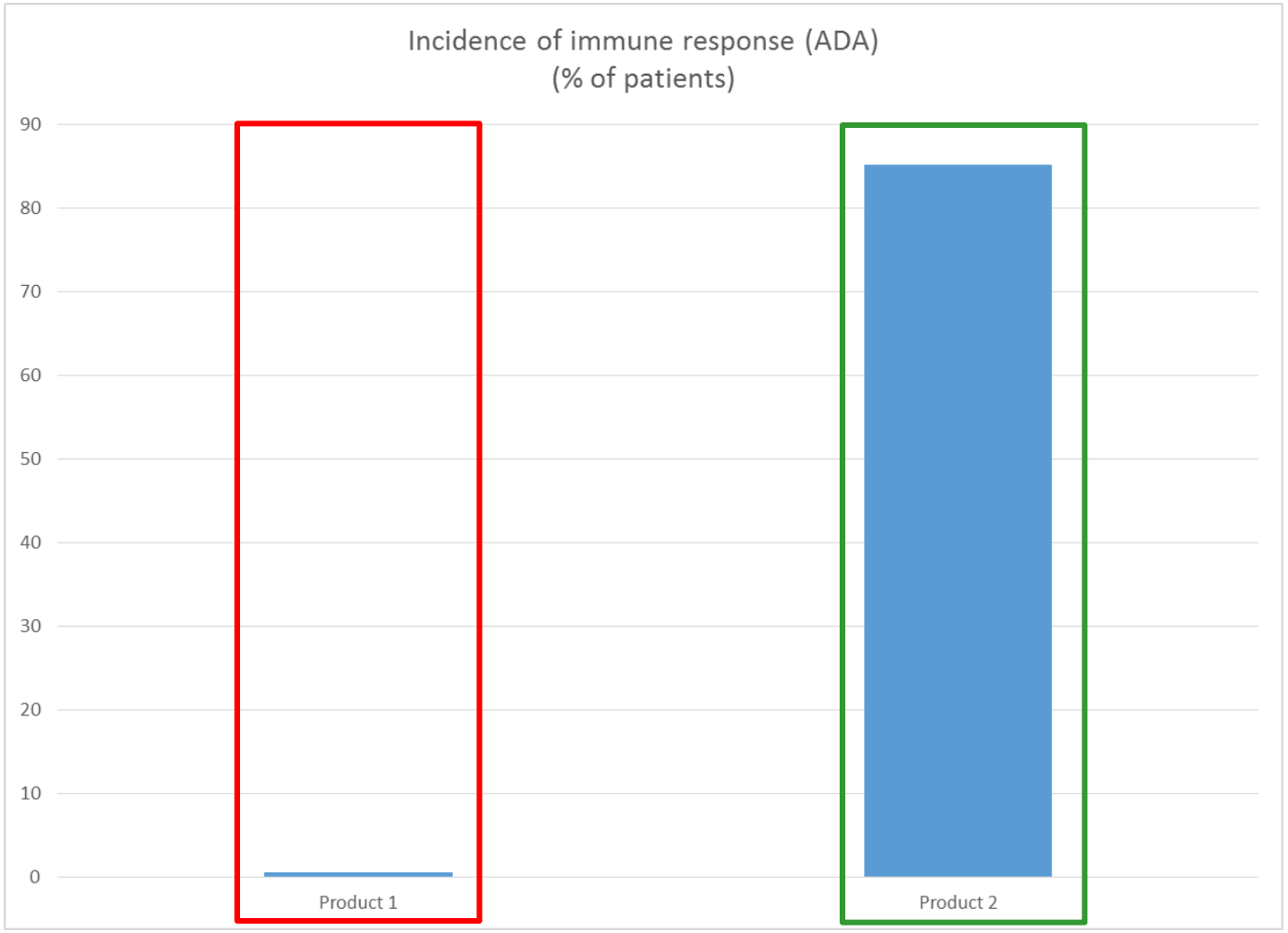
- Less intensive evaluation for „low risk drugs“ can lead to regulatory concerns:
  - **Unexpected product characteristics might be missed** (e.g., due to manufacturing or impurities)
  - **Structure might imply „low risk“, but other attributes could pose „higher risk“** (e.g. novel expression system of an anti-TNFalpha mAb)
  - **Consequences like infusion reactions are usually less severe than e.g. a PRCA,** but: They also impact Benefit-Risk assessment, and need to be linked to immunogenicity
  - **Neutralising antibodies are usually considered important for mAb applications**

Schneider CK, Papaluca M, Kurki P (2009), *Nat Biotechnol* 27(6): 507-508

What is „risk“?



A risk-based approach to immunogenicty



High risk **Low risk**

Product 1: Erythropoietin

Kidney International, Vol. 67 (2005), pp. 2346–2353

The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes

KATIA BOVEN, SCOTT STRYKER, JOHN KNIGHT, ADRIAN THOMAS, MARC VAN REGENMORTEL, DAVID M. KEMENY, DAVID POWER, JEROME ROSSERT, and NICOLE CASADEVALL

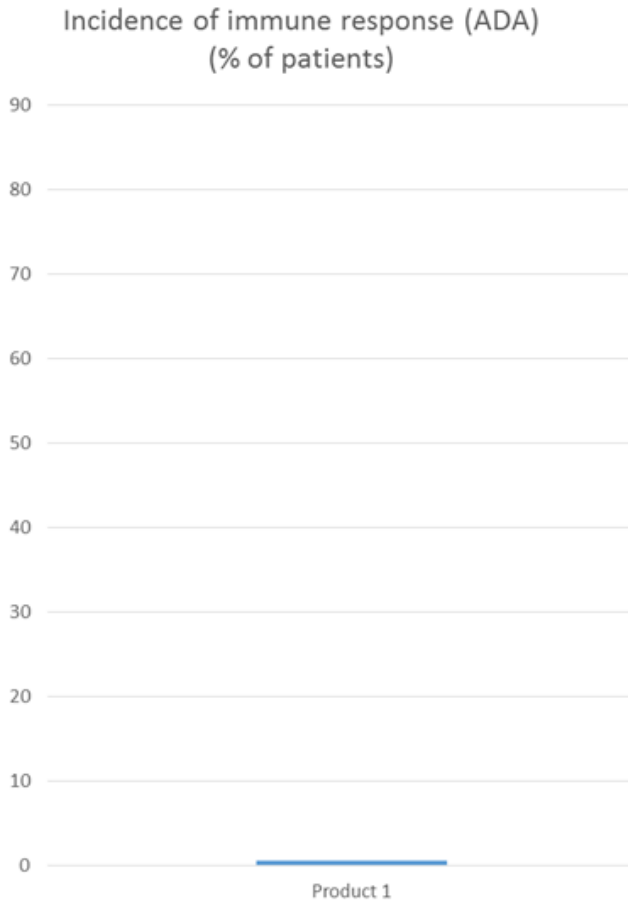
Johnson and Johnson, Pharmaceutical Research and Development, L.L.C, Raritan, New Jersey; Centre National de la Recherche Scientifique, Ecole Supérieure de Biotechnologie de Strasbourg, France; Department of Microbiology, National University of Singapore, Singapore; Kidney Laboratory, Austin Research Institute, Austin, Australia; Service de Néphrologie, Hôpital Tenon, Paris, France; and Service d'Hématologie Biologique, Hôpital Hôtel-Dieu, Paris, France

Pharm Res (2012) 29:1454–1467
DOI 10.1007/s11095-011-0621-4

RESEARCH PAPER

Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity

Andreas Seidl • Otmar Hainzl • Marleen Richter • Robert Fischer • Stephan Böhm • Britta Deutel • Martin Hartinger • Jörg Windisch • Nicole Casadevall • Gerard Michel London • Iain Macdougall



Incidence of immunogenicity: 2 patients in the entire safety population (314 patients)

Source: Abraham and Mc Donald, Biosimilars 2012:2, 13-25

Product 2: Alemtuzumab

27 June 2013
EMA/563018/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lemtrada

International non-proprietary name: ALEMTUZUMAB

Procedure No. EMEA/H/C/003718/0000

Note

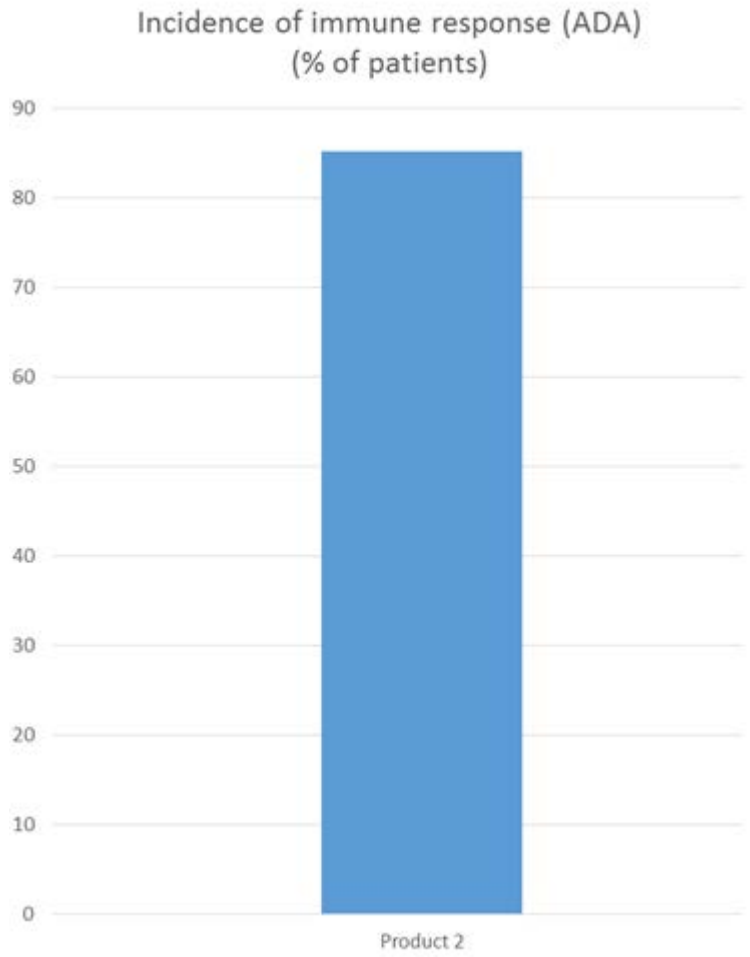
- Indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features
- Humanized monoclonal antibody
- Posology:

  The recommended dose is 12 mg/day administered by intravenous infusion for 2 treatment courses.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003718/WC500150522.pdf

Product 2: Alemtuzumab

- **85.2%** of patients in the pooled Phase 3 studies tested **positive** for anti-alemtuzumab antibodies.
- Of those, **92.2%** tested positive for **inhibitory antibodies**.
- **Higher proportion of patients tested positive in Cycle 2** compared to Cycle 1 and peak antibody titres for both types of antibodies were higher following Cycle 2 than Cycle 1.



http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003718/WC500150522.pdf

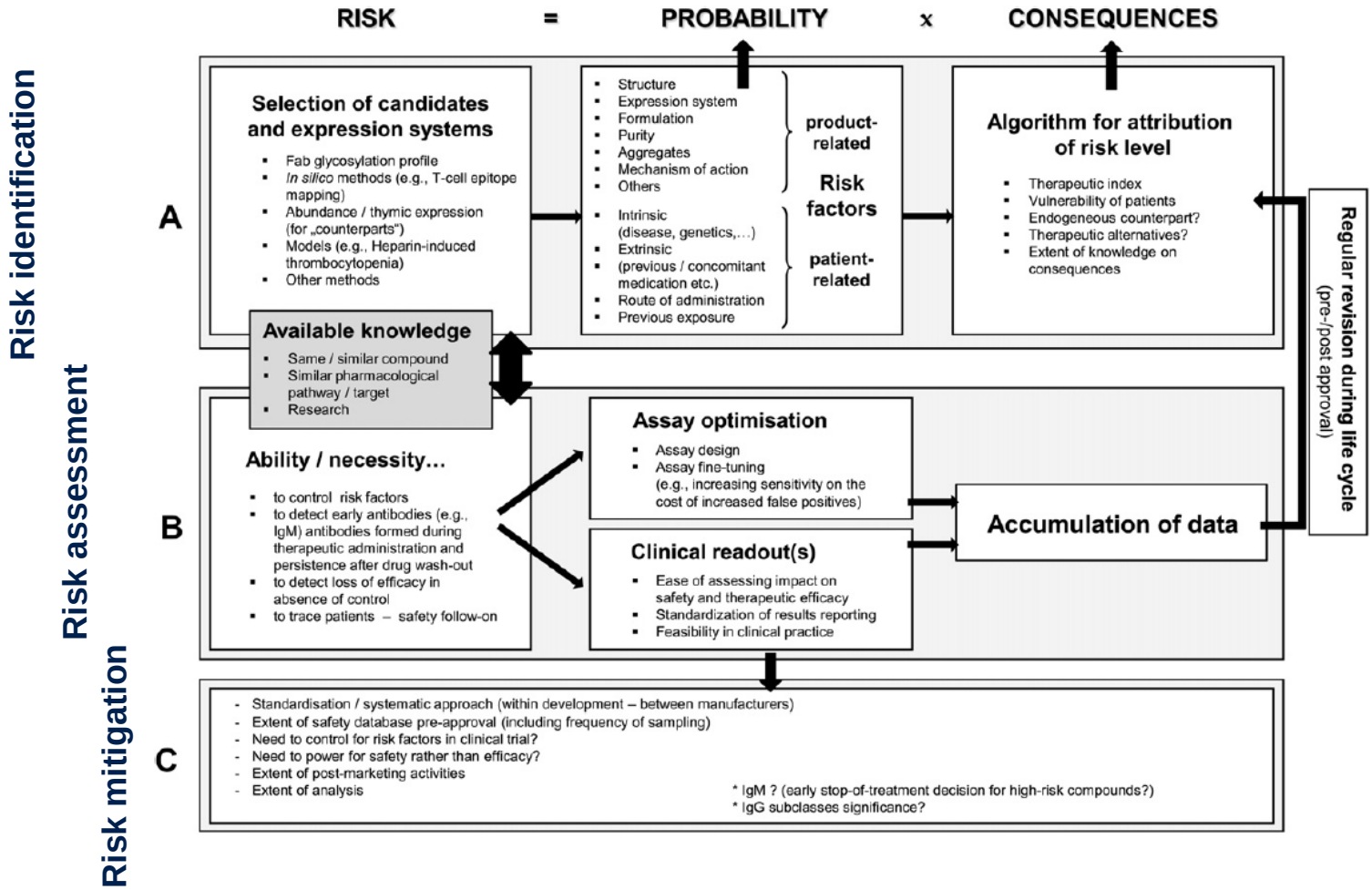
Product 2: Alemtuzumab

Why then ”lower risk”? Risk-based thinking!

- Considerable efficacy overall
- No impact on safety, based on data
- No infusion reactions due to standard methylprednisolone pre-treatment
- No impact on T cell depletion, based on data
- No impact on MRI parameters, based on data
- No impact on efficacy, based on data
- Loss of efficacy would be detected (MRI!, clinical)
- Availability of alternative treatments

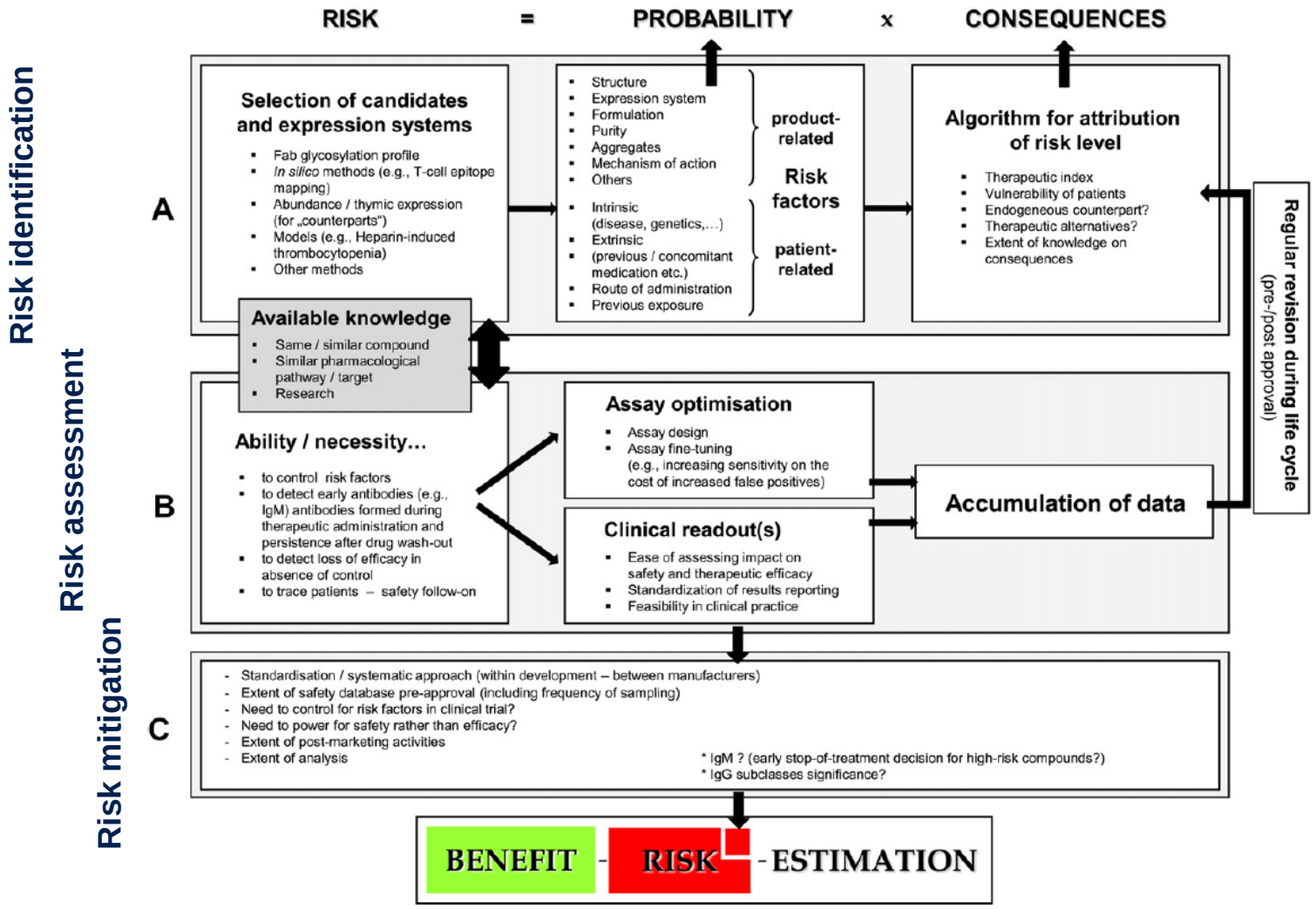
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003718/WC500150522.pdf

Taking immunogenicity assessment of therapeutic proteins to the next level



Büttel IC et al (2011); Biologicals. 2011 Mar;39(2):100-9

Taking immunogenicity assessment of therapeutic proteins to the next level



Büttel IC et al (2011); Biologicals. 2011 Mar;39(2):100-9