Next generation and biosimilar monoclonal antibodies
Essential considerations towards regulatory acceptance in Europe
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The Next Generation and Biosimilar Monoclonal Antibodies: Essential Considerations Towards Regulatory Acceptance in Europe workshop, organized by the European Centre of Regulatory Affairs Freiburg (EUCRAF), was held February 3–4, 2011 in Freiburg, Germany. The workshop attracted over 100 attendees from 15 countries, including regulators from 11 agencies, who interacted over the course of two days. The speakers presented their authoritative views on monoclonal antibodies (mAbs) as attractive targets for development, the experience to date with the regulatory process for biosimilar medicinal products, the European Medicines Agency draft guideline on biosimilar mAbs, as well as key elements in the development of mAbs. Participants engaged in many lively discussions, and much speculation on the nature of the quality, non-clinical and clinical requirements for authorization of biosimilar mAbs.

Day 1: February 3, 2011

The workshop was opened by Gabriele Schäffner Dallmann (European Centre of Regulatory Affairs Freiburg), who welcomed the audience to Freiburg and the venue, the Historisches Kaufhaus, and introduced Johannes Löwer as the Chairman of the meeting. Professor Löwer, who was the President of the two German Health Authorities (i.e., the Federal Institute for Vaccines and Biomedicines, Paul-Ehrlich-Institut and the Federal Institute for Drugs and Medical Devices) until the end of 2010, discussed briefly the evolution in attitude toward complex biologics from the dogma that the source material defines the product (i.e., the process is the product) to the current thinking that the process affects the quality of the product, but does not uniquely define it. He noted that the current substantial interest in the development of biosimilars is due to a variety of factors, including the large global markets for therapeutic biologics and a need to reduce costs to overburdened health care systems. Professor Löwer noted that regulators have a responsibility to ensure safety and efficacy, but availability is also important. A reduced development program might allow lower cost products to be marketed and have the added benefit that unnecessary animal and human studies might be avoided. Regulators are thus challenged to find the right balance in the requirements for quality, safety and efficacy for authorization of biosimilar medicinal products.

Monoclonal Antibodies as Attractive Targets for Development

Michael Reth (Albert-Ludwigs-Universität Freiburg, Max-Planck-Institut for Immunology Freiburg and the Centre for Biological Signalling Studies) provided a historical overview and commentary on the future prospects of mAbs in Europe. Professor Reth explained that the concept that immunity could be transferred with blood originated with work by Emil Behring and Shibasaburo Kitasato on tetanus “anti-toxins” that was done in the 1890s at the Robert Koch Institute. Paul Ehrlich rejected the notion that the blood itself generates anti-toxins and suggested that they are products of cells carrying the anti-toxins as “side chains” on their cell surface. This first receptor-ligand concept was proposed by him in his famous Croonian Lecture “On immunity with special reference to cell life,” which was delivered to the Royal Society of London on March 22, 1900. In the early 1920s, Karl Landsteiner discovered that proteins modified with chemical groups would elicit an immune response specific to the modified proteins. During the 1930s and 1940s, numerous groups worked to establish how antibodies could bind so many different structures. Professor Reth briefly discussed the
clonal selection theory of Sir F. Macfarlane Burnet and colleagues that evolved in the 1950s and then highlighted the Nobel Prize winning work of Susumo Tonegawa on the genetic principle for generation of antibody diversity. He concluded his historical overview with a discussion of the ground-breaking work of Georges Köhler and César Milstein on the production of mAbs, which (famously) was not patented.

In looking toward the future, Professor Reth speculated that the 2010s–2030s might involve research based on either a fusion of immunology and mathematics, which he termed “systems immunology” or a fusion of immunology and engineering, which he termed “synthetic immunology.” He then discussed examples of the latter, such as controlling antibody production from B cells coated with smart nanobeads. The synthetic biology approach to the study of immunology is being pursued at the Centre for Biological Signalling Studies (BIOSS), Albert-Ludwigs-Universität Freiburg. In concluding, Professor Reth emphasized that many areas of immunology research and praxis could profit from adapting synthetic biology approaches.

Gabriele Schäffner-Dallmann (Study Director, European Centre of Regulatory Affairs Freiburg) provided a brief overview of antibodies as an attractive class of medicinal products. She reviewed the early history of recombinant product approvals of insulin, human growth hormone, interferon and a murine mAb (muromonab-CD3) in the 1980s. Dr. Dallmann noted that the number of approved mAb therapeutics did not increase by much until the late 1990s, but, with the exception of 2002 and 2008, at least one mAb was approved in the European Union (EU) each year starting in 1998. In fact, a total of six mAbs were EU-approved in 2009 (Table 1). She concluded by remarking that the future for mAbs looks bright, with over 300 antibody-based therapeutics in clinical studies, as well as numerous novel antibody formats undergoing preclinical evaluation.

Christian K. Schneider (Paul-Ehrlich-Institut; EMA, Chairman of the Biosimilar Medicines Working Party and member of the Committee for Medicinal Products for Human Use and the Committee for Advanced Therapies) presented an overview of what makes mAbs special. He first reviewed the features that make mAbs highly complex molecules: high molecular weight; primary/secondary/tertiary/quaternary structure; post-translational modifications; heterogeneity; presence of process- and product-related impurities; low stability of the drug substance/drug product; species specificity; and potential for immunogenicity. Dr. Schneider then noted that the established paradigm of ‘the process is the product’ implied that large or small alterations in the manufacturing process (e.g., change in expression system; fluctuations in pH, temperature, culture media) might result in a new product. The question is whether clinicians should care about the differences.

Dr. Schneider explained that the quality, non-clinical and clinical evaluation of complex products such as mAbs can be thought of as pillars within a structure, and that the data from one area does not provide a complete picture. He then discussed relationships between the quality and clinical areas, with a focus on the impact of immunogenicity on efficacy and safety. After noting that immunogenicity generally decreases with the inclusion of increasing amounts of human sequence (i.e., immunogenicity rates generally decrease in going from murine to chimeric, humanized or human versions), he explained that many other factors can have an effect. As an example where a lot of experience already exists, Dr. Schneider discussed immunogenicity rates for infliximab, a chimeric IgG1 targeting tumor necrosis factor (TNF). The rates have been shown to be quite variable (i.e., range from less than 5% to more than 35%) depending on factors such as the administration of concomitant immunomodulators/immunosuppressives, age of patients, indication and dose. In fact, a comparison of immunogenicity rates indicated the rates were not proportional to dose in juvenile idiopathic arthritis (JIA) patients administered methotrexate and 3 mg/kg infliximab (rate over 35%) compared with either adult rheumatoid arthritis (RA) patients administered methotrexate and 3 mg/kg infliximab or JIA patients administered methotrexate and 6 mg/kg infliximab (rates under 15% in both cases). Dr. Schneider allowed that the assays and studies were different, but the results were unexpected. Such cases led EMA to develop the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006; Table 2). The main points concerning his discussion of bridging the quality to clinical areas were that assay development and validation are key to understanding clinical relevance (e.g., can assay measure anti-drug antibodies in the presence of residual drug in serum?); immunogenicity is inherently linked to structure (e.g., presence of non-human structures, pegylation, glycosylation); and effects of quality attributes such as impurities and aggregates should be assessed.

Dr. Schneider then discussed relationships between non-clinical and clinical data. He discussed the example of TGN1412, a super-agonistic, anti-CD28, humanized IgG4 mAb that had been developed by TeGenero as a potential treatment for patients with B cell chronic lymphocytic leukemia (B-CLL) or autoimmune diseases such as multiple sclerosis or RA. However, preclinical models did not predict adverse effects experienced by humans in the first Phase 1 study conducted in March 2006. As a consequence, regulators revisited guidelines for the conduct of first-in-human studies and the question of the relevance of preclinical data from non-human species. The CPMP/ICH/302/95 and ICH S6 documents indicate that a relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of mAbs), but a central aspect of biotechnology products, including mAbs, is that they are species-specific. Dr. Schneider explained that an EMA Committee for Medicinal Products for Human Use (CHMP) guideline issued in final form in July 2007 provides strategies to identify and mitigate risks for first-in-human studies. The principles articulated by regulators include a strong focus on demonstration of the relevance of the animal model; careful selection of the target population (e.g., healthy volunteers vs. volunteer patients) with justification of the final choice and appropriate consideration given to the relevance of the data generated and potential long-term consequences; justification for the calculation of the starting dose; and sequential inclusion of subjects with the safety interval to be selected based on pharmacokinetics (PK) and pharmacodynamics (PD).

In discussing the clinical trials of mAbs, Dr. Schneider emphasized that enhanced safety measures may be required and these
| International non-proprietary name | Trade name | Type | Indication first approved | First EU (US) approval year |
|-----------------------------------|------------|------|---------------------------|----------------------------|
| Muromonab-CD3                     | Orthoclone Okt3 | Anti-CD3; Murine IgG2a | Reversal of kidney transplant rejection | 1986* (1986#) |
| Abciximab                         | Reopro      | Anti-GPIIb/IIa; Chimeric IgG1 Fab | Prevention of blood clots in angioplasty | 1995* (1994) |
| Rituximab                         | MabThera, Rituxan | Anti-CD20; Chimeric IgG1 | Non-Hodgkin lymphoma | 1998 (1997) |
| Basiliximab                       | Simulect    | Anti-IL2R; Chimeric IgG1 | Prevention of kidney transplant rejection | 1998 (1998) |
| Daclizumab                        | Zenapax     | Anti-IL2R; Humanized IgG1 | Prevention of kidney transplant rejection | 1999 (1997)* |
| Palizumab                         | Synagis     | Anti-RSV; Humanized IgG1 | Prevention of respiratory syncytial virus infection | 1999 (1998) |
| Infliximab                        | Remicade    | Anti-TNF; Chimeric IgG1 | Crohn disease | 1999 (1998) |
| Trastuzumab                       | Herceptin   | Anti-HER2; Humanized IgG1 | Breast cancer | 2000 (1998) |
| Gemtuzumab ozoigamicin            | Mylotarg    | Anti-CD33; Humanized IgG4 | Acute myeloid leukemia | NA (2000)* |
| Alemtuzumab                       | MabCampath, Campath-1H | Anti-CD52; Humanized IgG1 | Chronic myeloid leukemia | 2001 (2001) |
| Adalimumab                        | Humira      | Anti-TNF; Human IgG1 | Rheumatoid arthritis | 2003 (2002) |
| Tosotumomab-t131                  | Bexar       | Anti-CD20; Murine IgG2a | Non-Hodgkin lymphoma | NA (2003) |
| Efalizumab                        | Raptiva     | Anti-CD11a; Humanized IgG1 | Psoriasis | 2004 (2003)* |
| Cetuximab                         | Erbitux     | Anti-EGFR; Chimeric IgG1 | Colorectal cancer | 2004 (2004) |
| Ibritumomab tiuxetan              | Zevalin     | Anti-CD20; Murine IgG1 | Non-Hodgkin lymphoma | 2004 (2002) |
| Omalizumab                        | Xolair      | Anti-IgE; Humanized IgG1 | Asthma | 2005 (2003) |
| Bevacizumab                       | Avastin     | Anti-VEGF; Humanized IgG1 | Colorectal cancer | 2005 (2004) |
| Natalizumab                       | Tysabri     | Anti-a4 integrin; Humanized IgG4 | Multiple sclerosis | 2006 (2004) |
| Ranibizumab                       | Lucentis    | Anti-VEGF; Humanized IgG1 Fab | Macular degeneration | 2007 (2006) |
| Panitumumab                       | Vectibix    | Anti-EGFR; Human IgG2 | Colorectal cancer | 2007 (2006) |
| Eculizumab                        | Soliris     | Anti-CS; Humanized IgG2/4 | Paroxysmal nocturnal hemoglobinuria | 2007 (2007) |
| Certolizumab pegol                | Cimzia      | Anti-TNF; Humanized Fab, pegylated | Crohn disease | 2009 (2008) |
| Golimumab                         | Simponi     | Anti-TNF; Human IgG1 | Rheumatoid and psoriatic arthritis, ankylosing spondylitis | 2009 (2009) |
| Canakinumab                       | Ilaris      | Anti-IL1b; Human IgG1 | Muckle-Wells syndrome | 2009 (2009) |
| Catumaxomab                       | Removab     | Anti-EPCAM/CD3; Rat/mouse bispecific mAb | Malignant ascites | 2009 (NA) |
| Ustekinumab                       | Stelara     | Anti-IL12/23; Human IgG1 | Psoriasis | 2009 (2009) |
| Tocilizumab                       | RoActemra, Actemra | Anti-IL6R; Humanized IgG1 | Rheumatoid arthritis | 2009 (2010) |
| Ofatumumab                       | Arzerra     | Anti-CD20; Human IgG1 | Chronic lymphocytic leukemia | 2010 (2009) |
| Denosomab                         | Prolia      | Anti-RANK-L; Human IgG2 | Bone Loss | 2010 (2010) |
| Belimumab                         | Benlysta    | Anti-BlyS; Human IgG1 | Systemic lupus erythematosus | In review (2011) |
| Raxibacumab                       | (Pending)   | Anti-B. anthrasis PA; Human IgG1 | Anthrax infection | NA (In review) |
| Ipilimumab                        | Yervoy      | Anti-CTLA-4; Human IgG1 | Metastatic melanoma | In review (2011) |
| Brentuximab vedotin               | (Pending)   | Anti-CD30; Chimeric IgG1; immunonconjugate | Hodgkin lymphoma | NA (Application submitted) |

Note: Information current as of March 25, 2011. *Country-specific approval; approved under concertation procedure; #Voluntarily withdrawn from market. BlyS, B lymphocyte stimulator; CS, complement S; CD, cluster of differentiation; CTLA-4, cytotoxic T lymphocyte antigen 4; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; GP, glycoprotein; IL, interleukin; NA, not approved; PA, protective antigen; RANK-L, receptor activator of NFκb ligand; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.
In discussing risks associated with chronic treatment and the management of these risks, Dr. Schneider presented case studies of infliximab (Remicade®) and natalizumab (Tysabri®). Infliximab is an anti-TNF mAb approved in 1999 in the EU under exceptional circumstances as a second line therapy for treatment for severe active Crohn disease in adult patients. It was subsequently approved for RA, pediatric Crohn disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. There was, inherently, limited data on efficacy and safety of the mAb at the time of approval. During 1999 to 2002, there were reports of numerous severe adverse events in patients, e.g., reactivation of tuberculosis, severe infections including opportunistic infections and sepsis, infusion reactions, immunogenicity and, potentially, lymphoma. The CHMP issued an urgent safety restriction on January 17, 2002 that restricted infliximab to use as a third-line treatment and, in February 2002, introduced use of a patient alert card that was intended as a measure to improve should be implemented proactively. The specific measures should be based on considerations of the mechanism of action, potential unknown mechanisms that might underlie safety signals, and other factors such as impurities, quality defects, stability defects, inappropriate handling of the mAb and cross-reactivity. In answering the question of whether the clinical development of mAbs has special features, Dr. Schneider explained that it depends on the product. The mechanism of action and safety considerations may indeed be special. For example, the mechanism of action of mAbs may involve different targets compared with those of chemical drugs (e.g., tumor cell epitopes, neutralization of cytokines) or overcoming resistance to other drugs (e.g., chemotherapy with irinotecan for cetuximab). Safety and immunogenicity considerations for mAbs can also be special, thus leading to study designs that can be different or “expanded” relative to those of other types of therapeutics.

Table 2. European Medicines Agency guidelines relevant to biosimilar development and approval

| Reference | Date | Title |
|-----------|------|-------|
| EMEA/CPMP/BWP/3207/00; effective December 2003. | | Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance. Quality issues. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003573.pdf) |
| EMEA/CPMP/3097/02; effective June 2004. | | Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance. Non-clinical and clinical issues. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003963.pdf) |
| CHMP/437/04; effective October 2005. | | Guideline on similar biological medicinal products. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf) |
| EMEA/CHMP/BWP/49348/2005; effective June 2006. | | Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf) |
| EMEA/CHMP/BWP/42832/2005; effective June 2006. | | Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf) |
| CHMP/14327/2006; Draft (deadline for comments July 2007). | | Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003947.pdf) |
| EMEA/CHMP/BWP/157653/2007; effective July 1, 2009. | | Guideline on development, production, characterization and specification for monoclonal antibodies and related products. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003074.pdf) |
| EMA/CHMP/BWP/86289/2010; Deadline for comments May 31, 2011. | | Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC50009362.pdf) |
| EMA/CHMP/BWP/403543/2010; Deadline for comments May 31, 2011. | | Guideline on similar biological medicinal products containing monoclonal antibodies. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC50009361.pdf) |
| EMA/CHMP/BWP/617111/2010; Deadline for comments May 31, 2011. | | Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. [Link](https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102285.pdf) |

Notes: BWP, Biologics Working Party; BMWP, Biosimilar Medicines Working Party; CHMP, Committee for medicinal products for human use; CPMP, Committee for proprietary medicinal products; EMEA, European Medicines Agency.
risk communication and information of patients and health care providers. During 2002 to 2004, there were additional clinical studies in various indications, periodic safety update reports (PSURs), which are legally required, were submitted and patient registries were established. The requirement for an annual re-assessment was lifted after the fourth re-assessment and the marketing authorization was renewed in 2004. In 2005, the sponsor requested that infliximab be changed from third-line back to second-line therapy based on new clinical data (ACCENT-I, GETAID studies), data from the Crohn therapy resource evaluation and assessment tool (TREAT) registry and cumulative data on drug safety between August 1998 and August 2004. CHMP adopted a positive opinion in July 2006 because there were no new safety findings based on a huge amount of data, data analysis suggested that risk for severe adverse events is similar to other treatments in this severe indication or can be controlled with the measures previously introduced, and clinical management of patients with severe disease requires flexibility for the treating physician. There was also a commitment to continue and finalize the registries. However, new reports of a rare and fatal type of lymphoma, hepatosplenic T-cell lymphoma, in children and adolescents were a cause of concern.

Dr. Schneider noted the importance of risk identification and minimization in discussing the case study of natalizumab, which impedes diapedesis of lymphocytes into the brain. Natalizumab was authorized for marketing in the EU in 2006 as a treatment for highly active relapsing, remitting multiple sclerosis, despite the known risk to induce progressive multifocal leukoencephalopathy (PML), because of the clinically relevant efficacy of the mAb. To minimize risk, use was limited to patients with high disease activity despite treatment with a β-interferon or patients with rapidly evolving severe relapsing remitting multiple sclerosis and distribution of physician packs containing product information, physician information about Tysabri and patient alert cards were required. Dr. Schneider concluded by explaining the knowing risk can mean controlling risk and that regulators now have numerous means to control risk, including conditional marketing authorization, restrictions of the indication, warning statements in the summary of product characteristics, systemic risk evaluation by registries and observational studies, and requirements for use of special centers, educational material and patient alert cards. Nevertheless, it is likely that balancing early market access with the need for benefit/risk data will continue to be a dilemma.

Experience in the Regulatory Process of Biosimilars

Ann Johnsson (Läkemedelsverket; Medical Products Agency, Sweden) discussed the experience of authorized biosimilar products. She noted that her presentation was kept to general terms because the number of products approved to date is limited, and only a few companies are involved in production of the products biosimilar to somatropin, erythropoietin and filgrastim (Table 3). It was thus not possible to use the currently licensed products as specific examples because the individual product would have been identifiable, at least by the competitors.

Dr. Johnsson briefly reviewed the EMA’s overarching biosimilar guidelines, as well as the guidelines that are specific for a biosimilar product, e.g., erythropoietin, low-molecular weight heparins, interferon α, granulocyte-colony stimulating factor, somatropin and human insulin (Table 4). She also mentioned other guidelines that are relevant for biosimilars, such as the guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issues. Dr. Johnsson explained that the guidelines’ requirement on quality is consistent, the non-clinical requirements are defined based on experience with the reference products, and that the clinical program requires assessment of changes in PK/PD, efficacy and safety, especially immunogenicity. She emphasized that the same reference product should be used in all sections of the dossier.

Dr. Johnsson then discussed the Module 3 requirements for extensive state-of-the-art characterization studies on the similar biological and reference medicinal products in parallel at both the active substance and the medicinal product levels. She noted that the methods used in the comparability exercise must be able to detect slight differences in all aspects pertinent to the evaluation of quality, and this relates to physicochemical properties, biological activity, purity and product-related substances/impurities. Dr. Johnsson explained that so far the experience with biosimilars licensed in the EU has been limited, but that the basic requirements on the quality documentation have been met. There were no major objections raised on the content or design of the comparability studies, i.e., there was adequate characterization; the stability studies were useful; the companies have so far met the challenge to demonstrate comparability on the level of drug substance even when the concentration of active substance in drug product was very low; process-related problems have been solved.

In concluding, Dr. Johnsson wondered why no biosimilar insulin products have been approved. Marketing applications for three insulin products (insulin human rapid Marvel, insulin human long Marvel, insulin human 30/70 mix Marvel) sponsored by Marvel LifeSciences, Ltd., were withdrawn in December 2007 after the CHMP expressed concerns regarding the comparability of the biosimilar products to the reference product (Humulin). Dr. Johnsson speculated that sponsors might consider the production costs too high, the market too limited or the development process too difficult.

Lessons learned and the future challenges awaiting a pioneer in biosimilar development were presented by Thomas Kirchlechner (Regulatory Affairs, Sandoz). His main points addressed challenges in technical, preclinical, clinical and regulatory requirements. In a brief introduction, Dr. Kirchlechner noted that development of a biosimilar therapeutic requires complete, target directed process and product development, as well as comparative testing with the reference product at all stages of development in order to gain approval. The choice and consistent use of the reference product is a key element to a successful program. Dr. Kirchlechner explained that the criteria for the comparison of the purity profile of the biosimilar candidate and the reference product are based on: (1) understanding batch-to-batch variability of the reference product; (2) classification of the product variants into product-related substances or impurities (as per ICH
Q6B); (3) the level of understanding of the relevance of subtle differences in the levels of these variants on safety/efficacy (as per ICH Q5E). The manufacturing process for the biosimilar is systematically designed to meet the required comparability criteria and ensures appropriate quality and consistency of the product. Using such an approach, a total of 14 biosimilars of three product types (somatropin, epoetin, filgrastim) have been approved in the EU to date (Table 3).

Dr. Kirchlechner then described two case studies of the technical challenges of biosimilar development. In the first case study, impurities were found to cause an increase in anti-human growth hormone (hGH) antibody incidence. Physicochemical, biological and preclinical biosimilarity was shown with state-of-the-art methods, but unexpectedly an increased ratio of patients showed elevated levels of anti-hGH antibodies. An evaluation of potential root causes included examination of product-related substances and impurities, process-related substances, the identity and higher order structure, as well as physical parameters, of the drug product. The investigation confirmed the root cause to be host cell proteins (HCP). Dr. Kirchlechner explained that the commercial HCP assay used for initial drug substance development did not detect one specific HCP relevant for the final drug substance. The issue was detected once a sensitive, process-specific HCP assay became available. Process optimization resulted in a significant reduction of HCP content in the final drug substance. In a pivotal efficacy study, the anti-hGH antibody incidence declined after patients were switched to the final drug substance. An additional Phase 3 study with naïve patients confirmed low immunogenicity. Dr. Kirchlechner indicated that the lessons learned were that sensitive and process-specific host cell protein monitoring tools are an important part of mitigating risks with immunogenicity for both innovative and biosimilar products, and Phase 3 studies are an essential part of biosimilar development.

The second case study involved the examination of the quality range of an originator product over time, which can set the “goal posts” for product attributes for biosimilars. Dr. Kirchlechner presented data for a reference darbepoetin α product before and after a process change. The parameters evaluated included Neu5Gc, Neu5, 9Ac2, total O-acetylation, tetrasialo glycans, average number of sialic acids per glycan, 4A1F glycans, average number of antennae per glycan and CZE isoform 5. In each case, parameters for the post-change product were found to be outside the ranges observed for the pre-change product, which suggests that biosimilars with parameters within the expanded target range may be considered highly similar because patients were safely treated with both versions of the reference product. Dr. Kirchlechner noted that originators often make changes to their manufacturing processes after launch and that similarity is evaluated by accepted scientific processes that can also be used to evaluate biosimilars.

In discussing preclinical and clinical challenges, Dr. Kirchlechner presented a roadmap to preclinical and clinical development of therapeutic protein biosimilars, as well as a case study involving PD and clinical efficacy. Dr. Kirchlechner explained that preclinical development can be thought of as having four pillars: (1) a reference product with well-established clinical efficacy and safety data; (2) rigorous manufacturing and quality control for the biosimilar; (3) proof for matching molecular characteristics of the reference and its biosimilar; (4) selection of appropriate in vitro assays and animal models. The roadmap’s preclinical section thus includes collection of in vitro data from receptor and target binding assays, functional assays and bioactivity assays, as well as animal studies involving PK and PD studies in relevant species, short term repeated dose toxicity and immunogenicity study in relevant species, and assessment of local tolerance and efficacy data in relevant animal disease models where needed to complement clinical trials. The clinical aspect of the roadmap includes PK and PD data in the most sensitive target population, PD assessment based on validated disease outcome-predictive markers, as well as data from potentially novel approaches, e.g., PK/PD modeling.

### Table 3. Biosimilar therapeutic protein products approved in the European Union

| Non-proprietary name | Reference product trade name | Biosimilar product trade name | Biosimilar sponsor company | Year of biosimilar product approval |
|----------------------|------------------------------|------------------------------|----------------------------|----------------------------------|
| Somatropin           | Genotropin*                  | Omnitrope*                   | Sandoz GmbH               | 2006                             |
| Somatropin           | Humatrope*                   | Valtropin*                   | BioPartners GmbH          | 2006                             |
| Epoetin alfa         | Eprex*                       | Binocrit*                    | Sandoz GmbH               | 2007                             |
| Epoetin alfa         | Eprex*                       | Epoetin alfa Hexal*          | Hexal AG                  | 2007                             |
| Epoetin alfa         | Eprex*                       | Abseamed*                    | Medice Arzneimittel Putter GmbH | 2007                             |
| Epoetin zeta         | Eprex*                       | Retacrit*                    | Hospira Enterprises B.V.  | 2007                             |
| Epoetin zeta         | Eprex*                       | Silapo*                      | STADA Arzneimittel AG     | 2007                             |
| Filgrastim           | Neupogen*                    | TevaGrastim*                 | Teva Generics GmbH        | 2008                             |
| Filgrastim           | Neupogen*                    | Biogratistim*                | CT Arzneimittel           | 2008                             |
| Filgrastim           | Neupogen*                    | Ratiogratistim*              | ratiopharm GmbH           | 2008                             |
| Filgrastim           | Neupogen*                    | Filgrastim ratiopharm*       | ratiopharm GmbH           | 2008                             |
| Filgrastim           | Neupogen*                    | Filgrastim Hexal*            | Hexal AG                  | 2009                             |
| Filgrastim           | Neupogen*                    | Filgrastim Zarzio*           | Sandoz GmbH               | 2009                             |
| Filgrastim           | Neupogen*                    | Nivestim*                    | Hospira Enterprises B.V.  | 2010                             |
Dr. Kirchlechner argued that the healthy volunteer study was more sensitive than a patient study because the bone marrow of healthy subjects is fully responsive to G-CSF treatment, unlike the bone marrow of immunosuppressed cancer patients. Comparable clinical efficacy could be shown by this approach and a single arm Phase 3 study in patients was then considered sufficient to demonstrate clinical safety, instead of a comparative Phase 3 study.

The regulatory challenges to global biosimilar development comprised Dr. Kirchlechner’s final topic. He noted that, in addition to independent product and process development, biosimilar product development requires a thorough comparison to a reference product at all levels. The reference product chosen has to be used for all parts of the comparability exercise and needs to be compartmental analysis. The final section of the roadmap included efficacy and safety comparisons in the most sensitive target population, as well as the use of established disease outcome—predictive PD markers as surrogate endpoints for efficacy comparison, novel PD markers to strengthen the claim of comparability and innovative statistical approaches and meta-analysis data to optimize study design.

Dr. Kirchlechner’s case study involved the clinical development of a biosimilar that was compliant with the biosimilar G-CSF guideline, which indicates that alternative models, including PD studies in health volunteers, may be pursued for the demonstration of comparability if justified. PD was evaluated in healthy volunteers during four Phase 1 studies and clinical efficacy was based on absolute neutrophil count, which was an accepted PD marker. Dr. Kirchlechner argued that the healthy volunteer study was more sensitive than a patient study because the bone marrow of healthy subjects is fully responsive to G-CSF treatment, unlike the bone marrow of immunosuppressed cancer patients. Comparable clinical efficacy could be shown by this approach and a single arm Phase 3 study in patients was then considered sufficient to demonstrate clinical safety, instead of a comparative Phase 3 study.

The regulatory challenges to global biosimilar development comprised Dr. Kirchlechner’s final topic. He noted that, in addition to independent product and process development, biosimilar product development requires a thorough comparison to a reference product at all levels. The reference product chosen has to be used for all parts of the comparability exercise and needs to be
authorized in a highly regulated market by ICH standards, e.g., EU, US, Japan. The biosimilar development and comparability exercise has to be performed according to the stringent requirements laid down in a highly regulated market. Dr. Kirchlechner also noted that on the approval in a highly regulated market qualifies the product to be named a “biosimilar product” or “biosimilar medicine.”

Dr. Kirchlechner then discussed an issue specific to global biosimilar development, i.e., many countries have recently established legal frameworks and regulatory pathways for biosimilars that require either that the comparison occurs against the reference product approved in their jurisdiction or are silent on this point. Thus, for all recent EU authorizations of biosimilar medicinal products, appropriate reference products had to be those authorized in the EU. However, reference products are often the same or highly similar in different countries, even though licensed under different jurisdictions and thus legally “different.” Dr. Kirchlechner stated that documentation confirming that the products are the same can often be found in the public domain, and comparability of reference products of one original manufacturer but sourced from different countries can be clearly established by stringent analytical and functional studies. Despite this, the current system would appear to mandate that separate, full development programs be performed for each country. In addition to being costly, such duplication of preclinical and clinical studies raises ethical concerns.

In conclusion, Dr. Kirchlechner proposed a global biosimilar development program that included physicochemical and biological comparison of reference product and biosimilar, preclinical studies with reference product from one region, rigorous PK/PD comparison as needed on a case-by-case basis and a clinical Phase 3 study with reference product from one region. Bridging studies to a reference product from a different ICH jurisdiction could then be done. He noted that a helpful step forward would be for ICH regulatory agencies to interface in order to determine the sameness of the manufacturing sites registered in each of their jurisdictions for a particular product, rather than relying on the biosimilar industry to prove sameness. Indeed, an FDA/EMA interface, the Transatlantic Administration Simplification Action Plan, is already in place.

**Update on Upcoming Biosimilar Guidelines**

Christian K. Schneider (Paul-Ehrlich-Institut, Germany) gave a status update on the guideline on biosimilar mAbs. He noted that regulatory agencies have experience with mAbs as medicinal products with ~30 having achieved authorization; however, numerous challenges to their development remain, e.g., mechanisms of action can be complex. Given the experiences to date, a variety of questions arise when considering how to design a biosimilar development program, especially in the case of a mAb with multiple licensed indications, e.g., Should therapeutic equivalence or non-inferiority be shown? Is extrapolation of efficacy or safety possible? What endpoints—activity or benefit?

Dr. Schneider then discussed the July 2009 EMEA workshop on biosimilar mAbs and its key messages on quality, non-clinical and clinical aspects in more detail. The philosophy of the meeting was enablement of open discussion on the pros and cons of biosimilar mAbs concerning their possibility and feasibility, which was helpful in informing the EMA Biosimilar Medicines Working Party’s work on a guideline in this field. Questions from EMEA were posed to the audience as a starting point, and focused presentations from regulators and industry were meant to initiate discussions. Key messages from the discussion on quality were that the existing guidelines for quality are sufficient and that it is impossible to replicate exactly the innovator product, which is itself changing over time. Variability is set by the innovator in terms of production process, and not so much in impurity profile, which can be different and needs to be justified. Use of different expression systems was discussed, but it was noted that this approach might be the source of many difficulties. Regarding analytical tools, Dr. Schneider noted that a paradoxical situation exists whereby the biosimilars might be blunter, but methods for physicochemical characterization can be very sensitive. A combination is thus necessary, and the main question is how to assess the impact on safety and efficacy.

Key messages from the EMEA workshop on non-clinical aspects were that reduced non-clinical programs may be possible (and may be more acceptable from an ethical standpoint), and that they should focus on the specific needs and mechanism of action, e.g., as regards to the requirement to show comparable impact on signaling events. Toxicity of mAbs is mostly target-related, and use of non-relevant species is not appropriate (agreed upon by a majority). For evaluation of “unknown” impurities, alternative approaches such as tissue cross-reactivity or reduction of impurities were mentioned at the workshop as potential alternatives. No consensus of the workshop participants was reached on whether toxicity studies have to be comparative.

At EMEAs workshop, participants in the discussion on the clinical development of biosimilar mAbs did not reach a consensus on the question of using the most sensitive model vs. the clinically most relevant model, although there might have been a slight majority for the most sensitive model. An open question was: Do we need the data in the most severe patient population and risk that the data are confounded? It was suggested that the endpoint should be the most sensitive one, not necessarily the one initially chosen by the innovator or the one recommended by the clinical guidelines for the respective clinical indications, which can still be asked for as a secondary endpoint. Another key message was that PK/PD can be different between indications and modeling approaches might help. The final point was that understanding of the mechanism of action is often not yet complete. It is not known to what extent the subpopulation of molecular species contributes to activity in an indication, so this had to be shown “somewhere” with data. The key message is then that the totality of evidence leads to a convincing dossier.

With the discussion of the 2009 EMEA workshop as background, Dr. Schneider presented key principles of the non-clinical and clinical aspects of the draft CHMP guideline on biosimilar mAbs released for consultation in November 2010. For non-clinical development, a risk-based approach is recommended. The extent of studies will depend on the risk identified
with the mAbs, e.g., if significant differences in impurities are observed. The starting point is the in vitro and ex vivo work, e.g., comparative concentration/activity studies, coverage of all functional aspects. Animal studies would be done on a case-by-case basis, mainly depending on the availability of a relevant species. Specific read-outs (e.g., PK, PD, toxicity) would depend on the need for additional information. Large comparative studies in non-human primates are not recommended; rather studies that include one dose, one gender and no recovery group, but that are comparative unless otherwise justified.

Dr. Schneider indicated that PK and PD studies are an integral part of biosimilar mAb development. The draft guideline indicates a parallel group design with no cross-over. The clinical context is important, e.g., the clearance may change after the first dose; therapeutic response can affect PK; antigen levels have an impact on PK, and so single dose PK studies may be the most sensitive in some cases. The primary principle emphasized is that a sensitive and homogeneous patient population should be included. In addition, studies in every indication licensed may not be needed; however, separate PK studies may help in the biosimilarity exercise for bridging between indications. The draft guideline provides some guidance on multidose PK studies. PK may be variable, and so evaluation could be undertaken as part of the Phase 3 study to establish clinical biosimilarity. In this case, an exploratory PK study could be done first to investigate tolerability and to get a rough idea and go/no-go indicator for biosimilarity. Dr. Schneider noted that statistical rigor and integrity must be ensured, an interim analysis for PK equivalence might be considered and discussions with regulatory agencies should occur first. Other key principles included in the draft guideline are that sponsors should always explore possibilities to study dose-concentration-response relationships since this approach, if successful (and medically acceptable), may provide strong evidence of biosimilarity; and that a single or repeat dose study in the saturation part of the dose-concentration-response curve is unlikely to discriminate between different activities, should they exist. A final key point made was that PK data from lower dose(s) may, in principle, provide already pivotal information in the biosimilarity exercise.

Regarding clinical efficacy, the draft guideline notes that “if dose comparative and highly sensitive PD studies cannot be performed convincingly showing comparability in a clinically relevant manner, similar clinical efficacy between the similar and the reference product should be demonstrated in adequately powered, randomized, parallel group comparative clinical trial(s), preferably double-blinded and normally equivalence trials.” Dr. Schneider noted that this means that in some, albeit most probably rare, occasions, PD markers may be available and may be more sensitive than clinical efficacy. He also noted that use of the phrase “normally equivalence trials” was meant to acknowledge debates as regards acceptance of non-inferiority. A guiding principle is the use of a homogeneous and sensitive population for demonstration of clinical efficacy, as opposed to a clinically challenging one. It is understood that deviations from the clinical guidelines may be necessary, but full justification is then required. Dr. Schneider noted that the aim of the studies is to establish biosimilarity between products, not the clinical benefit per se of the biosimilar; benefit has already been established by studies of the reference mAb. He mentioned that by this a biosimilar development is not necessarily “abridged,” but rather “tailored” based on scientific principles. The “usual” endpoints might be secondary endpoints where feasible, although Dr. Schneider emphasized that this point is not unattended. A key principle of the guideline is stated as “Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions (whether licensed or not), and the applicant should justify that the model is relevant and sensitive to demonstrate comparability in relation to efficacy and safety in the indication(s) applied for. It is recommended that such approach is discussed upfront with regulatory authorities, e.g., via CHMP Scientific Advice.”

Dr. Schneider’s final comments on key principles of the draft guideline were on the topics of safety, pharmacovigilance and extrapolation. He explained that clinical safety is normally evaluated as part of the efficacy study, and that use of similar definitions, where available, as were used for the reference mAb development is advisable. Key principles are that safety as regards pharmacologically mediated adverse reactions can be a measure for biosimilarity (e.g., cardiotoxicity), and that when PD is used as primary pivotal evidence, the applicants need to provide sufficient reassurance of clinical safety, including immunogenicity. Regarding extrapolation, the draft guideline states that it “is possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification,” and “If pivotal evidence for biosimilarity is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then Applicants should provide relevant data to cover PD for all claimed clinical indications.”

Dr. Schneider concluded by quoting Paul Ehrlich as saying “No estimates, exact measurements. I have always found facts to be true.”

An update on the World Health Organization (WHO) guideline on biosimilar product development was presented by Martina Weise (Bundesinstitut für Arzneimittel und Medizinprodukte; Federal Institute for Drugs and Medical Devices, Germany; Vice-Chairman of the EMA’s Biosimilar Medicines Working Party). Dr. Weise first provided a short overview on the parallel development of the legal framework and regulatory pathway for biosimilars in the EU. Directive 2003/63/EC “Annex I,” which provided recognition of “biosimilars,” was published in 2003, and the amended Directive 2001/83/EC was published in 2004 and took effect in 2005. In the same period, EMEA published revised comparability guidelines in 2003; followed by guidelines on quality issues and non-clinical and clinical issues of biosimilar biotechnology-derived medicinal products, released product class-specific draft guidelines and approved the first biosimilar for marketing in the EU in 2006. Dr. Weise noted that the EU has held a leading role in development and implementation of a specific legal framework and a regulatory pathway for biosimilars, and the EU guidelines have largely influenced guidance documents subsequently issued by other countries or they were referred to or simply adopted (e.g., in Malaysia in July 2008, Australia in August 2008, Turkey in August 2008, Taiwan in 2008, etc.).
November 2008, Japan in March 2009, Singapore in September 2009, Canada in March 2010 and Saudi Arabia in December 2010). In addition, a consensus group of experts have recommended implementation of the EMA guidelines in the near and Middle East. In the US, healthcare reform legislation signed into law in 2010 includes a regulatory pathway for biosimilars, but the FDA has yet to define criteria on how to demonstrate biosimilarity.

With this background as context, Dr. Weise explained that there is a need for global consistency. Problems currently exist because there is a huge unregulated market for "copy" versions of innovator biologicals that are licensed based on reduced data packages without clear regulatory pathways in many countries. Different terminology, definitions and data requirements for licensing of such "copy" biologicals around the globe have led to confusion and added to physicians' fears about safety and efficacy of biosimilars in the EU. At a WHO meeting in April 2007, an informal consultation group identified the need for a WHO guidance that would define regulatory expectations at a global level. The scope was to include formulation of key scientific principles for evaluation of similar biotherapeutic products (SBPs) that leave room for national regulatory agencies to formulate national-level requirements, and consideration of guidance issued by other bodies so that WHO guidance complemented the existing framework. Assistance with implementation into regulatory and manufacturers practice, e.g., through regional and national workshops, would be included.

Dr. Weise described the key events in the development of WHO’s guidelines on SBPs, which she participated in drafting. A drafting group meeting was held in March 2008 in Bonn and a WHO consultation meeting was held in May 2008 in Seoul. The first proposal to establish two separate abbreviated licensing pathways, a “biosimilar pathway” in accordance with EU requirements and a “clinical comparability pathway” with focus on clinical comparison of the SBP and the original biological, was rejected by the Expert Committee on Biological Standardization (ECBS) in October 2008 in Geneva, and a revised version was requested. The drafting group met in February 2009 in Tokyo, with another WHO consultation meeting held in July 2009 in Ottawa. The guidelines on evaluation of SBPs were then approved by the ECBS at their October 2009 meeting in Geneva.

Dr. Weise then discussed the similarities and differences of the EMA and WHO guidance. Importantly, the scientific principles are the same. A demonstration of similarity in terms of quality, safety and efficacy is necessary and the same reference product should be used for the whole comparability exercise. Similar physicochemical characterization is a prerequisite for the potential reduction of the (non)clinical data package, and the (non)clinical data requirements depend on the extent of possible characterization, observed/potential differences and clinical experience with the substance class. In principle, clinical studies are expected for demonstration of similar efficacy and safety, but, where appropriate, PK/PD studies might be preferable for demonstration of similar efficacy since PD endpoints are often more sensitive than clinical endpoints to detect product-related differences. Patient data on safety and immunogenicity are needed prior to licensing. Other similarities include the focus on demonstration of similarity, not of efficacy or patient benefit per se. Studies are thus principally comparative, sensitive test models are needed to detect potential differences, and endpoints may be different from those used in studies with the reference product. Extrapolation to other indication(s) of the reference product may be done only if scientifically justified. Dr. Weise noted that the development of biosimilars is a fast-evolving field, and the guidelines may need refinements (perhaps frequently) to incorporate on-going experience and scientific advances.

Dr. Weise also pointed out differences between the two documents. The WHO guideline is more limited in scope because it applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins only. Vaccines, plasma-derived products and their recombinant analogues are excluded. Another difference is that the WHO guideline also allows the use of a non-nationally licensed reference product if such use is approved by the national regulatory agency. The WHO quality evaluation and comparison guidance is much more detailed, e.g., because there are no other WHO guidance on evaluation and licensing of biologicals to build upon. The WHO clinical data requirements are also more detailed and use examples, e.g., explaining what defines a sensitive model. Compared to the EMA version, the WHO guideline is more flexible regarding acceptability of non-inferiority (instead of equivalence) studies, clearly explaining advantages and limitations of each approach.

In addition, the WHO guideline clearly states requirements for extrapolation of data to other indications of the reference product that were not studied with the SBP, including the need for similarity demonstrated in sensitive test model(s), the same mechanism of action or receptor, and sufficiently characterized safety and immunogenicity. The WHO guideline has a section on pharmacovigilance, which was needed because many WHO countries do not have appropriate pharmacovigilence surveillance. The final difference noted by Dr. Weise was that the WHO guideline clearly states that prescribing information should be as similar as possible except for product-specific aspects such as different excipient(s).

In concluding her presentation, Dr. Weise remarked that the EU system for biosimilars works, and the scientific principles defined in the EU are generally accepted and are being increasingly implemented globally. She also noted that the WHO guideline will help promote international standards for developing and licensing of SBPs, and that education and communication are important to convey “biosimilar thinking.”

The presentations were followed by a session of open discussion among workshop participants. The topics discussed included comparability after marketing approval; differences between the terms “interchangeability” and “automatic substitution”; product specifications in European Pharmacopoeia monographs; the definition of “sensitive and homogeneous study population”; and extrapolation of study data. On the question of whether an authorized biosimilar product should be considered “biosimilar” to itself or its reference product, i.e., are biosimilar products “stand-alone” once approved for marketing?, the general understanding was that a stand-alone product would have no further need to show comparability to a reference product. Opinions
were offered that the scientific principles underpinning the comparability exercises for biosimilar products and those done after manufacturing changes are the same, and that maintaining biosimilarity between products during their entire life cycle would be difficult. However, as a stand-alone product, a marketed biosimilar would still undergo a comparability exercise if a manufacturing change occurred, i.e., data would be needed to show comparability of pre- and post-change products. If there was substantial change in the manufacturing process, the manufacturer of a marketed biosimilar product would have to provide clinical data, but for their own product, not the reference product (which itself might also have changed over time). This line of reasoning was not unanimously agreed upon by participants.

Discussion of comparability exercises for marketed biosimilars and potential changes over the product life cycles led to the topic of interchangeability and automatic substitution, which is a national/regional decision in the EU in the competence of the EU member states. The current thinking is that interchangeability is acceptable when it is initiated by the prescribing physician. From a practical standpoint, automatic substitution would be a questionable practice because biologics are injected products and the devices used for delivery are not standardized. As a consequence, patient safety might be compromised if the patients are not properly instructed on the use of a particular device. The opinion was offered then that, for this practical reason, substitution without the physician’s knowledge does not seem advisable. Traceability of products, documentation of product switches and education of physicians were noted by participants as important.

The participants then considered the question of whether extrapolation of study data from one patient population to another could be considered “evidence-based” medicine. The opinion was offered that the extrapolation would be based on scientific evidence, although from data sources other than a randomized, controlled clinical study. In addition, the point was made that there is precedent for originators extrapolating study data, e.g., when there is a clear change in a quality attribute after a manufacturing change for a product approved for multiple indications. In these cases, regulators ask for confirmatory clinical data but not necessarily in all indications. As with biosimilars, extrapolation may then be possible based on the totality of the data, including the available knowledge, e.g., assay results.

**Day 2: February 4, 2011**

**Key Elements in Development of a Monoclonal Antibody**

Insight into the quality requirements for the lifecycle of biosimilars was provided by Kowid Ho (Agence française de sécurité sanitaire des produits de santé, France; Member of the Biologics Working Party and Biosimilar Medicines Working Party of the EMA). He first provided a historical overview of the legal environment relating to biosimilars development, which changed following the submission, in 2001, of the dossier for Sandoz’s biosimilar somatropin product (Omnitrop®). There was no legal pathway for registration of a biosimilar product in the EU at the time of this submission. The CHMP issued a positive opinion in 2003, but the European Commission issued a negative decision in 2004. Parallel with these events, the legal pathway was established and the “overarching guideline” defining key concepts and principles relevant to biosimilar medicinal product development (CHMP/437/04) became effective in 2005. Guidelines relating to quality, non-clinical and clinical aspects were adopted in 2006.

Dr. Ho reviewed important aspects of the guideline on similar biological medicinal products with regard to quality issues (CHMP/BWP/49348/2005), including manufacturing and comparability exercises. The guideline applies to new biological medicinal products claimed to be similar in terms of quality, safety and efficacy to a reference product with marketing authorization in the EU. Manufacture and control aspects have to be developed by the sponsor of the biosimilar taking into account relevant and up-to-date information. A comparability exercise at the quality level is an additional element to the normal requirements of the quality dossier, but such an exercise may allow a reduction of the non-clinical and clinical data requirements as compared with a full dossier. Non-clinical and clinical data are normally required. In terms of scope, the guideline applies to recombinant DNA-derived proteins and the principles apply to proteins and peptides, their derivatives and products of which they are components, e.g., conjugates. Dr. Ho noted that the guideline does not address the comparability exercise for changes introduced in the manufacturing process or a given product as addressed by ICH Q5E. The legal basis of the guideline is Directive 2001/83/EC as amended.
On the aspect of biosimilar manufacturing, Dr. Ho reiterated the point that the biosimilar sponsor will have developed their own specific manufacturing process that should be developed and optimized taking into account state-of-the-art information. The process will be defined by the molecular composition of the active substance that will result from the process, which may introduce process-related impurities. Formulation studies are needed even if the excipients are the same as those in the reference product, and the biosimilar product sponsor will need to demonstrate the suitability of the proposed formulation. The clinical data should then be generated with product produced using the final manufacturing process.

Dr. Ho then discussed the comparability exercise between biosimilars and their reference products in the quality aspects. He noted that the quality aspects should always be considered with regard to any implications for safety and efficacy, and that a stepwise approach to justify any differences should be taken. However, it is not expected that the quality attributes will be identical. Minor structural differences may be acceptable, if appropriately justified, although this may depend on the specific case. Comparability needs to be shown for both the medicinal product and the active substance in the medicinal product. Importantly, the same reference product must be used for all three parts of the dossier, i.e., quality, safety, and efficacy. The comparability exercise may be facilitated when the biosimilar uses the same pharmaceutical form, formulation and strength as the reference product, but other approaches may be considered. Dr. Ho mentioned that the shelf life of the reference should also be considered and the age of samples should be stated in the submission. The reference product itself should be clearly identified, and use of a publicly available standard as the reference active substance is not appropriate. The biosimilar product sponsor should demonstrate using state-of-the-art analytical methods that the active substance is representative of the active substance present in the reference medicinal product. If analytical tools are not capable of direct comparison, isolation may be required, in which case the suitability of the sample preparation process must be demonstrated.

In completing his review of the CHMP/BWP/49348/2005 guideline, Dr. Ho discussed analytical methods for similar biological medicinal products because extensive state-of-the-art characterization studies are required. Stress and accelerated stability studies should be done to determine the degradation profile of the biosimilar product. Stability studies of the reference and biosimilar product can be used to further support comparability of the products. He noted that biological assays using different approaches to measure the biological activity should be considered as appropriate.

Quality attributes are not expected to be identical, but the amino acid sequence is expected to be the same and product-related variants should be within the variability of the reference product. Minor structural differences in the glycosylation may be acceptable. Process-related impurities are expected to be different as different processes are employed. The formulation may be the same or different, but suitability must be demonstrated in either case. The differences will have to be justified taking into account their potential impact on safety and efficacy. In some cases, the differences observed may not support the reduction of non-clinical or clinical data as foreseen in the biosimilar guideline, although this would be determined on a case by case basis. The specifications for the biosimilar product should be set in accordance with ICHQ6B results and data obtained from the comparability exercise (i.e., from sponsor’s own experimental results obtained by testing the reference medicinal product), and the limits set for a given test should not be wider than the range of variability observed for the representative reference product unless justified.

Dr. Ho then discussed issues and perspectives on the lifecycle of a biosimilar medicinal product and the reference product. These included considerations on changes of product quality attributes, e.g., following a process manufacturing changes. ICH Q5E states that “The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product can be used to further support comparability of the product. Particularly when defining the target variability of reference product attributes. In addressing the question of what range is acceptable, Dr. Ho mentioned that depending on the quality attribute, its potential impact, the material used in the clinical trial and the differences observed, the ranges observed for the reference product, pre- and post-shift in quality attribute(s), could support and justify differences observed at the time of submission. Dr. Ho also raised the question of whether biosimilars can really remain similar throughout their entire lifecycle as they will also have their own and independent lifecycle once they receive marketing authorization.

Dr. Ho concluded his presentation with a brief discussion of interchangeability and substitution, which he noted are beyond the scope of the current EMA guidelines and are national issues. He pointed out that issues of interchangeability and substitution are not exclusive problems of biosimilars, and that the question of naming, i.e., whether to use the same international non-proprietary name (INN) for both biosimilar and reference product, is an ongoing challenge. Dr. Ho emphasized that biosimilars are not generics but are biological medicinal products that are similar to another one already marketed. For biological products, it is not recommended to switch patients from a biological product to another without therapeutic justification. For similar biological products, there is no reason to deviate from the general recommendations for biologics. A systematic and uncontrolled substitution based on prescription on the INN of the active substance does not appear to be reasonable at this time. Dr. Ho suggested that the current recommendation is that there be no automatic substitution but switches could occur under the supervision of a healthcare professional. He noted that perhaps this should be reconsidered upon larger experience, on a class by class or product by product basis.

R. Martijn van der Plas (Rijksinstituut voor Volksgezondheid en Milieu; National Institute for Public Health and the Environment, The Netherlands; Member of EMA’s Biologicals
Working Party) discussed the chemistry, manufacturing and controls (CMC) aspects of antibody development. In particular, he addressed what can be characterized well, where limitations lie, and what is special for the introduction of changes in next generation vs. biosimilar mAbs. Dr. van der Plas explained that, for regulators, “next generation” antibodies are a fundamentally different concept compared with biosimilar products because the phrase “similar biological medicinal product” (colloquially: a biosimilar), has a well-defined legal meaning, viz. a medicinal product authorized under article 10(4) of Directive 2001/83/EC. In contrast, the phrase “next generation” is informal and may have several, perhaps overlapping meanings. The current understanding is that a biosimilar must be identical with the originator product on the amino acid level, and that if the biosimilar is shown to be comparable/similar to the originator product, then safety and efficacy data can be extrapolated, thus obviating the need to prove safety and efficacy with extensive clinical data for the biosimilar. This regulatory reasoning is absent in the case of “next generation” products.

Dr. van der Plas then reminded the audience of the contents of specific ICH quality (Q) documents that discuss requirements for characterization: ICH Q5E (Comparability of biotechnological/biological products subject to changes in their manufacturing process), ICH Q6B (Test procedures and acceptance criteria for biotechnological/biological products) and ICH Q8 (Pharmaceutical development). His key points were that characterization/comparability is aimed at the determination of relevant (critical) quality attributes, and that the comparability exercise is a scientific endeavor. Dr. van der Plas noted that it is nearly impossible to exactly define beforehand which methods are necessary and what data, e.g., limits, are acceptable. He explained that the strategy can be well-defined, but it should be flexible to take into account new developments, based on available expertise/prior knowledge and determined on a case-by-case basis.

Points to consider regarding whether mAbs should be considered complex were Dr. van der Plas’s next topic. The key points to be addressed in the development of mAbs (e.g., determination of basic structure, glycosylation, microheterogeneity, pharmacology and immunogenicity) are well-known, and there is extensive experience with their use, which suggests that mAbs are not really that complex. Dr. van der Plas noted that the exact mode of action (MOA) of rituximab is unclear, although much data are available, e.g., the Fc portion mediates antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), it has a general regulatory effect on the cell cycle, it increases MHC II and several adhesion molecules, it elicits shedding of CD20, it down regulates the B-cell receptor, it induces apoptosis of CD20+ cells. Dr. van der Plas then referred to the anesthetic propofol (2,6-diisopropylphenol), which has a simple structure, but a very complicated MOA that may involve potentiation of the GABAA receptor and blocking of sodium channels. Dr. van der Plas’s provocative statement was that, like propofol, mAbs have a well-understood molecular structure with a complicated pharmacology.

Dr. van der Plas then discussed what properties of mAbs can be characterized well, and what and how much characterization is needed. He noted that detailed physicochemical characterization is technically challenging, but possible. Microheterogeneity and post-translational modifications such as deamidation, oxidation and removal of c-terminal lysine can be determined, but the effect, if any, on biological activity is unclear. Aggregation can be determined by size exclusion-high performance liquid chromatography, but Dr. van der Plas questioned whether this was the best assay. He noted that the three-dimensional structure of mAbs is highly stable. Characterization of glycosylation is necessary, especially in the case of mAbs with effector functions, because of the roles that glycosylation is known to play in ADCC, CDC and PK. For example, fucosylation is inversely correlated with ADCC for IgG1; high mannose and high sialylation correlates with afucosylation; and galactosylation is correlated with CDC. Dr. van der Plas raised the question of whether some characterization has limited relevance, e.g., is deamidation a critical quality attribute if it will occur at much greater levels in vivo? and asked, if so, are “comparable data” still necessary for assessment of comparability/biosimilarity. Finally, he noted that some physicochemical quality attributes may serve as a “proxy” (i.e., these attributes are not directly related to a difference in safety/efficacy, but they may indicate other physicochemical changes that are).

On the topic of biological data, Dr. van der Plas stated that the non-clinical biological data are complementary to the characterization data. The biological data is less precise, more holistic and often assumed to represent the clinical effect; however, as was discussed in the rituximab example, MOA is not always understood. Nevertheless, MOA models that include ADCC, CDC and cell-based assays can be studied, and the MOA can be broken down into separate binding interactions, e.g., binding to antigen, FcγR, FcRn, C1q (although technically problematic). Dr. van der Plas noted that there are limitations to the data results and their interpretation. For example, physicochemical data are precise, but the relevance is not always clear. Potency assays are less precise, but may be more relevant. Binding assays are somewhere in-between and represent a compromise between precision and relevancy. Another limitation is that immunogenicity is difficult to predict and a link with quality attributes has not been established. Dr. van der Plas also raised the issue of the drift or shift in (critical) quality attributes over time of the innovator product and asked the related question: Should biosimilar and innovator products remain similar throughout the lifecycle? He mentioned that there is no EU position on this point yet.

In conclusion, Dr. van der Plas likened the process of defining similarity to the famous story ‘The Blind Men and the Elephant’ by John Godfrey Saxe; the blind men cannot adequately describe the elephant because they do not integrate their observations. The currently accepted approach to defining similarity is to integrate available information from orthogonal sources, e.g., physicochemical, binding, potency and (pre)clinical characterization. In conclusion, he suggested that similarity is difficult to describe, but, after evaluating all the data, you know it when you see it.

The non-clinical development of new, next generation and biosimilar mAbs was discussed by Karen De Smet (Federal Agency for Medicines and Health Products, Belgium; member of
EMAs Biosimilar Medicines Working Party). She first reminded the audience of the relevant regulatory documents including: ICHS6 and its draft addendum which cover non-clinical safety evaluation for biopharmaceuticals; ICHM3(R2), which covers non-clinical studies done in preparation for human clinical trials and timing of these studies; ICHS9 which covers non-clinical evaluation for anticancer pharmaceuticals and relevant EMA guidelines (Table 2).

The majority of Dr. De Smet’s presentation was dedicated to discussion of three topics, which were (1) non-clinical studies done before the first-in-man (FIM) or Phase 1 studies, (2) calculation of a safe starting dose and (3) non-clinical studies done before Phase 3 studies or submission of a marketing authorization application (MAA). She explained that the non-clinical studies done before FIM are designed to provide information about the primary pharmacology (i.e., proof of concept), safety pharmacology, PK, dose toxicity, immunogenicity, and to establish the lack of genotoxicity. The primary pharmacology data for a mAb includes both in vitro and in vivo results such as binding to the target antigen, binding to Fcγ receptors, FeRn and complement, Fab-associated functions (e.g., neutralization, receptor activation or receptor blockade), Fc-associated functions such as ADCC and CDC assays and complement activation, tissue cross-reactivity studies, as well as animal models of disease (e.g., animal tumor model). The tissue cross-reactivity (TCR) studies assess the ability of a mAb to bind to target and non-target tissues.

Dr. De Smet mentioned that in vitro immunohistochemistry is not always feasible, but, if done, a full panel of human tissues should be used. Target distribution should be assessed and unexpected binding should be evaluated. She emphasized that binding data is not equal to data on biological activity. She also mentioned that TCR is not sensitive enough to detect subtle changes in quality of the mAb and so is not suitable for comparability testing.

On the topic of PK of mAbs, Dr. De Smet explained that PK is determined by target and non-target mediated mechanisms and classical PK absorption/distribution/metabolism/excretion (ADME) studies are thus not done. She then presented specific properties that affect ADME in which antibodies differ from small molecule drugs. mAbs are commonly administered i.v. or s.c. and circulate through the vascular or lymphatic system; they are not absorbed like orally delivered small molecule drugs. The distribution of full size mAbs is generally very poor due to their large size. mAbs are metabolized via proteolytic degradation (catabolism), but FeRn receptor binding protects IgG from catabolism, and there is no cytochrome P-450 metabolism. The renal and biliary clearance of mAbs is very low, and mass balance studies are not useful. In addition, immunogenicity can increase clearance of mAbs.

Regarding repeat dose toxicity studies, Dr. De Smet discussed the need for the use of pharmacologically relevant species; the observation of binding to animal tissue is not sufficient to establish relevance. Short-term studies of up to one month in duration are suitable prior to FIM. A recovery, i.e., non-dosing, period should be included in at least one study and at least one dose. She emphasized that in contrast to small molecules, for mAbs, the maximal dose tested does not need to be the maximal tolerated dose. The maximal dose tested may be the dose that gives the maximum intended pharmacological effect or the dose that gives an up to 10-fold exposure multiple over the maximum anticipated clinical exposure. The higher of the two doses should be chosen unless limited by the maximal feasible dose. Dr. De Smet also noted that the dose response can be non-linear or bell-shaped, and a higher dose may give longer, instead of more, toxicity. Assessment of local tolerance should be included in the repeat dose toxicity studies.

An important aspect of non-clinical studies is the choice of a pharmacologically relevant species, which ICHS6 defines follows: “A relevant animal species is one in which the test material is pharmacologically active, due to the expression of a receptor or an epitope.” Dr. De Smet explained that relevance should be demonstrated both in vitro and in vivo. The ICHS6 addendum provides clarification on the question of use of one or two species. If both a rodent and non-rodent relevant species are available, both should be used for short-term studies; if the findings are similar, then a single species (rodent) can be used for chronic studies. Dr. De Smet noted that use of one species is acceptable if two non-rodents are the relevant species or the mAb is pharmacologically active in only one species. When the only relevant species is a non-human primate, then cynomolgus or rhesus monkey is most commonly used, although scientific, ethical and economic issues can arise. For example, the monkey populations are heterologous, numbers per group are small (3–4/group), and limitations apply to reproductive toxicity and carcinogenicity studies. If there are no relevant species, then studies in non-relevant species are discouraged in favor of alternatives such as studies in transgenic animals or use of surrogate mAbs (i.e., homologous protein). For mAbs directed toward foreign targets (e.g., bacterial, viral), a short-term safety study in one species can be considered and should include safety endpoints in an animal model of disease. If this is not feasible, appropriate risk mitigation strategies should be considered.

Dr. De Smet briefly discussed immunogenicity in the context of non-clinical studies and noted that the results may not be predictive for human immunogenicity. However, ICHS6 states that antibody responses should be characterized and the appearance correlated with any pharmacological or toxicological changes, which may assist in the interpretation of the study results and design of subsequent studies. She explained that the current addendum ICHS6 proposal states that antibody response measurement is not routinely warranted if there is evidence of sustained pharmacological effect, no unexpected changes in PK or toxicity or no immune-mediated reactions, although blood samples should be taken and analyzed if needed. Dr. De Smet also noted that genotoxicity studies are generally not required, unless the mAb contains an organic linker or organic impurities, in which case direct interaction with DNA is possible.

The effect of the TeGenero case on the selection of the starting dose for first-in-human studies was then discussed by Dr. De Smet. The no observed adverse effect level (NOAEL) for TGN1412 in monkeys was 50 mg/kg. Although the clinical starting dose was 0.1 mg/kg, the mAb caused cytokine-release storms in healthy volunteers. This reaction led to reassessment by regulators of the safety of first in human studies. The current thinking
is that the starting dose should be calculated by considering all available non-clinical data, including PK, PD and toxicology. Allometric scaling should be used to derive the human equivalent dose from the NOAEL from relevant species, which should then be divided by a safety factor (usually 10). In certain cases, the minimally anticipated biological effect level (MABEL), which is the dose level anticipated to lead to a minimal biological effect level in humans, might be required. Interspecies scaling and safety factors need to be taken into account. From the calculated doses, the lowest value must then be chosen for the starting dose.

Dr. De Smet's third topic was non-clinical studies done before Phase 3 or MAA submission, which include repeated dose toxicity, carcinogenicity and reproductive and developmental toxicity studies. She explained that the repeat dose toxicity studies should be a maximum of six months, with the exception of mAbs studied as advanced cancer treatments (maximum three months). Use of a single species is appropriate, and immunogenicity should be evaluated in these studies. The objective of carcinogenicity studies is the evaluation of the effects on cell proliferation and tumor promotion, not direct interaction with DNA. ICHS6 indicates that “Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still be needed.” The ICHS6 draft addendum indicates a complex decision tree based on a weight of evidence approach including knowledge on the mechanism of action and data from in vitro and in vivo studies.

On the topic of reproductive and developmental toxicity, ICHS6 states that “Reproductive toxicity studies should be conducted only in pharmacologically relevant species.” Classically, the species are rat for male and female fertility studies, rat and rabbit for embryo-fetal toxicity studies, and rat for peri- and post-natal studies. However, the relevant epitope and differences in placental for embryo-fetal toxicity studies, and rat for peri- and post-natal species are rat for male and female fertility studies, rat and rabbit conducted only in pharmacologically relevant species.” Classically, the species are rat for male and female fertility studies, rat and rabbit for embryo-fetal toxicity studies, and rat for peri- and post-natal study. However, the relevant epitope and differences in placental transfer should be considered in the selection of species for the studies. The classical species usually are not relevant for mAbs. ICHS6 also states that the need for studies is dependent upon the product, clinical indication and intended patient population, e.g., inclusion of pregnant women or those of childbearing potential.

Dr. De Smet concluded her presentation with comments on next generation and biosimilar antibodies. The next generation molecules (e.g., nanobodies, minibodies, bispecific mAbs) can be quite different compared with the standard IgG1 or IgG2 format, and in general, there is limited experience with their clinical use. This suggests that the non-clinical development of next generation molecules would be like that of new mAbs. Regarding biosimilar mAbs, EMA’s guideline recommends a risk-based approach to evaluate mAbs on a case-by-case basis. Three steps are proposed: in vitro PD studies, identification of factors of importance for the in vivo non-clinical strategy, and in vivo studies. In step 1, in vitro PD studies would be used to evaluate the difference in biological activity between biosimilar and reference products. In step 2, factors such as differences in process-related impurities, formulation or dose would be considered to assess the level of concern and need for in vivo testing. In step 3, if no issues are identified at steps 1 and 2, then no in vivo studies are needed. However, if concerns are raised at step 1 and 2, then comparative in vivo studies might be needed as determined on a case-by-case basis. The focus of study (e.g., PK, PD or safety) would depend on the need for additional information. The relevant species would be non-human primate in most cases, and studies in non-relevant species are not recommended. Immunogenicity assessment and local tolerance studies would be conducted only if needed, while safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies would not routinely be required. Dr. De Smet noted that as more experience is gained, regulators will be able to define more precisely the non-clinical data required.

The workshop participants then engaged in open discussion moderated by Professor Löwer. The discussion focused initially on the implications of not requiring non-clinical in vivo studies for biosimilar antibodies. As stated in the EMA guideline “In vitro studies should be conducted first and a decision then made as to the extent of what, if any, in vivo work will be required.” Participants noted that not requiring the studies could be scientifically reasonable and that regulators have a duty to only ask for studies if there is a scientific reason to do them. Regulators do not want to ask for non-clinical studies that do not provide adequate safety data. For example, there is concern that toxicity studies in non-human primates, which include small groups of animals, done to assess comparability may not show differences, thereby providing a false sense of security when in fact the groups were too small to show differences between products. It was noted that regulators in the US and Japan might not have the same thinking, and that a reduction in the use of animals would not be expected if the regulations are not harmonized in the three regions. However, the guideline should be interpreted the same way in all EU member countries.

Participants then discussed whether bioassays were sensitive enough to be used in stability studies, e.g., to assess degradation. It was noted that there has not yet been a chance to review a full dossier for a biosimilar mAb, but bioassays may not be sensitive enough to detect the differences observed with physicochemical methods. This may also suggest that at least some changes may not be relevant to biological activity. The final topic discussed was manufacturing changes for biosimilars prior to approval. The general opinion was that any changes should be kept to a minimum, although it was recognized that it is likely unrealistic to expect a biosimilar company to have a fully scaled up process in place prior to starting clinical study. However, participants generally thought that this issue is the same for biosimilar and innovator companies, and the requirements should be the same.

Clinical Development

Frank Scappaticci (F. Hoffmann-La Roche, Clinical Lead) discussed the challenges in development of a new mAb and what needs to be considered for next generation and biosimilar mAb therapeutics. He noted that there are numerous platforms used to deliver next generation antibodies, including the humanizing of marketed chimeric products (e.g., ocrelizumab), conjugating drugs to antibodies (e.g., trastuzumab emtansine), glycoengineering antibodies (e.g., GA101), single chain antibodies (e.g., MetMab), and bispecific antibodies. The challenges to development of antibody-drug conjugates (ADCs) were briefly discussed
by Dr. Scappaticci. ADCs have added complexity compared with “naked” mAbs because, in addition to the antibody, the linker, drug, number of drugs per antibody, sites of conjugation and coupling chemistry must be optimized.

Dr. Scappaticci then presented an overview of the clinical experience of two anti-CD20 mAbs, ocrelizumab and rituximab, in studies of rheumatoid arthritis (RA) patients. Rituximab, a chimeric antibody, was first approved in the late 1990s for treatment of non-Hodgkin lymphoma (NHL) and later approved as a treatment for RA. Humanized ocrelizumab is a product candidate that was investigated in Phase 3 studies of RA patients in which a safety signal for increased risk of serious infection was detected. This signal was unexpected because no similar signal was observed for rituximab and the non-clinical and early stage clinical studies for ocrelizumab did not point to this risk. Dr. Scappaticci noted that there are structural differences between the two mAbs in addition to the differences in the amount of murine sequence, e.g., the mAbs bind different, although overlapping, CD20 epitopes, some residues in the Fc regions are different, the mAbs bind FcγRIII differently. Data from four placebo-controlled Phase 3 studies of ocrelizumab was provided by Dr. Scappaticci. These were the STAGE (NCT00406419), SCRIPT (NCT00476996), FILM (NCT00485589) and FEATURE (NCT00673920) studies. A key finding from the studies was that, although the clinical-safety profile of ocrelizumab and rituximab in RA is broadly similar, ocrelizumab showed consistent numerical increases in serious infection event rates compared with placebo when dosed at 500 mg according to the study protocol (infusions administered on days 1, 15 and weeks 24, 26). This signal was not observed in studies of rituximab dosed on either a 500 mg x 2 or a 1,000 mg x 2 schedule. Dr. Scappaticci noted that comparisons between the ocrelizumab and rituximab programs are limited by sample size, low event rates and differences in design of the Phase 3 development programs, but that the lesson learned was that extensive and adequately designed Phase 3 studies are needed to fully establish the overall safety profile of biologic therapies such as mAbs.

Roche’s view on biosimilar development was then outlined by Dr. Scappaticci. The first point was that patient safety is the primary concern. Following that, Roche supports the development of a regulatory framework for biosimilars. The term “biosimilar” should be limited to approved products intended to be copies of already licensed reference biological products that meet EMA or WHO criteria for biosimilars; products that do not meet the criteria should not be called biosimilars. The approval process for biosimilars must be based on the concept of “similarity,” i.e., rigorous head-to-head quality, non-clinical and clinical evaluation in comparison with a reference innovator product. Extrapolation of safety and efficacy across indications is possible with justification, but biosimilar entrants must meet defined criteria for immunogenicity testing and post-authorization risk management including pharmacovigilance. In addition, biosimilars should be uniquely identified and there should be no automatic substitution or interchangeability.

Dr. Scappaticci concluded by discussing the challenges in conducting clinical trials using surrogate endpoints. As examples, he noted that demonstration of equivalency using progression-free survival (PFS) in follicular NHL with rituximab as the reference standard would require ~3,000 patients (assuming a PFS margin of ± 4 months and 80% power), and demonstration of equivalency using PFS in metastatic breast cancer with trastuzumab as the reference standard would require ~2,400 patients (assuming a median PFS of 10 months and a margin of ±13% and 80% power). Studies of these types would be much larger than the original pivotal studies of the innovator product. Dr. Scappaticci noted that biosimilar trial design may be directed to settings where there is a sensitive endpoint such as complete response for NHL. Although such sensitive endpoints are not surrogate endpoints, they are less ideal since small studies with large equivalence margins will yield less certainty around establishing biosimilarity. His final question to the audience was: Would such uncertainty be acceptable in cases where there is a potential cure, e.g., rituximab for diffuse large B cell lymphoma, trastuzumab for adjuvant breast cancer?

Points to consider with regard to equivalence trials and extrapolation from clinical evidence were presented by Jan Müller-Berghaus (Paul-Ehrlich-Institut, Germany; Head of Section Mono/Polyclonal Antibodies). He noted that the clinical hurdles to achieving marketing authorization depend on the type of drug evaluated. For example, for many new substances, regulators request results from two independent pivotal trials with endpoints that are clinically relevant and statistically significant. In the case of new oncology drugs, the requirements have often been handled differently allowing a different level of evidence, e.g., one confirmatory trial using a surrogate endpoint which has historically been correlated to time-related endpoint before may be sufficient. For biosimilar products such as G-CSF, a PD endpoint might be acceptable for marketing authorization, while for a generic drug, bioequivalence and product characterization are sufficient. The reason for the differences is because regulators consider the science, make a judgment on the risk of the decision and accept a degree of uncertainty. This flexibility is allowed in the legal framework for approval of medicinal products.

Dr. Müller-Berghaus reitered the point that mAbs have numerous areas of possible variability (e.g., terminal amino acid cleavage/modification, glycosylation, oxidation, deamidation), and he noted that the presence of heterogeneity suggests that it is unlikely that biosimilarity could be demonstrated solely on quality characterization. He briefly discussed the well-known functional aspects of mAbs, but emphasized that numerous questions remain, e.g., Do mAbs bind the mannose receptor in vivo? Is there a human equivalent to the FcγRIV receptor recently detected in mouse? Dr. Müller-Berghaus emphasized that certain quality characteristics have a known impact on function and only the combination of analytical and functional assay data will likely be sufficient for characterization.

Theoretically, the best way to demonstrate differences between molecules would be through use of a dose-sensitive model, but Dr. Müller-Berghaus explained that this requires in-depth knowledge of dose-response relationships that is commonly difficult to obtain with mAbs due to a lack of PD biomarkers. As a consequence, there is often insufficient knowledge of the shape
of the clinical dose-efficacy relationship and which part of this relationship is relevant, although much more is known of dose/response from preclinical models. A dose/concentration sensitive functional assay thus has an important role. Dr. Müller-Berghaus noted that it seems unlikely at present that a clear difference in function demonstrated in a non-clinical assay can be compensated by the demonstration of clinical efficacy. Regarding PK of antibodies, Dr. Müller-Berghaus explained that the levels of the antibody and target antigen can affect PK. Results of PK studies in patients thus might vary with the characteristics (e.g., tumor burden) of the specific patient population included and therefore evaluation in healthy volunteers would provide cleaner data from a scientific point of view.

Dr. Müller-Berghaus then discussed equivalence trials (vs. non-inferiority), starting with an explanation of two basic assumptions. The first assumption is that an effective treatment can be distinguished from an ineffective treatment (assay sensitivity), and the second assumption is that the effect of the reference product compared with placebo is constant, e.g., with time, patient population, location, (constancy assumption). However, both assumptions cannot be checked without a placebo arm. Thus the patient population comparable to the population studied in the originator trials might be preferable; if more than one population was studied, then use of the more homogeneous population is preferable. The effect size of different populations should be considered. Regarding treatment, the established dose and posology should be used. Sufficient data on the endpoint, collected in a controlled setting, should be available from the originator; this data is needed to set the margins, but does not necessarily need to be from the pivotal trial. However, the endpoint should be sensitive, i.e., capable of detecting changes. Clinical relevance of the endpoint is preferable, but likely is not required for marketing authorization. The treatment effect for the originator product included in the comparative trial is compared to the original data, which provides a check on the constancy assumption. Regarding effect size, Dr. Müller-Berghaus discussed use of differences (e.g., between drug and placebo for a given measured effect) and odds ratios.

The equivalence margin was then discussed by Dr. Müller-Berghaus. He noted that the margin needs to be predefined and justified based on published data, e.g., statistical and clinical justification given, and that superiority to historical placebo should be ensured taking into account the uncertainty of the placebo point estimate. Regarding extrapolation, Dr. Müller-Berghaus explained that the possibility depends on the type of target. If the target is a soluble antigen, then it is more likely that there is only one mechanism of action and extrapolation would thus appear feasible. However, if the target antigen is cell-bound, then several mechanisms of action may be involved and extrapolation may be more difficult. Extrapolation between indications may be possible if there is thorough characterization at the quality and preclinical level and the results are consistent across these assays, e.g., comparable afucosylated variants and comparable FcγR binding and comparable ADCC.

The workshop concluded with open discussion among participants on questions concerning use of application devices, design of clinical studies, and assessment of immunogenicity, as well as comments regarding somewhat surprising aspects of EMA’s guideline on the development of biosimilar antibodies. Participants noted that the trend is toward use of a diverse array of application devices for subcutaneous (sc) administration of the biologic products on the market. Generally during development of an innovator product, sc administration is licensed first, then an application that is device-oriented follows. In these cases, PK comparability is requested by regulators, but not necessarily an efficacy trial. There has not yet been discussion about whether device-dependent studies would be required for biosimilar development, but the experience with innovator products could be taken into account.

On the topic of design of clinical studies, it was noted that a study in healthy volunteers done prior to a study in patients could provide valuable data. Single dose using the upper range of doses is the favored design for PK studies, e.g., parallel design using therapeutic dose. If one trial is designed (i.e., first-in-man, PK, efficacy evaluation are all included in one study), then it should be implemented in stages. An interim analysis to assess PK data would be needed, and this would be followed by a decision as to whether to proceed. A participant further noted that the EMA guideline has such safeguards built in because it emphasizes the establishment of biosimilarity as a stepwise approach. If large differences in data appear at any step, then the decision to pursue a biosimilar pathway should be revisited. Participants agreed that design of equivalence trials must be done carefully. Companies might consider inclusion of a placebo arm to mitigate risk. Regarding immunogenicity, it was noted that, at this point, it is not expected that a biosimilar at the prelicensing stage would be able to demonstrate equivalent immunogenicity compared with the reference product.

A participant then initiated discussion of the three “wow,” i.e., somewhat surprising factors of the EMA draft guideline. There is the potential to develop biosimilar mAbs (1) without animal data; (2) based on PD marker study and (3) in a non-licensed indication (assuming the clinical use is accepted). It was noted that it seems unlikely that PD would be acceptable as the sole proof of efficacy, but that it is not impossible. The importance of the interpretability of data collected from clinical studies was then emphasized. The controversial nature of the development of a biosimilar in a non-licensed indication (because of the lack of data for the reference product) was acknowledged, but the possibility was included because the non-licensed indication might be the model best suited to showing differences. The thinking was that companies should have the possibility of using the model that provides the best data whether the indication is licensed or not. EMA guidelines are intended to address scientific principles and not legal issues; however, it is up to the companies to decide whether a particular approach is practical. It was emphasized that the guideline is a draft document, thoughtful discussion on these topics is on-going and the final document may include changes.
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