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Workshop report

Biotherapeutics in non-clinical development: Strengthening the interface between safety, pharmacokinetics-pharmacodynamics and manufacturing

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ABSTRACT

Biological drugs comprise a wide field of different modalities with respect to structure, pharmacokinetics and pharmacological function. Considerable non-clinical experience in the development of proteins (e.g. insulin) and antibodies has been accumulated over the past thirty years. In order to improve the efficacy and the safety of these biotherapeutics, Fc modifications (e.g. Fc silent antibody versions), combinations (antibody-drug conjugates, protein-nanoparticle combinations), and new constructs (darpins, fynomers) have been introduced. In the last decade, advanced therapy medicinal products (ATMPs) in research and development have become a considerable and strongly growing part of the biotherapeutic portfolio. ATMPs consisting of gene and cell therapy modalities or even combinations of them, further expand the level of complexity, which already exists in non-clinical development strategies for biological drugs and has thereby led to a further diversification of expertise in safety and PKPD assessment of biological drugs. It is the fundamental rationale of the BioSafe meetings, held yearly in the EU and in the US, to convene experts on a regular basis and foster knowledge exchange and mutual understanding in this fast growing area.

In order to reflect at least partially the variety of the biotherapeutics field, the 2016 EU BioSafe meeting addressed the following topics in six sessions:

(i) In vitro Meets *in vivo* to Leverage Biologics Development
(ii) New developments and regulatory considerations in the cell and gene therapy field
(iii) CMC Challenges with Biologics development
(iv) Minipigs in non-clinical safety assessment
(v) Opportunities of PKPD Assessment in Less Common Administration Routes

In the breakout sessions the following questions were discussed:

(i) Cynomolgus monkey as a reprotoxicology Species: Impact of Immunomodulators on Early Pregnancy Maintenance
(ii) Safety Risk of Inflammation and Autoimmunity Induced by Immunomodulators
(iii) Experience with non-GMP Material in Pivotal Non-clinical Safety Studies to Support First in Man (FiM) Trials
(iv) Safety Assessment of Combination Products for Non-oncology

Abbreviations: ATMP, advanced therapy medicinal products; CAR, chimeric antigen receptor; CD, cluster of differentiation; CMC, chemistry manufacturing and control; CQA, Critical Quality Attributes; CRS, cytokine release syndrome; EMA, European Medicines Agency; FcRn, neonatal Fc receptor; FcyR, Fc gamma receptor; FDA, Food and Drug Administration; FiH, first-in-human; FiM, first-in-man; ICH, International Conference on Harmonization; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IV, intravenous; mAb, monoclonal antibody; MABEL, minimal anticipated biologic effect level; MRD, maximum recommended dose; MRSD, maximal recommended starting dose; NHP, non-human primates; NOAEL, No observed adverse effect level; PKPD, pharmacokinetics/pharmacodynamics; SC, subcutaneous; TCR, T cell receptor; TNF, tumor necrosis factor; WP, working party

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1. Introduction

BioSafe is the Non-clinical Safety expert group of the Biotechnology Innovation Organization (BIO), whose mission to identify and respond to key scientific and regulatory issues and challenges related to the non-clinical safety evaluation of biopharmaceuticals. In addition to the annual general membership meeting in the US, an annual BioSafe meeting is held in Europe for European BIO member companies. The 6th Annual BioSafe European General membership meeting was hosted by Novartis on November 2–3, 2016 in Basel, Switzerland. The attendees were from the biopharmaceutical industry, small biotechs and contract research organisations from Europe but also from the US, representing various disciplines including pharmacology, toxicology and pathology, pharmacokinetics and bioanalytics, shared experiences and insights into non-clinical safety assessment of biologics including monoclonal antibodies, recombinant proteins, and gene and cell therapies. The meeting covered various non-clinical safety and PKPD topics including *in vitro – in vivo* considerations and their implications for human risk assessment, new safety and PKPD findings, gene and cell therapy, CMC issues and their influence on non-clinical/clinical development, minipigs in non-clinical safety assessment of biological drugs, and PKPD assessment of less common administration routes. In each session, presentations were followed by podium discussions. As successfully started on the 5th meeting in 2015, four so-called “hot topics” were again selected by the planning committee and discussed during the meeting in breakout sessions in smaller groups, with the feedback being presented to all attendees afterwards by the breakout session leads.

2. In vitro Meets *in vivo* to Leverage Biologics Development (Session 1)

Andreas Baumann (Bayer) and Andrea Kiessling (UCB) co-chaired the session.

Four presentations covered toxicology as well as pharmacokinetic (PK) topics to demonstrate the value of *in vitro* versus *in vivo* methods in Biologics development, but also to highlight that many complex interactions occurring *in vivo* currently cannot be fully modeled *in vitro*. In addition, *in vitro* systems do not allow an understanding of the relationship between dose, exposure, pharmacological activity and toxicity, and do not predict other effects such as local effects at the delivery site.

Andreas Baumann (Bayer) presented the status of a white paper (WP) initiative of BioSafe on the use of nonhuman primates (NHP) in Biologics PKPD development There has been particular interest in animal use in biologics development since it was recognized that NHP may be the only relevant non-clinical toxicology species for many therapeutic proteins. Therefore, an increase in the development of biologics has led to an increase in the use of non-human primates, mainly the cynomolgus macaque. Review of the justification provided to support the use of NHP in development showed that in a number of cases the NHP was not considered to be a relevant model or alternative non-rodent species, or *in vitro* models were available as a suitable model. Some researchers went even further to discount most of the value of NHP use in drug development (Van Meer et al., 2013). NHP use is still necessary in toxicology studies during drug development not only to provide critical safety information, but also to provide important information including FiM dose selection, PKPD relationships, compound selection and program direction. However, NHP studies should not be performed as a default to satisfy a standard development and regulatory path but should use rational, science-based decision-making in the ethical and scientific use of NHPs based upon the specific attributes of the product (Brennan et al., 2018). BioSafe published a WP highlighting the value of the NHP for safety assessment (Brennan et al., 2018). In addition, a WP group of BioSafe has been founded to further discuss this topic based on individual case examples from the PKPD perspective. Many of the biologics currently in development target novel pathways and may comprise novel scaffolds with multi-functional domains. Hence the pharmacological effects and potential safety risks are much less predictable. The aim of the WP is to demonstrate usefulness of NHP PKPD studies and multiple applications by discussing several case examples falling into different categories, (i) PKPD support (e.g. NHP PKPD studies for first in human (FIH) dose and human therapeutic dose estimation, e.g. allometry and establishing a correlation between systemic exposure, duration, and extent of receptor occupancy, and pharmacodynamic activity in monkeys, (ii) decision making (e.g. discontinuation of the development of a compound or preventing the discontinuation of a compound by using NHP models), and (iii) reducing the number of NHPs used in PKPD studies (e.g. by reuse of monkeys, cassette dosing and use of alternative animal and/or *in vitro* models). A holistic, integrated approach to get the best data from the most appropriate technology or species is a ‘must have’ in the future of new biologics development. It is not only important to foster the translational efforts by the accumulation of knowledge in an individual drug development process but cross-company as well, as illustrated during discussions on animal use in biologics development at the annually BioSafe General Membership Meetings (Baumann et al., 2014; Blaich et al., 2016; Brennan et al., 2015).

The next speaker, **Michael Kammüller (Novartis)**, presented a case study to exemplify how possible concerns regarding infection risks upon treatment with biotherapeutics might be addressed. Secukinumab, a fully human monoclonal antibody that selectively neutralizes IL-17A, has been shown to have significant efficacy in the treatment of several autoimmune diseases, and has been approved for moderate-to-severe psoriasis, psoriatic arthritis, and ankylosing spondylitis, demonstrating a rapid onset of action and sustained responses with a favorable safety profile. Neutralizing IL-17A, is associated with mild to moderate, non-serious, transient, superficial mucocutaneous *Candida albicans* infections (Cypowyj et al., 2012; Whibley et al., 2016), which respond to conventional treatment. While anti-TNFα treatments have been associated with an increased incidence of acute tuberculosis and reactivation of latent tuberculosis infection, anti-IL-17A treatment has no such known associations to date. However, reports that IL-17A-producing γδT cells and $CD4^+$ T cells play a potential role during different phases of *Mycobacterium tuberculosis* infection emphasize the need to further explore the role of IL-17A, in comparison with TNFα. To investigate any associations of secukinumab with reactivation of latent tuberculosis infections, *in vivo, in vitro* and clinical investigations were performed. Initially, a 4-week mouse model study examined the effect of surrogate antibodies neutralizing IL-17A or IL-17F during early phase *M. tuberculosis* H37Rv infection in comparison with TNFα blockade, by evaluating lung transcriptomic, microbiological and histological analyses. Coinciding with a significant increase of mycobacterial burden and pathological changes following TNFα blockade, gene array analyses of infected lungs revealed major changes of inflammatory and immune gene expression signatures four weeks post-infection. IL-17A or IL-17F neutralization elicited only mild changes of a few genes without impaired host resistance four weeks after *M. tuberculosis* infection (Segueni et al., 2016). A follow-on *in vitro* study, using a novel human 3-dimensional microgranuloma model, examined the effect of the anti-TNFα antibody adalimumab at 10 ng/ml, and the anti-IL-17A antibody secukinumab at 10, 100, and 1000 ng/ml, on human peripheral blood mononuclear cells infected with *M. tuberculosis* H37Rv, using auramine-O – nile red staining and rifampicin resistance as indicators of *M. tuberculosis* dormancy or activation. The *in vitro* study showed that anti-TNFα (adalimumab) treatment increased staining for auramine-O, and decreased nile red staining and rifampicin resistance, indicative of mycobacterial reactivation. In contrast, anti-IL-17A antibody (secukinumab) treatment was comparable to control indicating that the drug did not affect *M. tuberculosis* dormancy (Kapoor et al., 2016). Finally, secukinumab safety data were pooled from five randomized, double-blind, placebo-controlled phase 3 clinical trials in 2044 subjects with