Antibody biosimilars: Fears or opportunities?
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Abbreviations: mAb, monoclonal antibody; MA, Market Authorization; CQA, Critical Quality Attributes; EU, European Union; EEA, European Economic Area; US, United States; PK/PD, pharmacokinetic/pharmacodynamic

The annual “LabEx MAbImprove industrial workshops” are primarily intended to provide scientists involved in therapeutic antibodies, a comprehensive view about topics of interest for the pharmaceutical industry. They are organized by the “LabEx MAbImprove industrial committee”, for this first edition especially in partnership with ARITT, the regional agency for innovation and technology transfer which operates in the French Région Centre, the 1st French region for pharmaceutical production. The 2013 edition, held May 28 at the Vinci Center of Tours, was dedicated to antibody biosimilars. Depending on opinions, the impending expiry of antibody patents and the imminent marketing approval of competitors to blockbusters can be perceived as good or bad things. Fears or opportunities? Risks for patients? Breath of fresh air for the health systems? Opportunity for re-industrializing France? In this context, it is necessary for people to form a fair and informed opinion on the current landscape of antibody biosimilars. In particular, this is especially important for scientists from the academic world, from the industry or from the regulation agencies, for pharmacists, for pharmacovigilance specialists, for health authorities, and staff from health insurance and decision makers.

The first session was devoted to market and regulatory issues, and included both an overview of the evolution of the patent landscape and a description of biosimilars regulation in the European Union (EU). This session was closed by a talk on manufacturing processes for biosimilars. In the next session, quality control attributes of biosimilars were discussed and compared with the consistent quality of biotechnology products to raise the question: “How close is close enough?” In vitro assays for evaluating the Fc function of therapeutic antibodies were also discussed. The third session focused on development of biosimilars and primarily on the stepwise process for introducing an antibody biosimilar on the EU market, and included a presentation of the ongoing clinical evaluation of an infliximab biosimilar. The session concluded with a rich debate on the indication extrapolation of a biosimilar compared to the originator. The last session was dedicated to societal issues and focused on two aspects: (1) the need of biosimilars for EU health economy; and (2) last but not least, the ethical issues about clinical evaluation of biosimilars. All speakers and attendees enjoyed this very stimulating and rewarding meeting, which gathered many people with divergent scientific backgrounds from the academic or industrial world.

Introduction

The industrial workshop “Antibody biosimilars” was opened by Hervé Watier (CNRS UMR 7292, Université François-Rabelais de Tours, France), coordinator of the MAbImprove Laboratory of Excellence. He delivered his welcome address, starting with a quick recall of the LabEx MAbImprove story. This LabEx was created in 2011 and funded by “Investment for the Future” program (French “Big Loan”). He then introduced this industrial workshop as a yearly event dedicated to real life in the biopharmaceutical industry, invited to present and to discuss current issues to academics. He invited all attendees to debate in depth on this very timely “Antibody Biosimilars” topic, and to open discussions between the industry developing biosimilars and those who develop only novel products. Finally, he reminded participants that biosimilarity is not only a matter of structure, but also of function and pharmacology, which are the main topics of the LabEx MAbImprove. Prof. Loïc Vaillant (President of the Université François-Rabelais de Tours, France) welcomed all attendees, in particular those from outside France. After a brief presentation of the University, he emphasized the importance of interdisciplinarity and international research networks. Moreover, he underlined the necessity of tight collaboration between the educational institution and the industrial field. He pointed out the importance of the LabEx MAbImprove in the French biotechnological landscape. Indeed, France is an outsider in the field and the government is willing to change this situation. MAbImprove is not only a research tool (with 200 researchers working on monoclonal therapeutic antibodies in Tours and Montpellier), but also a support for biopharmaceutical
development in France. The topics addressed during the workshop, ranging from bioproduction, formulation and stability to product quality and authorization, were approached by a scientific, as well as pre-clinical/clinical and societal, point of view, taking the economical and ethical challenges into account. Mrs Marie-Madelaine Mialot (Vice-President of the Regional council) then pointed to the relevance of partnership between industrials and academics, and underlined the challenges of biotechnologies in Region Centre, whose policy is to give more opportunities for innovation. She also insisted on the need to install or re-install confidence between consumers, researchers and the pharmaceutical industry, referring to the recent Mediator affair. She reminded participants that biosimilars must be considered a need from economical and ethical points of view, these molecules raising societal questions of health cost in France.

The first two sessions devoted to regulatory and quality control issues were chaired by Roland Beliard (LFB, France) and Didier Laloye (Hospira, France).

Session 1: Market and Regulatory Issues

The first session started with a brief overview of the intellectual property (IP) landscape in the pharmaceutical field. After noting that the first antibody patents should expire in 2013, André Bourgouin (Grosset-Fournier & Demachy, Paris, France) introduced the various types of patent protection available to date, and the different ways existing to expand their life-span. Indeed, the patent landscape has evolved during the past 20 years and a widely used strategic tool for companies to expand the protection of a biotechnology product appears to be the Supplementary Protection Certificate (SPC), which allows the extension of the patent (providing 15 years of effective protection after a first marketing authorization in EEA), although it is a title of right different from patents. Even if SPC regulation is well defined, some questions regarding SPCs for new indications, new formulations or fixed combinations of products with a single EU market authorization (MA) are still undecided. Finally, some real-life examples of case-law decisions based on the current state of legal balance between the protection of the innovation and the need for cost effective medication were provided. Questions from the audience focused on antibody biosimilars, in particular an attendee asked why there are so few biosimilars coming out when patents are expiring and more specifically asking whether this is because of IP or SPCs or problems for producing these biosimilars? The answer was clearly that data protection plays a prominent role in keeping biosimilars off the market. As a conclusion, it was said that litigating with a view to breaking patents belonging to companies marketing mAbs is often the only way available to companies wanting to launch biosimilars.

Thereafter, Kowid Ho, Quality Assessor for Biological products at the French regulatory agency (ANSM, Department for evaluation of biological products, France) reported on regulatory perspectives on biosimilars in the EU. He focused on the lessons learned during the past few years with regard to the submission of biosimilars in the EU, starting with an overview of the evolution of the biosimilar registering framework. He showed that first legislation came between 2001 and 2004, with different directives issued, and then the guidance period arose with overarching guidelines appearing between 2005 and now. More precisely, the first biosimilars were authorized in 2006 (somatropin products Omnitrope® and Valtropin®) and since then, 27 MAAs, including 2 for infliximab biosimilars, were submitted in total, with 5 still under evaluation. As overarching guidelines are under revision, general principles arising from discussions were presented during the meeting. First of all, a stepwise approach is generally recommended when comparison is done between the biosimilar and its reference product. Dosing and route of administration should be the same; intended changes to improve efficacy are not compatible. Safety advantages may not preclude a determination of biosimilarity, but the choice of the manufacturing system is of importance because the differences that can be introduced may have an effect on safety. Finally, the importance of assessing the mechanism of action of mAbs biosimilars was mentioned, with an emphasis on the comparison of immunological properties between the biosimilar and the reference products.

To finish the session, Steve Flatman (Head of Biosimilars R&D at Lonza Biologics) presented the challenges in the manufacturing process for antibody biosimilars and the key factors to implement a process. He first provided a brief overview of the biosimilar market and the opportunities for companies to produce and market new molecules, and noted the predicted biosimilar market penetration of 30.4% in 2021 versus 0.6% in 2011. He then presented a detailed picture of the different steps of a process. In his opinion, a strong experience in biopharmaceutical development overall, and proven competence specifically in cell line/strain process development, analytical methods, scaling up, pilot and clinical trial/commercial manufacture, is mandatory. It is necessary to have tight control of the product development and fulfill the criteria for manufacture defined by the comparison with the originator (similarity should be assessed at all relevant steps in the development pathway as during the process). This talk gave Dr. Flatman the opportunity to remind participants of the list of factors to be controlled, from the design to the final scale up and manufacture. Moreover, from a company point of view, robust and cost-effective manufacturing will be critical to the success of biosimilar development. The less complex a process is, the more successful and the more cost effective it will be.

Session 2: Quality Control Attributes, Bioequivalence and formulation

This session was dedicated to comparability exercises that should be carried out by a company before asking for the market authorization, and described the panel of analytical data required for objective biosimilarity.

To start the session, Hansjörg Toll (Chemist, Head of Analytical Characterization, Sandoz Biopharmaceuticals, Kundl, Austria) aimed at defining: (1) comparability as part of manufacturing process changes; and (2) comparability as the basis for biosimilarity assessment to a reference product, which led to the question How
close is close enough? Biopharmaceuticals already on the market depend on guidelines arguing that, upon a change in the manufacturing process, the company should take care that "existing knowledge is sufficiently predictive to ensure that any difference in quality attributes has no adverse impact upon safety or efficacy of the drug product" (ICH Q5E). The quality attributes of concern are some biological, as well as physico-chemical characteristics, covering both the Fab (antigen binding) and Fc (effector functions) part of mAbs. Guidelines for comparability of biological products subject to changes in their manufacturing process are available since the mid-90s, but until 2011 when the article entitled "Acceptable changes in quality attributes of glycosylated biopharmaceuticals" was published, actual analytical data from marketed pre- and post-change biologics were very scarce. Dr. Toll presented three case studies (Aranesp®, MabThera/Rituxan®, Enbrel®) from the article, arguing that during their life cycle, originator products can show significant variations in quality attributes that are most probably indicative of changes in the manufacturing process. As the pre- and post-change products were interchangeably on the market, and without a change in label, it can be assumed that the regulatory offices found these differences acceptable. The latter means that it was determined that the changes do not adversely impact safety and efficacy. So, what are the implications for biosimilars? The talk aimed at showing that the variability of a reference biologic over time, and especially after manufacturing changes that are regulated according to the strict standards of ICH Q5E ("no clinically meaningful differences"), provides a good target range for the development of a biosimilar product. As this range has been demonstrated to be safe and effective for the reference product, the same conclusion should be drawn for a biosimilar that lies within that range. Additionally, as pre- and post-change reference products are interchangeably on the market, and that the acceptance of the changes in quality attributes is extrapolated to all indications, the same criteria should be applied to biosimilars whose quality attributes lie within the originator range. In conclusion, as changes in manufacturing processes of biologics can lead to an acceptable, but different, product quality, biosimilars are one part of the necessary continuum of comparability. Consequently, a unique identity is not a valid concept for biologics, neither for reference products nor for biosimilars.

John Stults (Director of the Protein Analytical Chemistry Department, Genentech, USA) then discussed the myths and facts around the consistent quality of biotechnology products. The aim of the talk was to give some examples from a manufacturer to demonstrate that consistent product safety and efficacy are maintained while the process is periodically updated. As preliminaries, the speaker noted that a key focus of a biotechnology company is to maintain a stable supply of safe and efficacious medicines, and that this is the company’s and its employees’ personal responsibilities to patients. The first myth evoked was that innovator quality is not consistent. The opposed facts are: (1) the highly controlled and monitored process; (2) verification of CQA levels by product release and stability testing; (3) definition of specified ranges to assure production of a safe and efficacious therapeutic; (4) trend charting to ensure quality consistency; and (5) periodic control system updates to enhance the historic knowledge of the innovator. He emphasized that multiple analytical technologies are available to complete the historic results profile held by the company. In particular, a specification acceptance criterion is defined with the health authorities to build the comparability analysis (as mentioned in the previous talk). The second myth presented was that innovator manufacturing is not state of the art. The counteracting facts are: (1) Chinese hamster ovary cell line utilization and downstream purification approaches are industry standards, but need to be kept to date; (2) during the process lifecycle, improvements (to increase the titer and yield), changes (e.g., to remove animal derived raw materials), and site transfers (to ensure a stable supply of the product) are essential; and (3) thanks to this comparability exercise, the innovator uses its unique manufacturing process knowledge, which increases rapidly before the market authorization and then more slowly, but continuously, all along the period of production. The third myth submitted to the audience was that innovator quality is not consistent through the process lifecycle. The fact presented was that a process lifecycle uses objective criteria to demonstrate comparability in reference to ICH Q5E comparability guidance (already presented in a previous talk). Dr. Stults showed a picture of comparability essentials describing a stepwise approach to answer the question of comparable product quality. He emphasized that it is necessary to go through all of these details for mAbs because of the molecule’s complexity compared to a simple molecule such as aspirin (mAb heterogeneity leads to 10000² potential variants). He emphasized the need of a tightly controlled process using the iceberg analogy, where invisible characteristics are assured by process consistency in addition to the in-process controls. As a summary and to compare originator with biosimilars, he discussed internal (i.e., within a single company) versus external comparability. Indeed, only the innovator has access to all their own historical samples and data. A biosimilar company must use commercial drug product samples. The conclusion was that a drug innovator has substantial, continuously growing knowledge for its product, and the quality is maintained by a controlled process and objective comparability assessment even if a change in the process is performed, as modifications in manufacturing may be necessary to maintain a state of the art process and to meet evolving health authority expectations.

The last presentation of the session was given by Christian Behrens (LFB Biotechnologies, Les Ulis, France) on the design of functional in vitro assays for evaluating the Fc function of therapeutic mAbs. Dr. Behrens started his talk by referring to the European Medicines Agency (EMA) guidelines on monoclonal antibody (mAb) and biosimilars development that request in-depth characterization of the biological and immunological properties of mAbs using appropriate assays. He then presented the different Fc receptors and their expression by different immune cells that mediate the known Fc effector functions, in particular antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP). Using the example of LFB’s anti-RhD antibody rodulab, Dr. Behrens illustrated the in-depth in vitro characterization of a therapeutic mAb, including structural analysis, binding assays and functional assays, and showed that its Fc-dependent mechanism of action translates into efficacious red blood cell (RBC)
development of a mAb, from the quality aspects to the clinical
by reminding participants of the different steps required for the
audience that the views expressed in the talk were personal, and
biosimilars clinical development in Europe. After warning the
Regulatory Agency, London, UK) discussed the requirements for
trials are not classical Phase 1 and Phase 3 trials, but compara-
possible to the final commercial product. Indeed, the required
and demonstrate enough evidence of comparability from one
reference products. Applicants should follow a stepwise approach
the objective is to show similarity between the biosimilar and
demonstrate the efficacy and safety of the biosimilar mAb, but
required to reproduce the development of the originator, i.e., to
and in particular no toxicity studies, are required. Neither is it
vincing evidence of similarity. In most cases, no animal studies,
risk of error. Hence, bioequivalence studies are mandatory.

Dr. Bielsky ended with the issue of extrapolation, which involves
allowing a biosimilar to be authorized in all the indications of
the reference product when a limited number of indications have
been studied in the comparative clinical trials. She argued that
extrapolation is based on overall evidence of comparability and
may be possible with adequate justification, which is mainly based
on the knowledge of the mechanism(s) of action of the origin-
tor molecule. To summarize, the challenges are to overcome the
variability of mAbs’ modes of action (Fab- and Fc-related) and to
justify extrapolation based on comprehensive in vitro data covering
all the functionalities of the molecule. The PK trial (cohort of
healthy subjects or sensitive patients, one unique sensitive dose)
and an efficacy/safety trial, adequately powered, in at least one
sensitive indication should be carefully designed.

Continuing on the biosimilars development topic, Dae Hyun
Yoo (Department of Internal Medicine, Hospital for rheumatic
diseases, Hanyang University, South Korea) presented the first
clinical study of a biosimilar mAb. Two randomized clinical trials
were designed to show similarity between the anti-tumor necrosis
factor (TNF) infliximab and the molecule CT-P13 (Remsima®)
in ankylosing spondylitis (PLANETAS, Phase 1)5 and rheuma-
toid arthritis (PLANETRA, Phase 3)6 respectively. This was a
concrete example of the requirements that must be met before
applying at the EMA for a biosimilar marketing authorization.
Dr. Yoo showed convincing PK curves demonstrating equiva-
lence in different characteristics, whether anti-drug antibodies
were detected or not. He went through the enumeration of the
comparison of responses to conclude that CT-P13 demonstrated
equivalent PK and efficacy to infliximab at week 30, and CT-P13
was well-tolerated, with a safety profile comparable to that of
infliximab. [Post-meeting note: Since the presentation of these
studies during the congress, CT-P13 molecule was approved and
licensed in UK and EU under Remsima® or Inflectra® trade
names in rheumatoid arthritis and ankylosing spondylitis indi-
cations with extrapolation to inflammatory bowel diseases and
psoriasis; Remsima® is distributed by Celltrion Healthcare, and
Inflectra® by Hospira in EU.]

Following this scientific interlude between regulation mat-
ters, the indication extrapolation issues were discussed among
specialists. Valentine Sallerin (Global Medical Affairs, AbbVie
Pharmaceuticals, France) gave the point of view of an innova-
tor on the justification criteria for extrapolating indications. She
emphasized the complexity of extrapolation in relation to the
molecule complexity and its relative instability, and the heteroge-
nenity of a mAb mixture, which makes characterizing mAb pro-
duction a great challenge. This is true even more so for biosimilar
production. Similarity uncertainty is present at different levels,
from the physical properties to the mode of action of the mAb,
which comes back to the question raised earlier: “How close is
close enough?” Even if non-clinical and clinical studies are sup-
posed to be abbreviated before requesting biosimilar regulatory
approval, generating clinical data is important. Indeed, key fac-
tors for indication extrapolation are the definition of modes of
action in all the diseases considered and the choice of the most
sensitive patient population/indication to be able to detect the
differences between reference product and biosimilar, if any exist.

Session 3: Development of Antibody Biosimilars

Marie-Christine Bielsky (Medicines and Healthcare products
Regulatory Agency, London, UK) discussed the requirements for
biosimilars clinical development in Europe. After warning the
audience that the views expressed in the talk were personal, and
not to be taken as the current regulatory opinion, she started by
reminding participants of the different steps required for the
development of a mAb, from the quality aspects to the clinical
studies. She emphasized the principle that developing a bio simi-
lar first requires in-depth knowledge of the relation between the
physico-chemical and functional characteristics of the origina-
tor molecule and the pharmacokinetics (PK), efficacy and safety
of the reference medicinal product. Structural and functional
characterization is usually much more extensive for a biosimilar
than for a new molecule because the tests used for the compara-
rability exercise need to be sufficiently sensitive to provide con-
vincing evidence of similarity. In most cases, no animal studies,
and in particular no toxicity studies, are required. Neither is it
required to reproduce the development of the originator, i.e., to
show similarity between the biosimilar and reference products. Applicants should follow a stepwise approach
and demonstrate enough evidence of comparability from one
step before embarking on the next one. In principle, no clinical
trial should be initiated before evidence of quality and PK/phar-
macodynamics (PD) similarity has been generated. The clinical
trials should be conducted with a medicinal product as close as
possible to the final commercial product. Indeed, the required
trials are not classical Phase 1 and Phase 3 trials, but compara-
tive clinical trials designed to show PK/PD and efficacy/safety
(including immunogenicity) similarity to the reference product.
After discussing the different steps of the clinical development,
After detailing the anti-TNF case, Dr. Sallerin concluded that, to her point of view, until then, indication extrapolation for complex biosimilars is not justified and that biosimilar mAbs have to be tested in each indication for which approval is sought, which raised some strong reactions in the audience and an impassioned debate.

Session 4: Societal Issues

The meeting concluded with a final session on health economical and ethical issues. Paul Greenland (Vice President of Biologics, Hospira, UK) presented the economic reasons for why we need biosimilars. As economic pressure in the EU is set to affect health care, providers are looking for a way to remove non-essential spending and improve their procurements of goods and services. One target is the high-cost biopharmaceutical sector, which is in a growing phase mainly due to the prescription of mAbs (notably in oncology). Biosimilars can be part of the solution to decrease the cost, which can improve patients’ access to biopharmaceuticals and, at the same time, induce savings that allow funding increases for new innovative high-cost therapies. Most of all, introducing biosimilars can induce competition on the market. However, biosimilars uptake is inconsistent in Europe and only 8 biosimilars have been approved since 2006 (one mAb in 2013). Indeed, biosimilars are not generics: they are more complex, their development is longer, they are more costly and riskier and there are limitations on substitution. Whereas generics induced 60% price reduction, 20 to 25% of reduction is expected for a biosimilar when it is launched compared to the originator. So, prices and reimbursement cannot be compared to what exists for generics. Nevertheless, efforts must be made to boost the market access for biosimilars in the EU, in particular by establishing a strong and vibrant biosimilar industry in Europe to induce competition, forming a clear and rapid price and reimbursement process, removing the procurements barriers that may slow access, establishing supporting mechanisms to encourage uptake, communicating the benefits among the active stakeholders, and being clear on when and where biosimilars should be prescribed. In summary, from the society perspective, biosimilars represent more than just lower priced versions of the originator products.

The final speaker, Emmanuel Gyan (CHRU and Université François Rabelais de Tours, France), steered the discussion on ethical issues about the clinical evaluation of biosimilars. The main political issues are lowering the cost of healthcare with an equitable approach and, concomitantly, allowing for drug availability in emerging countries. But examples from available biosimilars show that only 20 to 40% price lowering are achieved compared to the reference molecule price when it was launched. Moreover, reference molecule and biosimilars prices eventually became very close. This raises question by physicians on the advantage of prescribing a biosimilar preferentially to the originator drug, if the cost is the same. Concerning clinical trial design, one of Dr. Gyan’s everyday concerns in his teaching hospital department was the difference between the recruitment of patients for a clinical study evaluating a new drug or a biosimilar trial. The main motivation for a patient to participate to a clinical trial testing a new drug is the potential health benefit he can gain from it, whereas a patient who chooses to participate in a biosimilar trial will eventually express more altruistic reasons and will be aware of health economy stakes. From the physician point of view, clinical research needs clinically-oriented endpoints to verify that the biosimilar is as efficient and safe as the reference molecule because of the well-known fact that some degree of difference is inevitable. The last slide opened the discussion on the political issues, stressing the key role of politicians in fixing the rules for biosimilar prescription in order to participate in the health insurance balance in the developed countries through the support of the biosimilar industry.

Hervé Watier came back on stage for the last words of the meeting. After congratulating the last speaker for his concluding presentation on the different aspects of biosimilar development challenge, he emphasized the variety of topics and views addressed by the speakers during the day, constituting a good enrichment for the attendees. He ended by thanking the speakers, the attendees, the sponsors and the LabEx team for their participation to the meeting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Antibody biosimilars: fears or opportunities? http://antibodybiosimilars.fr/en/index.html
2. Laboratoire d’Excellence MAbImprove http://mabimprove.univ-tours.fr/lang=en
3. EMA guidelines on Biosimilars. http://www.ema.europa.eu/en/index.jsp?curl=pages/regulation/general/general_content_000408.jsp
4. Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol 2011; 29:310-2; PMID:21478841; http://dx.doi.org/10.1038/nbt.1839
5. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, Mikazane H, Gutierrez-Ureña S, Lim M, Lee YA, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013; 72:1605-12; PMID:23687259; http://dx.doi.org/10.1136/annrheumdis-2012-203691
6. Yoo DH, Hrycaj P, Miranda P, Ramitrette E, Piotrowski M, Shevchuk S, Kovalenko V, Prodanovic N, Abello-Bañi M, Gutierrez-Ureña S, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013; 72:1613-20; PMID:23687260; http://dx.doi.org/10.1136/annrheumdis-2012-203690