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European Medicines Agency workshop on biosimilar monoclonal antibodies

July 2, 2009, London, UK

The European Medicines Agency (EMEA) workshop on biosimilar monoclonal antibodies (mAbs), held July 2, 2009 at the EMEA headquarters in London, was a harbinger with potentially far-reaching implications for all groups interested in antibody therapeutics development. These groups include not only regulators and the innovator and generic biopharmaceutical industries, but also physicians, patients and payers. The objective of the workshop was to discuss and assess the feasibility of the development and authorization of mAbs using EMEA's biosimilar regulatory pathways. The workshop sequentially focused on questions relevant to three areas: (1) chemistry, manufacturing and controls (CMC), (2) non-clinical issues and (3) clinical issues, including outcome measures. Proceedings of the workshop are presented in Part 1 of this report, and discussed within the context of the legal, regulatory and business environments of the European Union, Asia and the United States in Parts 2, 3 and 4, respectively.

Part 1: Proceedings of the European Medicines Agency Workshop on Biosimilar Monoclonal Antibodies

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The European Medicines Agency (EMEA) workshop on biosimilar monoclonal antibodies (mAbs), held July 2, 2009 at the EMEA headquarters on Canary Wharf in London, was a harbinger with potentially far-reaching implications for all groups interested in antibody therapeutics development. These groups include not only regulators and the innovator and generic biopharmaceutical industries, but also physicians, patients and payers. The workshop was led by **Christian Schneider**, chairman of EMEA's Similar Biological (Biosimilar) Medicinal Products Working Party (BMWP), with assistance by **Falk Ehmann**, Scientific Secretariat of the BMWP. Representatives of the Committee for Human Medicinal Products (CHMP), Biologics Working Party (BWP), Safety Working Party (SWP), Efficacy Working Party (EWP) and Scientific Advice Working Party (SAWP) also participated.

The objective of the workshop was to discuss and assess the feasibility of the development and authorization of mAbs using CHMP's biosimilar regulatory pathways. The workshop sequentially focused on questions relevant to three areas: (1) chemistry, manufacturing and controls (CMC); (2) non-clinical issues; and (3) clinical issues, including outcome measures. The CMC session was chaired by **Jean-Hugues Trouvin** (chairman of BWP), the non-clinical issues session was chaired by **Beatriz Silva-Lima** (chairwoman of SWP), and the clinical issues session was chaired by **Dr. Schneider**. Each session opened with presentations giving the perspectives of the innovator industry, the biosimilar industry and regulators. Discussion of various points then followed. Participation was by invitation only. Over 160 people attended, including representatives from regulatory agencies in the European Union (EU), United States (US) and Canada, and approximately 40 biopharmaceutical companies located

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The views expressed in this article are the personal views of the authors and may not be understood as reflecting the position of their respective employers. In addition, the article reports open discussions of the EMEA workshop on biosimilar mAbs and may not be understood as reflecting current or future positions of EMEA or industry organizations.

Table 1. Biosimilar therapeutic proteins approved in selected countries*

Non-proprietary name	Approximate MW	Trade name	Company	Country (year) approved
Somatropin	22 kDa	Omnitrope	Sandoz GmbH	Australia (2004)
				EU (2006)
				US (2006)
				Canada (2009)
				Japan (2009)
Somatropin	22 kDa	Valtropin	BioPartners GmbH	EU (2006)
Epoetin alfa	30–40 kDa	Binocrit	Sandoz GmbH	EU (2007)
Epoetin alfa	30–40 kDa	Epoetin alfa Hexal	Hexal AG	EU (2007)
Epoetin alfa	30–40 kDa	Abseamed	Medice Arzneimittel Putter GmbH	EU (2007)
Epoetin zeta	32–40 kDa	Retacrit	Hospira Enterprises B.V.	EU (2007)
Epoetin zeta	32–40 kDa	Silapo	STADA Arzneimittel AG	EU (2007)
Filgrastim	18.8 kDa	TevaGrastim	Teva Generics GmbH	EU (2008)
Filgrastim	18.8 kDa	Biograstim	CT Arzeimittel	EU (2008)
Filgrastim	18.8 kDa	Ratiograstim	ratiopharm GmbH	EU (2008)
Filgrastim	18.8 kDa	Filgrastim ratiopharm	ratiopharm GmbH	EU (2008)
Filgrastim	18.8 kDa	Filgrastim Hexal	Hexal AG	EU (2009)
Filgrastim	18.8 kDa	Filgrastim Zarzio	Sandoz GmbH	EU (2009)
Glucagon	3.5 kDa	GlucaGen	Novo Nordisk	US (1998)
Hyaluronidase (bovine)	55 kDa	Amphadase	Amphastar Pharm	US (2004)
Hyaluronidase (ovine)	55 kDa	Vitrase	ISTA Pharms	US (2004)
Hyaluronidase (bovine)	55 kDa	Hydase	PrimaPharm	US (2005)
Hyaluronidase (human, rDNA)	61 kDa	Hylenex	Halozyme Therapeutics	US (2005)
Calcitonin (salmon, rDNA)	3.5 kDa	Fortical	Unigene Laboratories	US (2005)
Abciximab	48 kDa	Clotinab	ISU Abxis Co.	South Korea (2007) Chile (2009)

*See Part 3 'EMEA workshop on biosimilar monoclonal antibodies: Perspective from India' for information for biosimilar products approved in India and China. Notes: For US products, only 505(b)(2) approved therapeutics marketed in the US were included. EU, European Union; kDa, kilo Dalton; MW, molecular weight; US, United States.

worldwide. Presentations from the innovator industry were coordinated by the European Biopharmaceutical Enterprises (EBE) and the European Association for Bioindustries (EuropaBio), while the biosimilar industry presentations were coordinated by the European Generic Medicines Association (EGA).

It is important to note that the workshop itself follows on a long, complex history surrounding marketing approvals for biosimilar products that have occurred over the last decade. EMEA has been at the forefront of regulatory agency activities concerning approval of biosimilars, although the US Food and Drug Administration (FDA), Health Canada, Australia's Therapeutic Goods Administration and Japan's Ministry of Health, Labor and Wealth, as well as other regulatory agencies, have approved biosimilar therapeutics (**Table 1**). The products are referred to as biosimilars in the EU and other countries, but Health Canada and FDA use the terms 'subsequent entry biologics' and 'follow-on protein products,' respectively.[1] The term biosimilars will be used herein.

Questions surrounding quality, non-clinical assessment and clinical evaluation of biosimilar therapeutics have been raised in the EU, US and other regions of the world. Interestingly, the questions apply to the current conundrum of requirements for biosimilar mAb approval, but also to the much older issue of assessing comparability of biological products following manufacturing process changes. The FDA issued guidance on this problem, in which "those steps that manufacturers may perform and which FDA may evaluate to allow manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy"[2] were described, as early as April 1996. The problem is an ongoing concern—one role of BMWP, established in 2005 following the Biosimilar Task Force (2004–2007), is to provide recommendations to CHMP on the conduct of tests conducted to ensure the comparability of new and old versions of biologically similar products.[3] CHMP also has a guideline, Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issues, that came into effect in November 2007.

Innovator and biosimilar companies thus have some common general problems, but there are obvious differences in the specifics, i.e., whereas innovators are comparing versions of products produced using internally-vetted processes, biosimilar companies are comparing their products with externally-sourced mate-

rial. The EMEA workshop focused on discussion of the points of commonality and difference.

Workshop Introduction

To open the proceedings, **Dr. Schneider** introduced 'pro and con' points of biosimilar mAbs marketing approvals. There are several key questions on this topic for regulators. One is how much do we need to know? Like an incomplete puzzle, the overall picture supplied by CMC, non-clinical and clinical data comparing only key elements of a biosimilar to a reference product might be sufficient to extrapolate the whole picture, or it might be missing key pieces. Another important question is how much 'similarity' do we need? With an average molecular weight of 150 kilo Dalton for full-size molecules, it would be quite difficult to verify that each atom of a biosimilar mAb mapped exactly to those in a reference product. In fact, for both reference and biosimilar mAbs, the product likely consists of more than one drug substance, with minor differences in glycosylation, aggregation or other characteristics occurring between batches and over time. The differences might be due to fluctuations in the manufacturing process, e.g., pH, temperature, culture media, or changes in the expression system. The small changes might be meaningless, or they might have a high impact. However, industry and regulators now have ample experience with mAbs as therapeutics, with 23 marketed in the US, and nearly as many marketed in the EU. Although complex,[4] manufacturing processes have also become quite consistent through-out the industry.

For non-clinical testing, a central aspect is that mAbs are species-specific and so the animal species relevant for testing a therapeutic intended for humans is an important question. A relevant species, as defined in EMEA's Note for Guidance on preclinical safety evaluation of biotechnology derived pharmaceuticals (CPMP/ICH/302/95; ICH S6), is 'one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies).' Importantly for biosimilar mAb developers, the relevant species for approved mAbs have been described. Potency assays for various approved mAbs are also known and available, including an anti-proliferation bioassay used to evaluate bevacizumab (Avastin), inhibition of binding assays suitable for evaluation of basiliximab (Simulect) and omalizumab (Xolair), and an in vivo potency assay in cotton rats for evaluation of palivizumab (Synagis).

There is also extensive patient experience with mAbs. For example, the anti-TNF product infliximab (Remicade), which was first approved in 1998, is currently approved for seven indications; there is cumulative product safety data for approximately 576,000 patients totaling 1.34 million patient years. However, on the con side, there is increasing evidence that glycosylation differences can affect mAb function.[5,6] The current methods for characterizing mAbs, including physicochemical characterization, antigen-antibody interaction and secondary structure detection are increasingly sensitive, but, if differences are observed, the questions becomes what, if anything, should be done about these differences. On the other hand, if no differences are observed, then the question might be: Were the methods sensitive enough to find them?

Chemistry, Manufacturing and Controls Session

The stage was thus set for a point-counterpoint exchange on CMC by the innovator and biosimilar industries. EMEA had established key questions regarding CMC to be addressed, including: Are mAbs considered to be 'well-characterized' biologicals? Is available guidance for quality characterization sufficient for biosimilar mAbs? How well do current methods detect physicochemical differences between mAbs? To what extent do biological and functional assays substitute for a gap in sensitivity? What role should the biological assays play in comparisons of biosimilar mAbs? Can quality data substitute for gaps in knowledge in functional assays? How similar does the glycosylation need to be? Does a biosimilar mAb need to have the same distribution of antibody variants compared to the innovator product? What differences should be considered acceptable? What role should ICH Q8 and Q9 (quality risk analysis and risk management) play?

The innovator industry presentation was given by **Georg-Burkhard Kresse** (Hoffmann-LaRoche), who emphasized that the available guidance for quality characterization is applicable for biosimilar mAbs. These guidelines are quality characterization of mAbs (CHMP/BWP/157653/2007) and quality issues of biosimilar products (CHMP/BWP/49348/2005). However, he cautioned that it is not possible to characterize the quality attributes of mAbs completely by physicochemical analysis alone, or fully predict the impact of differences on clinical efficacy and safety. Similarity thus has to be shown in terms of quality, efficacy and safety in head-to-head comparative studies. A key point was that the 'biosimilarity' scenario differs from the 'comparability after manufacturing changes' scenario regulated by the International Conference on Harmonization (ICH) document Q5E.

Dr. Kresse noted that antibody modes of action are complex and may involve contributions from multiple mechanisms, and that the in vivo net contribution of different modes of action described for one mAb is often incompletely understood and may also be different in different indications. As a consequence of this multi-functionality, mAb characterization should include both Fab and Fc mediated functions unless there is justification to omit these studies. He emphasized that biosimilars must have the same amino acid sequence as the reference product, and that both reference and biosimilar mAb products will be microheterogeneous mixtures of a large number of post-translationally modified molecular species. The relevance of major variants on clinical efficacy and safety thus has to be established, and, since the exact composition of the mixture cannot be reproduced using a different manufacturing process, comparative non-clinical and clinical data will always be necessary for biosimilar mAbs.

The key question of glycosylation differences was then raised by Dr. Kresse. The fact that glycosylation can be critical for the biological function of mAbs has been established.[7,8] In theory, IgGs can contain up to approximately 500 different glycoforms due to Fc glycosylation, and these differences may influence

solubility, stability, clearance, immunogenicity and immune effector functions of the molecules. Even small differences in glycosylation, e.g., deletion of fucose residues,[9] can have significant effects. Up to 30% of human IgGs contain N-linked oligosaccharides in the Fab region, and the functional significance of these has not been fully evaluated, e.g., impact of Fab galactosylation on hypersensitivity reaction. The experience of the innovator industry is that the pattern of glycosylation will vary between products because it depends on the manufacturing process. As a consequence of the critical nature of this attribute, the impact of glycosylation differences on clinical properties, which may be different for mAbs using different modes of action, should be proven or disproven.

In discussing functional assays, Dr. Kresse noted that quality data cannot substitute for gaps in knowledge. In the experience of the innovator industry, it may be difficult to understand critical quality attributes and predict the impact of differences on clinical efficacy and safety. For example, XOMA and Genentech separately produced batches of efalizumab that were found to have minor physicochemical differences, but gave notably different clinical results. Hence, only those differences known or proven to have no impact on clinical efficacy and safety should be acceptable without additional justification. Gaps in functional knowledge present at an early stage in the development process will lead to the requirement for additional non-clinical and clinical data, the specifics of which should be based on knowledge of the mode of action of the particular mAb. Quality (i.e., CMC), non-clinical and clinical aspects, are linked, and so a 'holistic' approach is needed for the evaluation of mAb-based drugs to connect analytical data with clinical safety and efficacy results.

Dr. Kresse's final point addressed the role of ICH Q8 (Pharmaceutical Development) and ICH Q9 (Quality Risk Management); he stated that these are applicable for biosimilar manufacturers for their own development processes in the same way as for the originators. However, he noted that the 'design space' concept depends on a particular manufacturing process connected to clinical studies results, and cannot be 'borrowed' from an innovator and used to demonstrate similarity of a biosimilar product to a reference product made by a different process. A biosimilar company has no access to the proprietary data of the innovator company needed to assess product quality attributes and batch-to-batch variability, or to understand batch difference relevance or impact on clinical safety and efficacy. As a consequence, the design space of the reference product cannot be utilized by a biosimilar manufacturer, and this manufacturer needs to establish a control strategy based on data generated for their own product.

On counterpoint, **Martin Schiestl** (Sandoz GmbH) first suggested that the phrase 'well-characterized' biological should be avoided because the term is not defined. He noted that mAbs can be characterized by DNA sequence; identity and amount of variants; glycosylation profile, including identity and content of individual glycans; and relevant bioassays for pivotal Fab and Fc-related biological functions, but whether this means the mAb is 'well-characterized' is subjective. The critical question is the clinical relevance of detected differences between the biosimilar and reference product.

Dr. Schiestl then noted that current physicochemical tools are able to detect batch-to-batch differences in reference product mAbs, and that these same tools should be applied to biosimilar mAbs. He emphasized again that the question is not the ability to detect differences, but the determination of their clinical relevance. In addition, a bioassay toolbox is available to characterize the relevant biological properties, and these bioassays complement physicochemical methods for determination of higher order structure. The bioassays help to establish structure-function relationships; they are an essential part of biosimilar comparisons and are equally needed in the holistic evaluation of biosimilarity together with physicochemical, preclinical and clinical data. Indeed, a comprehensive evaluation of multiple functional assays may enhance overall product understanding, and allow a reduction of the preclinical and clinical program.

Regarding substituting quality data for gaps in knowledge in function assays, Dr. Schiestl suggested that comprehensive quality data mitigates the risk of the unknown. As an example, he discussed that the combination of functional binding, complement dependent cytotoxicity (CDC) and antibody-dependent cell cytotoxicity (ADCC) assays, together with sensitive quantitative glycan data may also serve as a surrogate for unknown additional Fc functionality not directly covered by CDC and ADCC. On the question of how similar glycosylation should be, he stated that the identity of the individual glycan structures should be the same, and that the quantitative glycan composition should be comparable. However, the degree of acceptable differences in qualitative and quantitative composition would depend on the relevance of the respective individual glycan.

Dr. Schiestl noted that generally a biosimilar mAb should contain the same variants in comparable amounts as the reference product, but that deviations from this rule are acceptable depending on the level of understanding of the clinical relevance of the variants and differences. For example, differences in levels of terminal lysine variants may not affect the biological function, and glycosylation is known to play a reduced role for some mAbs exhibiting no effector functions. He emphasized that differences between biosimilar and reference products can be accepted based on the level of understanding of clinical relevance. An understanding of the process relative to product and critical quality attributes is needed, and existing public knowledge provides valuable input for risk assessments. However, final justification for remaining differences must be established by the biosimilar sponsor. Differences may be accepted based on the outcome of the overall comparability exercise, including physicochemical, biological, preclinical and clinical data, although a holistic interpretation of overall comparability data is needed. The existing knowledge of the mAb class may increase the level of confidence.

Regarding the question of ICH Q8 and Q9, Dr. Schiestl referred to ICH Q8 concepts of quality-by-design (QbD) and design of experiment (DoE) as of key importance in biosimilar mAb development. These concepts are recommended for development of a process that consistently delivers a comparable product.

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

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.
www.emea.europa.eu/pdfs/human/ewp/309702en.pdf
CHMP/437/04; effective October 2005.
Guideline on similar biological medicinal products.
www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf
EMEA/CHMP/BWP/49348/2005; effective June 2006.
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues.
http://www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf
EMEA/CHMP/BMWP/42832/2005; effective June 2006.
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.
www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf
EMEA/CHMP/BMWP/94528/2005; effective June 2006.
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing somatropin.
www.emea.europa.eu/pdfs/human/biosimilar/9452805en.pdf
EMEA/CHMP/BMWP/32775/2005; effective June 2006.
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant human soluble insulin.
www.emea.europa.eu/pdfs/human/biosimilar/3277505en.pdf
EMEA/CHMP/BMWP/31329/2005; effective June 2006.
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor.
www.emea.europa.eu/pdfs/human/biosimilar/3132905en.pdf
EMEA/CHMP/BMWP/94526/2005; effective July 2006.
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant erythropoietins.
www.emea.europa.eu/pdfs/human/biosimilar/9452605en.pdf
EMEA/CHMP/BMWP/170734/2008; Deadline for comments October 2008.
Concept paper on the revision of the guidance on similar biological medicinal products containing recombinant erythropoietins.
www.emea.europa.eu/pdfs/human/biosimilar/17073408en.pdf
EMEA/CHMP/BMWP/14327/2006; Draft (deadline for comments July 2007).
Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins.
www.emea.europa.eu/pdfs/human/biosimilar/1432706en.pdf
EMEA/CHMP/BMWP/102046/2006; Draft (deadline for comments April 2008).
Guideline on similar medicinal products containing recombinant interferon alpha.
www.emea.europa.eu/pdfs/human/biosimilar/10204606en.pdf
EMEA/CHMP/BMWP/118264/2007; Draft (deadline for comments October 2008).
Guideline on similar biological medicinal products containing low-molecular-weight-heparins.
www.emea.europa.eu/pdfs/human/biosimilar/11826407en.pdf
EMEA/CHMP/BMWP/114720/2009; Deadline for comments June 2009.
Concept paper on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.
www.emea.europa.eu/pdfs/human/biosimilar/11472009en.pdf
EMEA/CHMP/BWP/157653/2007; effective July 2009
Guideline on development, production, characterization and specification for monoclonal antibodies and related products.
www.emea.europa.eu/pdfs/human/bwp/15765307enfin.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.

He stated also that ICH Q9 risk management procedures can be applied to the evaluation of biosimilarity, including the definition of comparability criteria, and evaluation and management of remaining differences. In concluding remarks, Dr. Schiestl noted that the expertise to develop and evaluate biosimilar mAbs is available at companies and regulatory agencies, as demonstrated by recent cases of approved and rejected applications for manufacturing process changes.

In the final presentation of the CMC session, **Kowid Ho** (Agence francaise de sécurité sanitaire des produits de santé) reviewed the European regulatory guidelines for similar biological medicinal products (**Table 2**). Dr. Ho briefly outlined the timeline of changes in the legal environment in the EU that ultimately allowed approval of Omnitrope in 2006 under the biosimilar framework. A critical factor was the issuance of an 'overarching' guideline in 2005, Guideline on similar biological medicinal products (CHMP/4307/04), that defined key concepts and principles for approval of biosimilar products. He then discussed aspects of guidelines CHMP/BWP/49348, CHMP/BWP/157653, and the availability of guidelines for specific products, including erythropoietins (CHMP/94526/05), granulocyte-colony stimulating factor (CHMP/31329/05), somatropin (CHMP/94528/05), human insulin (CHMP/32775/05), low molecular weight heparins (CHMP/BMWP/118264/07), interferon alpha (CHMP/BMWP/102046/06).

Dr. Ho emphasized that the target for quality of biosimilars is the quality profile of the reference product. There are a wide variety of physicochemical and biological characteristics to assess, including deamidation, oxidation, N-terminal pyro-Glu, glycosylation, glycation, constant region differences (e.g., deamidation, oxidation, C-term Lys), binding (e.g., affinity avidity, immunoreactivity), effector functions, epitope immunogenicity, modulatory region (e.g., Tregitope), and pharmacokinetics. Given the battery of available technology to assess these variables, he asked a key question: What differences in structure and function might be acceptable?

The CMC session group discussion was led by **Jean-Hugues Trouvin**. All participants were invited to make comments on CMC-related issues. First, there was general agreement that the 'well-characterized' term should be avoided. Dr. Kresse noted that the term was introduced by FDA in 1995, but abandoned in 1996,[10] because it was difficult to achieve a sufficiently clear and specific understanding of the term. It was noted that variability is also a problem for innovators, and that it is the duty of all companies to maintain product consistency and eliminate uncertainty in the use of products. However, key questions remained for participants: What does it mean if differences are detected between biosimilar and reference products? What are the critical attributes of the product?

From the biosimilar industry perspective, the main point was that the manufacturing process will not be identical to that of the innovator, but the process will be controlled, and the product will be characterized sufficiently to support a claim of similarity to a reference product through linking physicochemical data with bioassays and clinical study results. Quality limits for a biosimilar attribute will be the range for the reference product. From the innovator industry perspective, the main point was that although mAbs have platform processes for manufacturing, the processes can still give variable products. The innovator has the experience to know how the variations might affect product attributes, including clinical results, but a biosimilar company does not.

The disconnection between knowledge about the product prior to administration to patients, and what happens in the patient was also discussed. Analytical methods can provide precise information about product characteristics, but what happens to the product in the patients is less well-understood. An example was given of a product that was carefully controlled for the presence of deamidation during manufacturing, but was found to be completely deamidated after administration to patients, suggesting that patients can and do tolerate product variants. In general, it was agreed that clinical studies are a blunt instrument for assessment of product differences.

The session was summarized by Jean-Hugues Trouvin. There was general agreement on the following points: (1) there is no need for new guidelines specifically for biosimilar mAbs, but application of the current provisions should be more consistent; (2) it is not possible to exactly reproduce a mAb product, which likely changes somewhat over time anyway; (3) the product and impurity profile of the reference product is the target for the biosimilar mAb; (4) different expression systems can be used, but problems are more likely to arise due to the increased difficulty in matching profiles; (5) better links between physicochemical analysis, bioassays and clinical data are needed; and (6) further work is needed to understand quality attributes and what they mean.

Non-Clinical Issues Session

EMEA posed the following questions on non-clinical issues: What non-clinical studies should be requested, given that the studies often need to be done in monkeys to be relevant, and thus the number of animals per group will be limited? How can pharmacodynamic (PD) measures ('fingerprinting') be supplementary to quality development? For antitumoral mAbs, to what level would a comparison on the functional level besides ADCC/CDC (if relevant) be required or feasible? What is the impact of formulation on in vivo behavior (injection site and infusion rate comparability), and how could it best be studied?

The innovator industry representative, **Danuta Herzyk** (Merck), initially discussed the role of non-clinical assessment of biosimilar mAbs. She emphasized that non-clinical pharmacology, pharmacokinetic and toxicology studies are key components of an integrated assessment of comparability between biosimilar and reference products. For comparative pharmacology, the equivalence of biological endpoints in response to both products needs to be demonstrated, i.e., in vitro potency assays at a functional level. Such comparative evaluations might include ligand binding as assessed by ELISA or Biocore, Fc receptor binding, cell-based assays (e.g., mitogenesis, flow cytometry, apoptosis), bioassays and in vivo animal models (e.g., murine xenographs, transgenic animals). For comparative pharmacokinetics (PK), the equivalence of PK parameters for both products in relevant animal species needs to be demonstrated. For comparative

toxicology, the lack of toxicologically meaningful differences between toxicity profiles of the biosimilar and reference products needs to be demonstrated.

On the question of appropriate use of relevant species, Dr. Herzyk noted that comparative PK/PD obtained in a relevant species should be mandatory, but, where possible, PK, PK/PD (including dose response) studies should be combined to reduce the number of animals used. A head-to-head comparative PK/PD evaluation in an adequate animal model, if feasible, should be done to understand how in vitro PD results translate into in vivo effects. Toxicology studies should include one repeat dose study of minimal, but sufficient, duration to evaluate the toxicity profile in relation to that of the reference product. In principle, a comparator arm should be included unless exclusion is justified, but there is a need to balance extensive animal use against the ability to detect potential unexpected toxicity of a biosimilar relative to the described toxicity (or lack of it) for the reference product. A repeat dose toxicity study, typically done in non-human primates, that includes PD markers should be done, if feasible. The treatment duration should be adequate to detect potential differences between products. Recovery groups generally should be included, with control and high-dose recovery groups generally sufficient. However, if toxicity is known to be reversible, then there is no need to evaluate. Immunogenicity should be included to explain potentially unexpected PK/PD profiles or toxicity. Safety pharmacology should be included on a case-by-case basis, e.g., cardiovascular endpoints should be included in a repeat dose toxicology study. Injection sites should be evaluated to determine local tolerance.

Dr. Herzyk addressed the question of PD measures by explaining that PD markers for biosimilars should be chosen appropriately to demonstrate equivalent target binding or capture and other relevant functional endpoints. PK-PD characterization may utilize downstream markers from primary target binding based on known, relevant biology. Either single or multiple PD markers (a fingerprint) may be relevant to profile a biosimilar. However, broad spectrum '-omics' approaches should be considered exploratory.

With regard to non-clinical evaluation of anti-tumoral mAbs, Dr. Herzyk stated that comprehensive, comparative (i.e., head-to-head) functional activity, in vitro characterization is needed. The need for such studies done in vivo in appropriate animal models should be considered based on results of in vitro characterization and the PK profile of the biosimilar mAb. These studies would be warranted when ADCC/CDC comparison results in significant differences, or the impact of the differences is not understood, and when PK profiles and in vivo findings in non-tumor animal models are significantly different. She further noted that the feasibility of the evaluation of anti-tumor mechanism of action-related endpoints, e.g., target dependent signalling pathways, is product dependent. In addition, she suggested that comparative evaluation might be enhanced if use of relevant endpoints in pharmacology studies generated with newly emerging methodology is considered.

Concerning the impact of formulation on in vivo behavior, Dr. Herzyk suggested that the pivotal non-clinical study for a biosimilar should mimic the injection site and infusion rate intended for use in clinical studies. However, if the injection site or infusion rate for a biosimilar is different from that used for the reference product, then a clinical study using the new conditions is warranted.

Dr. Herzyk summarized by noting that non-clinical pharmacology, PK and toxicology studies for biosimilar mAbs need to be adequately designed to detect potential relevant differences in therapeutic and safety profiles. The assessment criteria should be product-specific, and formulated in the context of full understanding of the product's structural, biochemical and bioactivity attributes, e.g., potency, PK/PD relationship, safety. She also explained that the extent of the non-clinical studies will be dependent on the nature of the pharmacology, as well as the nature of adverse effects and the dose-response relationship for known adverse effects. Her final point was that some aspects of biosimilarity, e.g., product label statements regarding immunogenicity, can currently only be addressed in properly designed clinical studies.

The biosimilar industry's perspective on non-clinical issues was provided by **Alexander Berghout** (Sandoz Biopharmaceuticals). He opened his presentation by emphasizing that the innovator has already established key factors for successful mAb development, including the availability of appropriate bioassays, the selection of appropriate animal species, antigen cross-reactivity, PK and PD, dose selection and treatment schedule, drug interactions, toxicity and safety profile, immunogenicity, and the history of clinical experience. Therefore, broad experience with the reference product will allow focused preclinical development of a biosimilar mAb. Dr. Berghout then noted that clinically-relevant PD effects of biosimilar and reference product should be compared in appropriate species. The non-clinical toxicity evaluation should be one repeat dose study that includes toxicokinetic measurements and local tolerance assessment. In addition, antibody titers and neutralizing capacity should be determined, and the study duration should be appropriate to allow detection of relevant differences in toxicity or immune responses.

On the question of appropriate use of relevant species, Dr. Berghout referred again to the fact that the innovator has already established key factors, including relevant species and the toxicity profile. He stated that dose-response is more suitably compared in non-clinical studies, rather than clinical trials, and, importantly, unnecessary duplication of toxicity studies with the reference product should be avoided. Dr. Berghout encouraged exploration of new methodologies, e.g., modeling, simulation, use of biomarkers, to optimize study design.

Dr. Berghout noted that functional bioassays to measure the principle mechanisms of action are indispensible in the target-directed development of a biosimilar, and are utilized throughout the process of engineering, selecting the desired clones and the final drug product development. All established effector functions should be investigated. Regarding antitumoral mAbs, Dr. Berghout commented that functional bioassays will usually be sufficient to establish the comparability of mAbs because the reference mAbs were generally selected by such assays. So, it may be expected that identical Fab binding to the target cell receptor

will control signaling events in the same way. He also noted that in the case where modulation of signaling is the predominant function, respective analysis may be required.

On the topic of formulation, Dr. Berghout stated that, in general, the formulation, injection site and infusion rate will be similar for the reference product and the biosimilar product, and comparability will be confirmed in human studies. He noted also that the best way to explore the impact of formulation on in vivo behavior will be in a relevant animal model, and that the use of new methodologies such as modeling and simulation should be considered. In summary, Dr. Berghout reiterated his points that mAbs, like all biosimilars, follow the same principles of focused preclinical development, mAbs are multifunctional proteins requiring an extended set of bioassays for evaluation, use of new methodology should be explored to optimize study design, and unnecessary duplication of toxicity studies comparing biosimilar to reference products should be avoided.

The non-clinical session chair, **Beatriz Silva-Lima** (SWP), then presented her remarks on the non-clinical issues questions. Regarding non-clinical studies in relevant species, she emphasized that only informative studies should be requested, but that alternatives such as other models, e.g., in vitro or tissue cross-reactivity studies, may be considered and may be more informative. In any case, a thorough justification for the model used should be presented. On the question of PD measures as supplement to quality development, she noted that PD and quality are inter-related when relevant differences are identified, e.g., receptor-target interaction as assessed by potency, Emax, binding site, off-target characteristics, cellular cascades. Assessment of these qualities may reveal relevant differences and indicate when the products are not similar. For comparison of the functional activity of antitumoral mAbs, she stated that the feasibility level is dictated by the approaches taken for previous characterization of the reference product, taking into consideration relevance suggested by the biosimilarity exercise. Regarding formulation, she noted that the impact may be local, and these effects would be application-site and vehicle dependent. However, systemic variation, e.g., different kinetics, enhanced activity, modified immunogenicity, would need to be assessed in the case of different formulations.

Dr. Silva-Lima also raised some additional questions for consideration. These were: (1) If non-similarity of the biosimilar product is concluded, due for example to a different glycosylation pattern compared to the reference product, but the basic molecule and mechanism of action are the same, then how should the development of the product proceed? (2) What about non-human primate (NHP) developmental and reproductive toxicology (DART) studies for biosimilar mAbs or a 'non-similar' product when there is experience, presumably in humans also, with the reference product?

The discussion on non-clinical issues was moderated by Beatriz Silva-Lima. The point of only repeating studies that were indicated as relevant in innovator development programs was reiterated. The role of comparative toxicology, considering the small number of NHPs used, was questioned since understanding the resulting outcomes could be challenging. A representative of the innovator industry suggested that creation of animal models, e.g., transgenic mouse model, might be a solution to the limited size of NHP studies.

Numerous exchanges occurred concerning the non-clinical evaluation of potential impurities. It was suggested that if toxic effects of impurities needed to be assessed, then perhaps a non-relevant species such as the rat or even human tissues could be used for these studies. A rodent model might also be used to assess toxicity of glycoforms. However, representatives of the biosimilar industry questioned the basic assumption. If CMC-related studies and PK/PD studies have indicated that the biosimilar is comparable to the reference product, then why are toxicity tests of putative variants and impurities necessary? Process-related impurities are in fact not an issue specific to biosimilars, but a general problem that is dealt with prior to the non-clinical evaluation stage. There are no known examples of toxic or negative clinical outcomes that have been specifically linked to a product variant. Regarding DART studies for mAbs, the question of relevance was raised, since other biosimilar products are not required to undergo reproductive toxicology evaluation. Also from the perspective of the biosimilar industry, head-to-head comparability studies in toxicology do not make sense.

The final question discussed during the session related to how much information should be asked for at the non-clinical stage. For example, regulators could request studies on mechanism at the target, i.e., the effects of the signaling pathway. Studies like this might not have been done by the innovator. It was noted that, from the regulator's perspective, teasing apart what an innovator has done and what biosimilar companies should have to do might be a challenge. However, from the biosimilar industry perspective, the fundamental question remains the same: if similarity has been established, then why are studies that should provide expected results necessary? Addressing the specific example, if binding to the target has been shown to be comparable to the reference product, then one would expect that the downstream effects of binding by either the biosimilar or reference product would be the same. Dr. Silva-Lima summarized the main points of the discussion as: (1) it was generally agreed that comparative PD studies are useful; (2) a case-by-case approach for non-clinical evaluation is justified; and (3) dedicated studies for effects of impurities are not needed.

Clinical Issues Session

The clinical issues session included topics relating to PK/PD, extrapolation of efficacy and safety, and outcome measures. The PK/PD-related questions to be considered were: (1) What role could new methodologies such as simulation, modeling and biomarkers play in clinical studies? (2) In which population(s) should PK/PD be measured? Questions relating to the extrapolation of efficacy and safety were: (1) To what extent can efficacy be extrapolated from one indication to another in different scenarios, provided that physicochemical and biological characterization has been shown to be comparable? For this question, EMEA requested that three specific cases (immunomodulatory mAbs that might involve extrapolation from psoriasis to rheumatoid arthritis,

antitumoral mAbs and antitumoral mAbs that are also indicated in inflammatory conditions) be considered; (2) To what extent can safety be extrapolated, and what can be done post-marketing?; and (3) For antitumoral mAbs, what would be acceptable as patient subpopulations for studies in different indications?

In the outcomes measures area, EMEA's questions for discussion were: (1) Of the following, which endpoints should be used as a general strategy—endpoints that measure patient benefit, but might be less sensitive for detecting product differences; endpoints, e.g., activity endpoints, that measure similarity more sensitively; or, if similarity endpoints are used, should these conform to guidelines or could these be newly developed endpoints? (2) What role could new methodologies such as simulation or modeling play? (3) to what extent would a risk-based approach to immunogenicity be applicable, given that mAbs do not have endogenous counterparts?

The perspective of the innovator industry was presented by **Jay Siegel** (Johnson & Johnson). He noted that once high similarity had been demonstrated in laboratory and non-clinical testing, clinical similarity may then be tested head-to-head. Extrapolation across endpoints, populations or diseases should be justified scientifically. However, he emphasized that applications of the principles should take into account particular properties of mAbs, such as the fact that multiple features of mAbs determine the clinical activity, critical structure-function relationships are often not well-understood, and mAbs are generally used to treat serious or life-threatening diseases.

A key point was that extrapolation of efficacy would likely be difficult to justify. Dr. Siegel stated that mAbs have diverse functional activities and may be used in diverse indications. However, different indications can require different activities and receptors (or combinations of these) in different sites over different time courses, and in different pharmacologic milieu. As a consequence, mAbs with similar effects in one disease may have different effects in a second indication if the second indication involves a different mechanism of action, action at a different site, a longer time frame, a change in the amount of target antigen expressed or use of different concomitant medications.

On the question of endpoints that measure patient benefits, Dr. Siegel suggested that the science-based principles presented in current EMEA guidelines will, for many mAbs, dictate study of clinical benefit endpoints. He explained that biomarkers may not reflect all relevant activities of mAbs, relevant activities of mAbs often are not fully understood, and dose-response relationships of competitive inhibitors are often complex. As a consequence, differences between biosimilar and reference products may impact the effect on clinical outcomes without impacting the effect on biomarkers. In fact, markers rarely provide quantitative prediction of efficacy. Modest differences in efficacy could have a significant, irreversible impact on many diseases treated by mAbs. Dr. Siegel also noted that where clinical outcomes data are needed, biomarker data can supplement those data, potentially decreasing the amount of clinical outcomes data needed and increasing confidence in the clinical similarity of the biosimilar and reference products.

Dr. Siegel continued by noting that biomarkers and activity endpoints can often be measured faster, cheaper and with more precision than can clinical outcome measures. A 'highly similar' biosimilar mAb should in fact be highly similar in all effects in patients. However, he reiterated the point that similarity in effects on biomarkers will not always predict similarity of effects on clinical outcome. The regulatory implications of these points are that head-to-head comparisons of effects on biomarkers will be powerful tools in identifying or excluding some clinical differences, and may prove valuable in supporting extrapolation to other indications, although demonstration of similar effects on easily measured biomarkers should be considered necessary, but not usually sufficient, to establish equivalence.

Regarding the question of immunogenicity data, Dr. Siegel emphasized that increased or altered immunogenicity in any biosimilar mAb has the potential for significant clinical implications. He recommended that all mAbs should be assessed for immunogenicity as described in EMEA guideline CHMP/BMWP/14327/2006, and suggested that biosimilars should be studied head-to-head with the reference product. He cautioned that similar incidence of immunogenicity does not necessarily mean similar immunogenicity.

In conclusion, Dr. Siegal noted that strong CMC and non-clinical data that limits potential differences between the biosimilar and reference product are critical. EMEA guidelines relevant to biosimilar biotechnology-derived proteins (**Table 2**) serve as a good starting point for clinical requirements for mAbs. However, key properties of mAbs have important implications for how EMEA guidelines should be applied. Extrapolating data between indications should only be done when mechanisms of action in both indications are understood and highly similar, bearing in mind that implications of immunogenicity for mAbs are always potentially substantial. Immunogenicity cannot be predicted, so it must be measured directly.

The biosimilar industry's perspective on clinical issues was presented by **Islah Ahmed** (Hospira), who first emphasized the point that prior to entering clinical development, biosimilar mAbs will have already demonstrated comparability to the reference mAbs in physicochemical characterization, non-clinical studies (e.g., PK, PD, toxicity profiling), and in vitro functional characteristics. The goal of the clinical development program is then to complement the comparability exercise by demonstrating therapeutic equivalence within an abbreviated pathway.

Regarding the question of new methodology applied to PK/PD studies, Dr. Ahmed noted that the PK of mAbs is well-understood, and basically follows the PK of human IgG. PK/PD are based on the type of mAb target, and he provided several examples: (1) if the target is a soluble antigen with low endogenous levels, then PK is often independent of PD, the PK is linear and the half-life is long; and (2) if the target is a soluble antigen or cell bound, then PK often depends on PD, PK is non-linear and the half-life is short for low dose and long for high dose. He also mentioned that the general clearance of mAbs is based on catabolism and the renal clearance is negligible. PK/PD modeling might be designed based on data from the reference mAb if such data are available. Dr. Ahmed emphasized that PK/PD is pivotal to the

comparability evidence, and with validated PK/PD models, the comparability study design can be optimized to minimize the number of patients and samples.

Dr. Ahmed addressed the question of which population should be studied by stating that there should be flexibility in the population selection on a case-by-case basis, although the selection would be done by mutual agreement with regulators. For example, a PK study in healthy volunteers may be technically preferable, but not acceptable because of ethical reasons. In other cases, a patient population in an approved indication with low variability in PK will be most suitable. Dr. Ahmed noted that patients in PK/PD trials must be treated for full clinical benefit, and not only for PK/PD comparability. He suggested that PK/PD can be combined within an efficacy and safety study. He also pointed out that PK/PD sampling depends on the PK/PD profile of the reference mAb, e.g., in selected cohorts or as sparse sampling for population kinetics.

Concerning the question of extrapolation from one indication to another, Dr. Ahmed stated that extrapolation of efficacy is acceptable, provided that the mAb has demonstrated comparability to the reference mAb in the parameters already discussed (physicochemical, non-clinical, and in vitro functional characteristics; bioavailability and clinical PK/PD; clinical efficacy in one indication). He emphasized that once comparability has been demonstrated in one indication, there is no scientific reason to expect that the response of the host to the biosimilar product should differ from that of the reference mAb in other indications.

Although noting that safety risk profiles may differ in different indications because of variables such as concurrent conditions or concomitant medications, Dr. Ahmed stated that extrapolation of safety is also acceptable. He noted that safety comparability could be demonstrated in an indication that was judged to have a high sensitivity toward detection of differences and extrapolated to all other indications. In addition, he suggested that a risk management program implemented to collect safety data for low frequency safety risk, e.g., immunogenicity as observed in the post-approval patient population, will usually be similar for biosimilar and reference products. With regard to patient subpopulations, Dr. Ahmed suggested any subpopulation that is most sensitive toward detection of differences between biosimilar and reference mAbs would be acceptable, and that subpopulations with high response rates, those who are more homogeneous with regard to disease stage, or those in which validated biomarkers could be used may be selected for comparability trials.

On the question of efficacy end points, Dr. Ahmed observed that the primary objective of the clinical study program is comparability, and not generation of new evidence of efficacy. Therefore, an abbreviated data package that includes minimal patient exposure to research is appropriate for biosimilar mAbs. A flexible approach would be suitable, with use of validated surrogate end points, if these are available. He suggested that long-term survival based on patient benefit end points is not always necessary, even for antitumoral agents. For example, the liposomal formulation of the antitumoral agent doxorubicin (Myocet) was approved based on an objective response rate as the primary end point. He then noted that an objective response can serve to demonstrate comparability, at least in some mAbs.

Regarding new methodology, Dr. Ahmed suggested that, as the state of science progresses, new methodologies should be applied wherever possible for biosimilar mAbs to achieve abbreviated clinical data packages and alternate statistical models, e.g., Bayesian statistics, can help to optimize clinical trial sample size. He briefly addressed the immunogenicity question by stating that a risk-based approach to immunogenicity should be applied to all biologics, including both biosimilar and reference products.

In conclusion, Dr. Ahmed restated his points that clinical development of biosimilar mAbs should be flexible in the design of PK/PD, efficacy and safety studies to demonstrate comparability in the most sensitive model; modeling, simulations, and statistical methods are applicable to achieve an abbreviated approach to the demonstration of comparability; a risk management program to monitor low frequency safety risk should be the same as for the reference product; and efficacy and safety demonstrated in one sensitive model can be extrapolated for all indications approved for the reference product.

The final speaker, **Christian Schneider** (EMEA BMWP) presented the regulators perspective on clinical issues. He began by acknowledging the oft-repeated observation that mAb mechanisms of action can be complex, then went on to ask what he referred to as the frequently asked questions' of a heretic: Can the mechanism of action be understood solely as a ligand-receptor interaction (or inhibition, as the case may be)? Is it important to know what comes after? Does the mechanism of action have to be known? Using efficacy and safety of marketed anti-TNF antibodies as an example, he asked how one would design a biosimilar development program that might allow licensure in the seven indications for which these mAbs are now approved? Is therapeutic equivalence or non-inferiority suitable? Should all indications be approved? Should extrapolation of efficacy or safety be allowed? What end points should be used—activity or benefit? What are appropriate for Phase 2 or Phase 3 endpoints? He pointed out that the 'Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues' (EMEA/CPMP/42832/05) already discusses extrapolation of therapeutic similarity shown in one indication to other indications of the reference product.

Dr. Schneider discussed the spectrum of uncertainty that is traversed when considering 'biosimilars' of peptides, non-glycosylated proteins, glycosylated proteins, mAbs, blood products and finally advanced therapy medicinal products, e.g., cell therapy. He pointed out that EMEA has already begun to address cases involving complexity and advanced degrees of uncertainty. He directed the workshop participants to the 'Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins' (EMEA/CHMP/BMWP/118264/2007) and also to the reflection paper 'Non-clinical and clinical development of similar medicinal products containing recombinant interferon alfa' (EMEA/CHMP/BMWP/102046/2006).

Dr. Schneider concluded by raising additional questions regarding immunogenicity and practical issues. He pointed out that mAbs do not substitute for endogenous proteins like other recently approved biosimilars such as epoetin and filgrastim. So, is the perception of risk different? Antibodies against mAbs are mostly anti-idiotype, not anti-isotype and endogenous IgG is abundant. While not suggesting that immunogenicity is unimportant, should immunogenicity be the 'highest' safety concern? On practical issues, he wondered about the extent to which the biosimilar philosophy is known to patients and physicians, which leads to questions regarding the acceptability of biosimilar mAbs, especially in an oncological setting. His final questions concerned how to practically deal with Phase 1 PK/PD studies in patients: These are usually single dose studies—should cross-over be used? How should treatment be continued—should patients be switched to the reference product?

Lively exchanges then followed in the clinical issues group discussion session moderated by **Christian Schneider**. Addressing the 'heretical' questions first raised by Dr. Schneider, the conservative response that efficacy is dependent on much more than blocking a ligand or receptor, and so knowing the downstream effects of disrupting the signaling pathway is important was given. However, from the biosimilar industry perspective, the determination that a biosimilar mAb binds to the same epitope as the reference product with same binding constant is part of preclinical evaluation, and, if non-clinical data shows similar results, then it follows that clinical results would also be similar. If differences are seen at the non-clinical stage, then decisions regarding clinical studies must be data-driven.

Further discussion was based on the assumption that hypothetical biosimilar mAb and reference products had demonstrated similarity in quality and non-clinical aspects. Questions and comments regarding extrapolation of results from one indication to another were made by participants. The extension of the use of rituximab from oncology to rheumatoid arthritis patients was given as an example. If extensive clinical studies of the biosimilars in both indications are not done, then there may be a risk of under-treating patients. In general, there may be different responses in different patient populations due to such factors as different receptor levels. However, the point was made that the evidence would have to suggest that patient safety is not at risk, and it is the task of regulators to determine risk to patients. If CMC and non-clinical data show similarity, then the science supports initial clinical studies, although at least one clinical study of each indication would likely be needed. The cases when extrapolation would be a challenge were enumerated: low dose to high dose, combination with other therapeutics and less severe to more severe indications. Other cases, such as extrapolating from first-line to second-line treatment, might be acceptable.

Other aspects of clinical studies were then discussed. Questions arose over how to map PD markers to efficacy since the PK/PD relationship to efficacy is weak, how to choose the most sensitive patient population, and selection of endpoints most sensitive to differences. It was noted that PK is non-linear (i.e., dose dependent), time dependent, and can differ across patient populations. Clinical testing should be comparative, and designed to asses these characteristics of mAb PK. Populations used for PK/PD measurement should be carefully chosen because PK or PK/PD can be different due to mechanism of action, patient age, other medication or disease state. For example, PK and immunogenicity of mAbs are different in pediatric and adult patient populations.

Regarding endpoints, it was noted that the primary endpoint used for clinical studies of the reference product would likely be suitable since regulators have dossiers for reference products. If alternate endpoints are used during the clinical development of a biosimilar product, then it would be difficult to compare with results for the reference product. A key question from the innovator industry was then posed: Do the clinical study results have to show similarity or rule out any possible difference? However, from the biosimilar industry perspective, practicality has to be taken into consideration. Comparison studies might be lengthy and require a large number of patients. Alternate or surrogate endpoints defined by regulatory agencies might be needed to ensure the clinical studies are feasible. For example, study of an antineoplastic mAb that used survival as an endpoint would take many years. The possibility of use of a conditional approval mechanism, whereby marketing approval was given but survival data for clinical study participants continued to be collected, was mentioned.

Additional points were made regarding safety and immunogenicity. In general, if there are safety concerns with the reference product, then biosimilars should be monitored for the same safety problems. It was noted that post-marketing safety might be challenging after biosimilars are approved because patients might not know what product they are taking and so spontaneous reporting of adverse events might not be accurate. The question of the use of a risk-based approach to immunogenicity was then raised. Problems could arise if biosimilar products are more immunogenic compared to the reference product because the immune response could affect dosing with the innovator product. However, it was noted that immunogenicity is part of the comparability exercise and a class effect that applies to all mAbs.

Concluding Discussion

In concluding the workshop, Dr. Schneider raised final two questions that were briefly discussed. The first question was, should the biosimilar framework be expanded to include products with differences in the amino acid sequence? The general consensus was that the two products have to be the same, and avoidable changes such as amino acid substitutions should not be allowed. The second question was, could some concepts relating to biosimilars be applicable to second-generation products, at least those that are functionally equivalent, but may be structurally different? The general consensus was that there is too much uncertainty surrounding potential differences in modes of action or off-target effects that might be seen with molecules that have structural differences. For example, the anti-TNF mAb infliximab is shows effects in Crohn disease patients whereas the anti-TNF fusion protein etanercept does not.

Dr. Schneider also answered a few questions from participants. The first question concerned international non-proprietary names (INNs). Dr. Schneider stated that INNs are assigned by the World Health Organization (WHO), but are requested on a voluntary basis by companies. The WHO majority decision is that different substances should have different names, leaving it likely that the same substance would be assigned the same name. Naming has ramifications for traceability, and whether confusion would result in cases of voluntary reporting of adverse events, i.e., whether the patient was taking a branded product or biosimilar version. The second question on interchangeability could not be addressed by EMEA regulators because there are country-to-country differences in requirements.

In conclusion, Dr. Schneider outlined the next steps for EMEA. Further internal discussion on whether another guideline is needed for biosimilar mAbs will occur. The group consensus of this workshop seemed to be that there is no need for a new guidance on quality, although a guideline for non-clinical and clinical requirements may be needed. However, writing one might be challenging because EMEA might have to anticipate what would be allowable for differences between reference and biosimilar products. If needed, EMEA would develop a concept paper that would be distributed for comment, then follow with a guideline. If done, it is unlikely that this would happen before 2010.

References

1. Woodcock J, Griffin J, Behrman R, Cherney B, Crescenzi T, Fraser B, et al. The FDA's assessment of follow-on protein products: a historical perspective. Nat Rev Drug Disc 2007; 6:437-42.
2. US Food and Drug Administration. Guidance concerning demonstration of comparability of human biological products, including therapeutic biotechnology-derived products. http://www.bcg-usa.com/regulatory/docs/1996/FDA199604A.pdf.
3. EMEA web site. http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP_BMWP.html.
4. Carson KL. Flexibility—the guiding principle for antibody manufacturing. Nat Biotechnol 2005; 23:1054-8.
5. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science 2006; 313:670-3.
6. Sheridan C. Commercial interest grows in glycan analysis. Nat Biotechnol 2007; 25:145-6.
7. Jefferis R. Recombinant antibody therapeutics: the impact of glycosylation on mechanisms of action. Trends Pharmacol Sci 2009; 30:356-62.
8. Jefferis R. Glycosylation as a strategy to improve antibody-based therapeutics. Nat Rev Drug Discov 2009; 8:226-34.
9. Yamane-Ohnuki N, Satoh M. Production of therapeutic antibodies with controlled fucosylation. mAbs 2009 1:230-6.
10. Federal Register/Vol. 61, No. 94/Tuesday 1996.

Part 2: EMEA Workshop on Biosimilar Monoclonal Antibodies: Perspective from the EU

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The European Union (EU) utilizes a centralized regulatory system for evaluation of some types of medicinal products. Use of this system, which includes the European Medicines Agency (EMEA) as the coordinating and evaluating institution, and the European Commission (EC) as the executive institution, has been mandatory for biotechnology-derived medicinal products since 2004.[1] EMEA's Committees and Working Parties (WPs) are recruited from the scientific staff of more than 40 European national competent authorities. EMEA's Committee for Medicinal Products for Human Use (CHMP) is in charge of the scientific assessment of medicinal products for human use. The CHMP is supported by several WPs, including the Efficacy WP, Biologics WP, Biosimilar Medicinal WP, and Safety WP, with each providing specific expertise in different scientific fields.

Briefly, the centralized review process is initiated by the applicant. Following validation of a marketing application, EMEA then initiates the centralized procedure. An initial review by two Rapporteurs is followed by a period during which comments from CHMP members are compiled into a list of questions for the applicant. Receipt of responses triggers a second round of review, after which a CHMP scientific opinion is issued. If the decision is positive, the applicant is required to provide translations of the product information in all European languages, and the EC decides whether to issue the marketing authorization (MA). Following a successful scientific review of a medicinal product for human use by the CHMP and approval of the application by the EC, the new product will automatically be authorized for marketing in all member states of the EU and the three member states of the European Economic Area.[1] Since late 2005, details of both positive and negative decisions have been made available to the public through publication of European Public Assessment Reports (EPARs), which are available on the EMEA web site. The EPARs contain a summary of medicinal product characteristics.

Biosimilar, Follow-On Biological and Second-Generation mAbs

Terminology must be clear when discussing biosimilar products. A biosilimar monoclonal antibody (mAb) will have the identical amino-acid sequence and a similar glycosylation profile compared to a reference product. The term biosimilar is used by EMEA for versions of marketed therapeutics that, from a regulatory perspective, cannot be considered like simple generic drug due to their structural complexity (e.g., insulin, somatotropin, epoetin).[2] The term 'follow-on biological' is used in the US and refers to peptide and protein biopharmaceuticals that are sufficiently similar to an approved product to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product.[3] The follow-on might be intended to be precisely identical (e.g., peptides), highly similar (recombinant proteins) or globally similar (natural biological products).

A biosimilar mAb must be distinguished from second-generation antibodies that are raised against the same molecular target, but have been designed to exhibit different properties such as lower immunogenicity (e.g., humanized and human mAbs) or improved pharmacological properties (e.g., has higher or lower affinity for the target, targets a different epitope, utilizes different or multiple mechanisms of action). The so-called second-generation products have major structural differences designed to improve performance while maintaining the same mechanism of action as the original product. The evaluation of second-generation protein products raises some issues that are similar to those raised during the evaluation of biosimilar products. Also, in some cases, approved protein products might undergo major manufacturing changes that introduce questions of uncertainty that are similar to those for a biosimilar product. However, neither second-generation products nor protein products resulting from manufacturing changes are considered biosimilars.

Biosimilar Product Challenges

Most small molecules approved as drugs have molecular weights (MWs) ranging from 150 to 500 Dalton (Da) and chemical synthesis yields copies with structures nearly identical to the original one. Molecular equivalence can be assessed using a panel of analytical methods, and bioequivalence can be documented by bioavailability studies. Biological drugs such as peptides, non-glycosylated proteins (e.g., insulin, somatotropin) or glycoproteins (e.g., granulocyte colony stimulating factor, epoetins, mAbs) are much larger, with MWs ranging from 5,600 Da to 150,000 Da for antibodies. Unlike small-molecule generic products, biosimilar products can exhibit a range of structural microdifferences compared to the original product.

EMEA's Committee for Medicinal Products for Human Use has developed guidelines that provide a framework for the development of biosimilars in the EU. Recent licensing of recombinant somatropins and several erythropoietins (EPOs) as biosimilars has prompted discussions as to whether the same regulatory path could also be applied to more complex biologics such as mAbs. Start-of-the-art physicochemical and biological methods for characterization of mAbs are becoming increasingly sophisticated. Nevertheless, the ability to compare a biosimilar mAb to a reference product on a molecular level remains limited, and the design of a clinical development program for a biosimilar mAb remains challenging.

Biosimilars Marketed in Europe

The CHMP issued guideline CHMP/437/04, which explains EMEA's general concept of biosimilars, and numerous other guidelines relevant specifically to biosimilar product development (Part 1, **Table 1**). The scope of CHMP/437/04 includes

any biological product, and it explicitly also mentions complex biotechnology-derived medicinal products such as mAbs. Vaccines and blood products are also discussed, but the guideline states that, due to their complexity, vaccines are considered on a case-by-case basis, and blood or plasma derived medicinal products (e.g., polyclonal immunoglobulins, antithrombin products, coagulation factors) are not acceptable as biosimilars due to their complex and variable physicochemical, biological and functional characteristics.

In the early 1980s, insulin and somatropin (also known as human growth hormone or hGH) were among the first recombinant DNA products to be approved by national regulatory agencies in Europe and the US Food and Drug Administration (FDA). However, regulatory pathways for approval of biosimilar versions had still not been established in either the EU or US by the early 2000s. Of the traditional generics companies, several took a proactive approach to biosimilar products. Sandoz began developing Omnitrope in 1997, more than a year before it received confirmation from the FDA that a regulatory pathway would be possible. Jerusalem-based Teva Pharmaceuticals started developing its biosimilar filgrastim product more than two years before European legislation was finalized. In 2006, somatropin became the first product to be approved as a biosimilar in the EU, and approvals for more complex biosimilar products (i.e., filgrastim, epoetin glycoproteins) have followed.

Somatotropin is a single chain, non-glycosylated, 191 amino acid, 22 kDa polypeptide produced in the anterior pituitary gland. Recombinant somatotropin has an identical amino acid sequence, and is produced using engineered *E. coli*, mammalian cells or yeast cells as the expression system. The structure and biological activity of somatropin can be characterized by appropriate physicochemical and biological methods. Several techniques and bioassays are available to characterize both the active substance and product-related substances or impurities such as deamidated and oxidized forms and aggregates. Current quality guidelines on comparability provide information on the characterization and analysis of a biosimilar and its reference product.

Human granulocyte colony stimulating factor (G-CSF) is a single polypeptide chain protein of 174 amino acids with *O*-glycosylation at one threonine residue, and an approximate MW of 20 kDa. Recombinant G-CSFs produced in *E. coli* (filgrastim) have been approved in the EU; a version (lenograstim) can also be produced in CHO cells. Compared to the human and mammalian cell culture derived G-CSF, the *E. coli* protein has an additional amino-terminal methionine and no glycosylation. The rG-CSF protein contains one free cysteinyl residue and two disulfide bonds. Physicochemical and biological methods are available for characterization of the protein.

Human erythropoietin (epoetin) is a 165 amino acid glycoprotein with MW in the range of 32–45 kDa. The protein is approximately 40% carbohydrates, with three N-glycosylation sites ($Asn^{24,36,83}$) composed of di-trisialylated, tri- and tetra-antennary complexes, and one O-glycosylation site (Ser^{126}). The product is produced by recombinant DNA technology using mammalian cells as the expression system. All marketed epoetins have a similar amino acid sequence as endogenous erythropoietin, but differ in the glycosylation pattern. Glycosylation influences pharmacokinetics and immunogenicity, and thereby may also affect efficacy and safety. Physicochemical and biological methods are available for characterization of the protein.[4]

Biosimilar mAbs—Why Now?

There has recently been increasing interest in the development of biosimilar products by both biopharmaceutical and generic drug companies.[5] However, lack of an abbreviated pathway for approval of biosimilar mAbs creates uncertainty for potential developers.[3] Because of the complex methods used to produce these multimeric glycoproteins, the time and cost required to develop a biosimilar mAb are expected to be significantly greater compared to time and costs for development of generic small-molecule drugs or less complicated biosimilar products. Once a reference product is selected, a biosimilar developer will need to establish an expression system that will produce the biosimilar product, and develop a commercial scale manufacturing process that will involve a closely monitored process of purification, formulation and testing of the product. Development time for a biosimilar product could range from 5–8 years, compared to as little as 1–2 years for a generic small-molecule drug.[3]

One of the main driving forces for the interest in biosimilars is the upcoming patent expirations for marketed products. However, this is modulated by the difficulty in determining a clear patent expiration date for protein products. Like other biopharmaceuticals, mAbs are usually protected by 'patent thickets', i.e., multiple patents that cover not only the product itself, but also the formulation and the manufacturing processes.[6,7] Estimated patent expiration dates for blockbuster mAbs and related products are 2012 for etanercept (Enbrel, a Fc-fusion protein); 2014 for infliximab (Remicade); 2015 for rituximab (Rituxan or MabThera), trastuzumab (Herceptin) and palivizumab (Synagis); 2016 for adalimumab (Humira); and 2017 for bevacizumab (Avastin).

Patents also cover the technologies used to generate the mAbs (e.g., humanization, phage display technology, transgenic mice with a human immune repertoire), as well as the vectors and cell lines used to produce the mAbs (e.g., CHO, CHO-K1SV, GS-NS0).[8] The opinions of experts differ on when certain protein products will lose their patent protection, and unpredictable legal and legislative events could influence how biosimilar developers will navigate through the existing patent landscape. Only a limited number of protein products are currently off patent.

Requirements for Biosimilar mAb Development

Over 20 antibodies have been approved,[9,10] and a wealth of experience in the development of these products, which often share 90% sequence identity, is available. Data on potency assays for mAbs approved in the EU can be found in the EPARs for the product. Many physicochemical methods, including electrophoretic profiling, liquid chromatography, mass spectrometry, and combinations of them, can be used to characterize the molecules.[11] Antigen-antibody interaction can be investigated by surface plasmon resonance or by non-

covalent mass spectrometry.[12] One key feature of mAbs is their species specificity; this requires that a relevant species must be chosen for preclinical testing. As defined in EMEA/CHPM/ICH/302/95, such species are ones in which the test material is pharmacologically active due to the expression of the receptor or an epitope in the case of mAbs.

Among the first antibody candidates for biosimilars are three chimeric blockbusters: anti-TNF infliximab, anti-CD20 rituximab, and anti-epidermal growth factor receptor (EGFR) cetuximab (Erbitux). All three mAbs are IgG1kappa with murine variable domains comprising approximately one-third of the molecule. As chimeric mAbs, the molecules exhibit a higher immunogenicity profile than humanized or human versions. Second generation mAbs targeting the same antigens have either been approved recently (human anti-TNF golimumab/Simponi, human anti-EGFR panitumumab/Vectibix), or are undergoing regulatory review (human anti-CD20 ofatumumab/Arzerra).

From the regulators perspective, a key question is the degree to which a biosimilar mAb has to show similarity to its reference counterpart. EMEA's overarching biosimilar guideline (CHMP/4307/04) states that a biosimilar product needs to be "similar, in molecular and biological terms, to the active substance of the reference medicinal product." The guideline gives an example to highlight this, stating that an interferon alfa-2b would not be acceptable as a reference product to a biosimilar interferon alfa-2a. Because interferon alfa-2a and alfa-2b differ in only one amino acid, the guideline thus indirectly indicates that the sequence of the entire molecule needs to be identical on the amino acid level.

Following this concept, in the current understanding a biosimilar mAb would indeed have to show the identical amino acid sequence in all parts of the molecule, including the framework regions and parts of the molecule that are not necessary for mediating the mechanism of action. The philosophy of biosimilar development is to develop a product that is, as much as possible, similar to a marketed reference product. This means that the quality, non-clinical and clinical development program is governed by the principle of showing similarity of the biosimilar to the reference product in any aspect.

The biosimilar products approved in Europe so far indicate that guidelines for the development of biosimilar products can be implemented. However, defining the comparability of two mAbs will require consideration of a wide range of aspects, including analytical and physicochemical characterization by several orthogonal methods, comparative biological assays and comparative immunogenicity assessment. As happened in the case of Valtropin, use of different host cells for the biosimilar and reference product may be possible, but extensive characterization of glycosylation will be necessary. Biosimilar developers should use EU-approved products as references, and should not change reference products during development of a biosimilar. The clinical program for a biosimilar should have the primary aim of establishing similarity to the reference product.

Challenging Features of mAbs

All currently approved therapeutic antibodies are IgGs or derivatives. Chimeric, humanized and human G immunoglobulins are tetrameric glycoproteins with molecular weights of approximately 150 kDa. The approved mAbs are composed of two heavy chains (HC, 50 kDa) and two light chains (LC, 25 kDa), and are selected from three isotypes defined by different heavy chains (gamma1, 2 or 4). Disulfide bridges (sixteen for IgG1 and IgG4; eighteen for IgG2) and non-covalent interactions maintain their 3-dimensional structure. The heavy and light chains are linked by one disulfide bond, and the heavy chains by two (for IgG1 and IgG4) or three (for IgG2) disulfide bonds located in the small hinge domain. The other twelve or fourteen cystine bridges are intramolecular and delimit six different globular domains: one variable (V_L) and one constant for the light chains (C_L); one variable (V_H) and three constant for the heavy chains (C_H1, C_H2 and C_H3).

Like natural IgGs, all recombinant antibodies contain an Asn-X-Ser/Thr (where X is any amino-acid except proline) consensus sequence for N-glycosylation in their heavy chain C_H2 constant domain. IgG glycans represent an average of only 2 to 3% of the total antibody mass, which is low compared to the 40% glycosylation of erythropoietin.[4] The glycosylation of antibodies varies depending on whether the molecules are produced in CHO or NS0 cells.[13] Known and unknown post-translational modifications may arise.[11] Depending on the clone and production process, micro-variation like asparagine de-amidation or iso-aspartic acid isomerization may occur, and impact both the 3D-structure and the antigen binding properties.[14] This phenomenon has been described for many antibodies including rituximab, trastuzumab, omalizumab (Xolair) and panitumumab.

The development programs of mAbs, and biosimilar versions, should be holistic, i.e., designed to join quality, non-clinical and clinical expertise in order to provide a high safety standard to patients in clinical studies.[15] However, recent experience shows that unwanted side effects can occur in some cases. Specific measures like adequate safety endpoints can be implemented that might nevertheless allow for relatively safe administration of such drugs to patients. Unwanted immunogenicity is a significant problem with biological therapeutics. EMEA has issued draft guidelines on the topic (Part 1, **Table 2**), and regulatory considerations on immunogenicity have recently been published.[16,17]

Glycosylation Issues

The currently approved mAbs are produced by mammalian cell lines[4] that secrete mAbs with glycosylation structures that are similar, but not identical, to their human counterparts. Cetuximab, a chimeric mouse-human IgG1 monoclonal antibody targeting EGFR, is approved for use in the EU and US as a treatment for colorectal cancer and squamous cell carcinoma of the head and neck. A high prevalence of hypersensitivity reactions to cetuximab has been reported in some areas of the US. Among 76 cetuximab-treated subjects, 25 had a hypersensitivity reaction to the drug. The IgE antibodies were shown

to be specific for an oligosaccharide, galactose-α-1,3-galactose, that is present on the Fab portion of the cetuximab heavy chain when the molecule is produced in the murine SP2/0 cell line used for commercial manufacturing, but not in the CHO cells used as control. The mechanism underlying a hypersensitivity reaction to cetuximab involves pre-existing IgE antibodies that target an oligosaccharide present on the recombinant molecule produced in the SP2/0 cell line.

These results have implications for evaluating risks associated with antibody-based therapeutics and for understanding the relevance of IgE antibodies specific for post-translational modifications of natural and recombinant molecules.[18] The second N-glycosylation site in the Fab portion on heavy chain Asn^{88} of cetuximab is of prime importance. For the marketed version of cetuximab produced in SP2/0 cells, 21 different glycoforms were recently identified with around 30% capped by at least one alpha-1,3-galactose residue, 12% capped by a N-glycolylneuraminic acid (NGNA) residue, and traces of oligomannose. Importantly, both alpha-1,3-galactose and NGNA were found only in the Fab moieties, rather than the Fc fragment for which only typical IgGs G0F, G1F and G2F glycoforms were identified. In a recent report on cetuximab-induced anaphylaxis, pre-existing IgEs specific for this alpha-1,3-galactose epitope were detected in patients treated with cetuximab. Using a solid phase immunoassay (ImmunoCAP), these IgEs were found to bind to SP2/0 produced cetuximab and $F(ab')^2$ fragment, but not to the Fc fragment. Interestingly, no IgE immunoreactivity was found against a CHO-produced version of cetuximab (CHO-C225).

Glycosylation of mAbs also influences their interaction with immune effector cells that kill antibody-targeted cells. Human antibodies with specific human N-glycan structures have been produced in yeast, and antibody-mediated effector functions have been optimized by generating specific glycoforms. The glycoengineered yeast *Pichia pastoris* provides a general platform for producing recombinant antibodies with human N-glycosylation.[19] Humanization of glycosylation in heterologous expression systems also allows effector function enhancement. Major advances in yeast glycoengineering were achieved to produce fully humanized sialylated glycoproteins. Yeast strains have also been engineered to produce anti-CD20 antibodies with unique glycan structures for each antibody, although these cannot be considered biosimilars.

International Non-Proprietary Names (INN)

As the biopharmaceutical and regulatory community has recognized, the introduction of biosimilars into medical practice presents specific challenges that are not ordinarily presented by small-molecule generic therapeutics. This is because a biosimilar product is similar, but not identical, to its reference product. Differences in starting materials, manufacturing processes and other characteristics mean that biosimilars, as well as other biological products, may have attributes that cannot be detected through pre-market testing, e.g., rare adverse events (especially immunologically mediated events), or medically significant increases in such events. It is therefore necessary to consider what special post-market requirements should be imposed to facilitate detection of such events. Modification of the WHO INN system to ensure that INNs for biotechnology products indicate the manufacturer of the product would help ensure that inappropriate substitution does not take place, and that prescribing and pharmacy records identify the actual manufacturer of the product that each patient receives.

Conclusion

EMEA is very pro-active concerning regulation of biosimilars, as illustrated by the recent approvals of biosimilar products, the publication of concept papers[2] and guidelines, and the organization of the workshop on the feasibility of biosimilar mAbs. The format of the workshop included open discussion on the pros and cons of biosimilar mAbs development, as well as the feasibility. No definitive conclusions were reached or expected, although the discussions might help clarify the path ahead in the EU, and perhaps also in the United States and other countries.

References

1. Schneider CK, Schäffner-Dallmann G. Typical pitfalls in applications for marketing authorization of biotechnological products in Europe. Nat Rev Drug Discov 2008; 7:893-9.
2. Schneider CK, Kalinke U. Toward biosimilar monocolonal antibodies. Nat Biotechnol 2008; 26:985-90.
3. Lanthier M, Behrman R, Nardinelli C. Economic issues with follow-on protein products. Nat Rev Drug Discov 2008; 7:733-7.
4. Beck A, Wagner-Rousset E, Bussat MC, Lokteff M, Klinguer-Hamour C, Haeuw JF, et al. Trends in glycosylation, glycoanalysis and glycoengineering of therapeutic antibodies and Fc-fusion proteins. Curr Pharm Biotechnol 2008; 9:482-501.
5. Hughes B. Gearing up for follow-on biologics. Nat Rev Drug Discov 2009; 8:181.
6. McCabe KW. Guardians at the gate: Patent protection for therapeutic monoclonal antibodies (Part 1). mAbs 2009; 1:382-4.
7. Holliday L. Patenting antibodies in Europe. mAbs 2009; 1:385-6.
8. Chartrain M, Chu L. Development and production of commercial therapeutic monoclonal antibodies in Mammalian cell expression systems: an overview of the current upstream technologies. Curr Pharm Biotechnol 2008; 9:447-67.
9. Reichert JM. Monoclonal antibodies as innovative therapeutics. Curr Pharm Biotechnol 2008; 9:423-30.
10. Beck A, Wurch T, Corvaïa N. Therapeutic antibodies and derivatives: from the bench to the clinic. Curr Pharm Biotechnol 2008; 9:421-2.
11. Beck A, Bussat MC, Zorn N, Robillard V, Klinguer-Hamour C, Chenu S, et al. Characterization by liquid chromatography combined with mass spectrometry of monoclonal anti-IGF-1 receptor antibodies produced in CHO and NS0 cells. J Chromatogr B Analyt Technol Biomed Life Sci 2005; 819:203-18.
12. Atmanene C, Wagner-Rousset E, Malissard M, Chol B, Robert A, Corvaïa N, et al. Extending Mass Spectrometry Contribution to Therapeutic Monoclonal Antibody Lead Optimization: Characterization of Immune Complexes Using Noncovalent ESI-MS. Anal Chem 2009; 81:6364-73.
13. Wagner-Rousset E, Bednarczyk A, Bussat MC, Colas O, Corvaïa N, Schaeffer C, et al. The way forward, enhanced characterization of therapeutic antibody glycosylation: comparison of three level mass spectrometry-based strategies. J Chromatogr B Analyt Technol Biomed Life Sci 2008; 872:23-37.
14. Vlasak J, Bussat MC, Wang S, Wagner-Rousset E, Schaefer M, Klinguer-Hamour C, et al. Identification and characterization of asparagine deamidation in the light chain CDR1 of a humanized IgG1 antibody. Anal Biochem 2009; 392:145-54.
15. Schneider CK. Monoclonal antibodies—regulatory challenges. Curr Pharm Biotechnol 2008; 9:431-8.
16. Schneider CK, Papaluca M, Kurki P. A European perspective on immunogenicity evaluation. Nat Biotechnol 2009; 27:507-8.
17. Jahn EM, Schneider CK. How to systematically evaluate immunogenicity of therapeutic proteins—regulatory considerations. N Biotechnol 2009; 25:280-6.
18. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 2008; 358:1109-17.
19. Li H, Sethuraman N, Stadheim TA, Zha D, Prinz B, Ballew N, et al. Optimization of humanized IgGs in glycoengineered *Pichia pastoris*. Nat Biotechnol 2006; 24:210-5.

Part 3: EMEA Workshop on Biosimilar Monoclonal Antibodies: Perspective from India

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The marketing of biosimilar antibodies is of seminal importance to healthcare worldwide because it enables access to best-in-class drugs for patients, and increases drug affordability. The recently concluded European Medicines Agency (EMEA) workshop on biosimilar monoclonal antibodies (mAbs) held in London on July 2, 2009 represents a very helpful step in providing impetus for all stakeholders to establish a regulatory framework that will allow these products to enter the marketplace sooner rather than later. This workshop provided a forum where regulators, the innovator and generics industries, and other interested parties could articulate their perspectives on three areas pertaining to biosimilar mAb development: quality, preclinical and clinical development. One of the key goals of the workshop was to determine opinions on the "level of biosimilarity" required for biosimilar mAbs, and to determine if additional guidelines should be framed for guidance on an approval pathway for biosimilar mAbs. In Part 3 of this workshop report, a perspective from India on this very important initiative is presented.

Background

The concept of biosimilars has been well-accepted in India over the last several years. The development path has been clearly laid out, with responsibilities shared between the Review Committee on Genetic Manipulation (RCGM; Department of Biotechnology) and the Drugs Controller General of India (DCGI), which is the Indian equivalent of the US Food and Drug Administration or EMEA at the Ministry of Health. The regulatory pathway for biosimilar drug development in India typically starts with permission from regulators to either develop a recombinant clone or, if a clone is imported, to perform toxicology studies. In order to obtain permission, a sponsor has to show consistency and comparability of manufacture of five batches to the RCGM. In addition to the data on multiple batches, a preclinical protocol is also submitted in accordance with the rules of Schedule Y.[1] As per these rules, preclinical toxicity study protocols for biosimilars (comparative at least at therapeutic Human Equivalent Dose) are typically to be done in two species (rodent and non-rodent). The species required and duration of these preclinical studies is specified in the Department's guidelines, but can be discussed and agreed upon through a case-by-case approach with the RCGM committee. Once preclinical studies are completed, the sponsor applies to the DCGI to conduct clinical trials (typically a non-inferiority study). Applications are accepted based on previously established laws.[2] Approvals are based on the acceptability of the study design endpoints and statistical analysis of data, as well as safety considerations.

Numerous biosimilars have been approved in India over the last several years using the approach outlined above (**Table 1**),[3] although only one of these is an antibody. However, mAbs represent a very critical segment of recombinant biologics that might be approved in the future because there are several in development in India (**Table 1**).[4] Other than India, it is likely that this industry will grow in key Asian economies such as China (**Table 2**),[5-8] Korea,[9] and other countries such as Singapore[10] and Japan.[11,12]

Public Health Perspective

mAbs represent a class of advanced, but very expensive, medicines that often cost US $25–100 k per year in drug-related costs. Prescription drugs are 10% of a rapidly increasing portion of healthcare even in high-gross domestic product (GDP) countries such as the United States.[13] With healthcare costs representing more than 16% of total GDP in the US, lowering the cost of medicine is a critical economic and public health priority. Similar considerations are relevant under the current conditions in many European countries.

From an Indian public health perspective, the current annual spending on drugs is estimated to be approximately $4 bn[14] of total healthcare cost of $24 bn. Biologics, with costs at approximately $300 mn, represent a small portion of this, but these costs are expected to top $3 bn because healthcare spending is likely to go up as a consequence of increases in both life expectancy and per capita income. Early acceptance of biosimilar antibodies will be essential to contain high healthcare costs, and is likely to be driven by a much-expanded insurance industry. In this scenario, India will play a critical role as a key, emerging hub for biosimilars in the world.

The Indian regulators have been proactive in evaluating biosimilars and India was among the first regions to approve both peptide hormones such as insulin, and more complex molecules such as rituximab. Regulators in China have also been quick to approve such biosimilar products.[5,6] Key criteria to approving such biosimilars should continue to include quality, safety and efficacy. Decisions should be informed by good scientific judgment and include an evaluation of the risk of an abbreviated approval pathway compared to the expected benefit to an increased patient population.

Among the first biosimilars to be approved in India was recombinant human insulin. The price of biosimilar insulin in India is approximately 50–60% of a comparable innovator product in India. The India biosimilar prices are themselves significantly lower and often only 20% of that in either the US or Europe. A similar pricing differential exists for biosimilar antibodies as well, although the cost of a dose of biosimilar rituximab being ~50% of the cost of the innovator's product. These differences are not as large as those seen for small molecule drugs. However, approval of biosimilar therapeutics has increased access to such products, and further competition is expected to bring down the price of medicine in countries like India.

Table 1. Biosimilar products approved or under development in India

Approved	Under development
Insulin	Interferons
Granulocyte Colony Stimulating Factor (GCSF)	Pegylated-GCSF
Erythrpoietin	Follicle Stimulating Hormone
Interferons	Insulin Aspart
Insulin Glargine	Bevacizumab
Rituximab	Etanercept
Pegylated Interferon	Trastuzumab
Recombinant Streptokinase	Human Growth Hormone
Tissue Plasminogen Activator	
Pegylated GCSF	
Human Growth Hormone	

Table 2. Biosimilar antibodies and fusion proteins approved or under development in China[5]

Approved	Under development
Muromonab	Daclizumab
Etanercept	Rituximab
	Trastuzumab
	Infliximab
	Abatacept
	Cetuximab
	Basiliximab
	Teplizumab

Chemistry, Manufacturing and Controls

The Indian regulatory system does not have chemistry, manufacturing and controls (CMC) guidelines specifically for biosimilar products, and relies on a case-by-case discussion between industry and regulators to evaluate the extent of research and development carried out. For most approved biosimilars, CMC requirements included demonstration of consistency in manufacturing, with full characterization to demonstrate physicochemical and biological consistency between the biosimilar and reference product. The RCGM requires that companies submit data from a minimum of five batches to demonstrate such consistency. For molecules such as antibodies, the CMC part of the submission package is typically very exhaustive, and includes results of a variety of physicochemical and biological characterization methods. The comparisons are done against the reference product either sourced in India or in one of the highly regulated markets such as Europe or the US.

For physicochemical characterization of polypeptides, state-of-the-art techniques are typically used.[15,16] These include methods that are able to identify primary, secondary and tertiary structures of the product, as well as aggregates, variants or fragments present in the drug product. Such techniques include:

(1) Size exclusion chromatography-high performance liquid chromatography (HPLC), used to assess physical state;

(2) Ion-exchange—HPLC, used to assess ionic variants;

(3) Reverse phase (RP)-HPLC, used to assess chains;

(4) Mass spectrometry (MS), used to provide data for the intact molecule, individual chains, disulfide bond pattern, and N-terminal variants, as well as MS/MS used for full sequencing;

(5) Isoelectric focusing (IEF) and capillary IEF;

(6) SDS-PAGE or CE-SDS;

(7) Tryptic mapping using RP-HPLC methods;

(8) Normal phase-HPLC used for glycan analysis;

(9) Circular dichroism spectroscopy, used to determine structure;

(10) Nuclear magnetic resonance (if applicable), used to determine structure.

Many of these techniques are exquisitely sensitive tools, and over the last decade have become very powerful in creating molecular fingerprints of complex peptide and mAb-related glycosylation structures. During an antibody biosimilarity exercise, the differences that are most often observed in such analyses are typically either N- or C-terminal variants, which are caused typically by carboxypeptidases in cell culture[17] or glycoform variation caused by mAb production in different expression systems (reviewed in ref. 18). C-terminal variants often do not cause an impact on biological activity,[19,20] and the effect of minor differences between the biosimilar and reference product should be considered on a case-by-case basis. The impact of glycoform variation and the appropriate specification needs to be assessed on case-to-case basis.[21,22]

Methods to characterize biological activity are determined on a case-by-case basis. Ligands are used for biosimilars targeted against soluble targets, cell lines are used for cell-based targets, or activity assays are used, e.g., complement-dependent cytotoxicity (CDC) or antibody dependent cellular cytotoxicity (ADCC). The methods used include:

(1) Immuno-recognition methods

(a) ELISA against soluble ligand

(b) Flow cytometry—recognition of cell-based targets

(c) On-rate and off-rate measurements (e.g., using radioisotopic methods or Surface Plasmon Resonance methods)

(2) Activity methods

(a) Inhibition of proliferation

(b) Cytoxicity (CDC, ADCC)

(c) Neutralization of ligand binding.

Preclinical Issues

From the perspective of India, one key preclinical issue is the lack of local access to monkey models for toxicology studies. The data used to support approval for first-in-human studies are typically derived from non-specific, non-comparative, off-target studies in rodent and non-rodent models. The underlying assumption is that adequate physicochemical and bioactivity characterization allows a sufficient understanding of activity and structure, and the key concerns may be only in off-target toxicology. Powering such toxicology studies with a comparator arm is certainly a considerable challenge for biosimilar drug development. Toxicology studies with monkey models are typically done outside the country for novel antibodies that are in development.[23]

Critical attribute studies done in preclinical models include assessment of the immunogenicity of the drug.[24] Most human biological drugs are expected to elicit immunogenic responses in animals, but an evaluation of these responses is not helpful in predicting human responses. The immune responses are categorized by the class of antibody response, and whether the antibodies generated neutralize mAb function or not. These effects are significant only if there are changes observed in toxicokinetics over the duration of the preclinical study.

Clinical: Safety and Efficacy Issues

In India, first-in-human studies for biosimilar products have typically included a comparison to control non-biologic therapies, or they have been non-inferiority studies done with locally-sourced reference drug. From a safety perspective, other than expected adverse reactions based on the pharmacology of the drug, the most important criterion for biologics is determination of immunogenicity in humans. Immunogenicity is typically determined in longer term studies in humans. There is considerable variation in the immunogenic response depending on the source of antibody (e.g., murine, chimeric, human mAbs), route of administration (e.g., subcutaneous, intravenous) or, surprisingly, the indication (e.g., oncology, autoimmune). Again, such studies are very expensive to perform, and, after early readouts in shorter studies, additional data should be collected in a post-approval setting.

For efficacy, biosimilar antibodies are expected to be evaluated in non-comparative Phase 3 studies with activity endpoints in the most sensitive model. If required, part of the efficacy studies should be devoted to determining comparative pharmacokinetics (PK), and, if applicable, pharmacodynamics of the drug. PK studies in relevant animal models might substitute for the requirement for human PK studies, as is often the case with changes in late-stage clinical studies for innovators.[25] For the demonstration of comparability, additional longer term studies should be powered either against historical controls or, if acceptable to ethics committees, against small molecule therapy. Use of a control arm with reference product can often be prohibitively expensive and add very little value because of difficulty with powering.

Extrapolation Across Indications

It is important that once adequate characterization has been performed on a biosimilar mAb, and appropriate toxicology studies and clinical testing in the most relevant or sensitive indication has been performed, mAbs should be approved across all indications. The same mAb should be approvable across indications as long as it has demonstrated similar biological activity across a panel of relevant assays. This extrapolation across indications can be justified primarily through the previous regulatory experience with the reference mAbs applied in multiple indications after initial approval was obtained. Such regulations are also likely to have a commercial impact on sustaining growth in the biosimilar sector.

Discussion

The role of advanced, complex biological medicines in public health is critical to improve the quality of life and longevity of patients. It is critical that more patients, even those in developing countries such as India, have access to such advanced medicines. The EU and US are critical bellwether territories that regulators in other countries look to for guidance on issues such as biosimilar antibody development. For benefits from the development of biosimilar antibodies to reach a broader population, irrelevant studies should not be required as these are barriers to development. It is well-understood that early physicochemical and biological characterization represents the best assessment of biosimilarity. It is also well-known even in the innovator industry that significant changes in process, including sometimes the cell line itself,[25] occur during the clinical development phase. In these cases, innovators often assess comparability through relatively small bridging studies, typically repeat-dose toxicology and PK studies, before moving on to Phase 3. These same approaches should be available to the biosimilar industry to expedite approval, and encourage the growth of competition in this key space.

Biosimilar mAb development is still at an early phase, as evidenced by the fact that only one molecule has gained marketing approval in India. However, biosimilar products from India have been approved in various parts of the world, including Latin America, Middle East and Southeast Asia. It is only a matter of time before the first biosimilar from India gets approval in highly regulated markets. As an important segment of biosimilars, it is expected that mAbs from India will also be approved in the rest of the world, including regions such as the US, Europe and Japan.[26] Therefore, there is a great deal of interest in the manner in which regulations will be framed in territories such as the EU. It is expected that regulations from EMEA will have an impact on the biopharmaceutical industry in India and other parts of Asia. It is critical that the guidelines are framed appropriately to provide benefits to patients, including access to the most advanced therapy at an affordable price and improvement in quality of life, while ensuring patient safety.

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References

1. Guidelines for generating preclinical and clinical data for r-DNA based vaccines, diagnostics and other biological. http://dbtindia.nic.in/pol_ggp2.htm.
2. The Drugs and Cosmetics Act, 1940 (23 of 1940) and The Drugs and Cosmetics Rules, 1945 (as amended up to the 30th June, 2005) http://www.cdsco.nic.in/.
3. Mody R, Goradia V, Gupta D. How similar are Biosimilars in India? Pharma Focus—Asia 2009; 11.
4. Indian GMO Research Information System. http://igmoris.nic.in/.
5. Guo Y. Large Scale Production of Therapeutic Antibodies in China: From Research to Market, presented at the Asia Antibody Congress, Singapore 2008.
6. Langer E. Biogenerics in China: an evolving industry. BioPharm International June 2007. http://www.bioplanassociates.com/publications/articles/Biopharm_Biogenerics_Jun07.pdf.
7. Che J, Wang H, Chen Z, Li X, Hou Y, Shan C, et al. A new approach for pharmacokinetics of single-dose cetuximab in rhesus monkeys by surface plasmon resonance biosensor. J Pharm Biomed Anal 2009; 50:183-8.
8. Kudrin A. Challenges in the clinical development requirements for the marketing authorization of new medicines in Southeast Asia. J Clin Pharmacol 2009; 49:268-80.
9. Moon J-Y, Kim W, Kim JH, Ahn A, Jeong MH, Kim Y-H, et al. A multicenter, randomized, open-label, therapeutic, and exploratory trial to evaluate the tolerability and efficacy of platelet glycoprotein Iib/IIIa receptor blocker (Clonib™) in high-risk patients with percutaneous coronary intervention. Yonsei Med J 2008; 49:389-99.
10. Health Sciences Authority. Guidance on Registration of Similar Biological Products in Singapore (draft). Singapore 2009; http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html.
11. Sandoz receives approval for first ever Japanese biosimilar. http://www.novartis.com/newsroom/media-releases/en/2009/1324821.shtml.
12. Horikawa H, Tsubouchi M, Kawakami K. Industry views of biosimilar development in Japan. Health Policy 2009; 91:189-94.
13. The Henry J. Kaiser Family Foundation. U.S. Healthcare costs. http://www.kaiseredu.org/topics_im.asp?imID = 1&parentID = 61&id = 358.
14. Ghoshal S. Finances for your health. Business India 2009.
15. Adhikary L. Characterisation and comparability of a biosimilar recombinant peptide—a case study of recombinant human insulin. Comparability for Biologics 2009 conference, Cologne 2009.
16. Iyer H, Akundi S, Suryanarayan S, Chandavarkar A. Insulin and GCSF as biosimilars. FDA Symposium: Follow-on Biologics: The Challenge of Establishing Comparability. American Chemical Society meeting, San Francisco 2006.
17. Dick LW Jr, Qiu D, Mahon D, Adamo M, Cheng K-C. C-terminal lysine variants in fully human monoclonal antibodies: Investigation of test methods and possible causes. Biotechnol Biotechnol Bioeng 2008; 100:1132-43.
18. Raju TS. Glycosylation variations with expression systems and their impact on biological activity of therapeutic immunoglobulins. BioProcess International 2003; 44-53.
19. US Food and Drug Administration. Blood Product Advisory Committee meeting notes 2005; 119:123.
20. Biocon, unpublished data.
21. Mostafa SS, Bioprocess 2009 Online Educational Series, Process Development, Characterization, Large Scale Production, and Quality Control of Follow-on Biologics.
22. Visser J. Biosimilar development: a pioneer's perspective, OBP, Belgium 2008; http://www.bio-events.com/presentations/Jan%20Visser.pdf.
23. Biocon's discovery pipeline. http://www.biocon.com/biocon_research_pipeline.asp.
24. Bussiere JL. Prediction of immunogenicity Peer Review Perspectives, in Experimental and Clinical Immunotoxicology 2005.
25. Scharf M. Analytical comparability of a human IgG1 after cell line switches and process changes: A case study. Comparability for Biologics 2009 conference, Cologne 2009.
26. Biocon Ties Up With Mylan For Generic Biopharma Drugs. The Wall Street Journal 2009; http://online.wsj.com/article/BT-CO-20090629-703234.html.

Part 4: EMEA Workshop on Biosimilar Monoclonal Antibodies: Perspective from the US

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As described in Parts 1 and 2 of this article, defining a regulatory pathway for biosimilar products in the EU was a necessary step in getting these less costly medicines on the market. However, the US Food and Drug Administration (FDA) is well behind the European Medicines Agency (EMEA) in defining pathways for biosimilar development because legislation addressing legal aspects has not yet been passed by the US Congress. FDA's authority to approve generic drugs extends only to medicines approved under the Federal Food, Drug and Cosmetic (FFDC) Act.[1,2] A few protein therapeutics are included in this group (e.g., insulin, human growth hormone, calcitonin),[3] and biosimilar versions of these products have been approved by FDA (see Part 1, **Table 1**). The legal pathway for these approvals is found in Section 505(b)(2) of the FFDC Act as modified in 1984 by the Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Amendments). According to FDA, "Section 505(b)(2) permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product".[4] Small molecule generic drugs are considered 'duplicate' products, and a separate pathway for approval, 505(b)(j), was created by the Hatch-Waxman Amendments for these molecules.

The current legal dilemma for biosimilar product developers exists because, for historical reasons, most biologic products marketed in the US have been approved under the Public Health Service (PHS) Act, which has no pathway similar to that described in Section 505(b)(2) of the amended FFDC Act. With the exception of gemtuzumab ozogamicin (Mylotarg), mAbs marketed in the US were approved under the PHS Act, and so biosimilar versions cannot be approved by FDA. Debate on the relative merits of proposed legislation to correct the problem is on-going.[5] Currently, the primary point of contention is the length of the data exclusivity period, which is defined as the period between the reference product's FDA approval date and the date when a biosimilar could be approved based in part on the reference product's safety and efficacy data.[6] The Hatch-Waxman Amendments provide a 5-year data exclusivity period.

Proposed legislation that would affect biosimilar development includes H.R. 1427, the "Promoting Innovation and Access to Life-Saving Medicine Act" sponsored by Representative Henry Waxman and colleagues; H.R. 1548, the "Pathway for Biosimilars Act" sponsored by Representative Anna Eshoo and colleagues; and S. 1695, the "Biologics Price Competition and Innovation Act" sponsored by Senator Edward Kennedy and colleagues. H.R. 1427 also has a companion bill of the same name in the Senate (S. 726) that is sponsored by Senator Charles Schumer and colleagues. The bills offer periods of data exclusivity that range from 5–12 years with the possibility of extensions. The Federal Trade Commission has suggested that a 12–14 year exclusivity period is unnecessary to promote innovation,[7] and the Obama administration has included a seven year policy in the fiscal year 2010 budget.[8] However, the Senate Health, Education, Labor and Pensions Committee voted in July 2009 to include an amendment with a 12-year data exclusivity period for biosimilar products in the "Affordable Health Choices Act", which is an over-arching healthcare reform bill. It remains to be seen whether any of the bills will actually become law; further work on legislation was delayed until September 2009.

A key consideration is that the data exclusivity period is independent of patent protection. Patents for therapeutics are often filed prior to the lengthy clinical development and regulatory review phase, but innovators do not receive a return on their investment until products are approved and available for purchase. In some cases, the patent life remaining after the approval date might not allow sufficient time for the innovator to recoup investment costs prior to the introduction of a generic version. Data exclusivity and patents thus provide complementary forms of intellectual property protection. These protections are also afforded in the EU, where the period of data exclusivity is ten years for biotechnology-derived products. For biosimilars that reference products with marketing applications submitted prior to late 2005, the period is extend by the time needed to review and approve the biosimilar product.[9] In the case of biosimilars that reference products with marketing applications submitted after late 2005, there is an eight-year data exclusivity period when a marketing application for a biosimilar cannot be submitted, followed by a two-year period of market exclusivity.

The ongoing debate about expanding biosimilar product approvals in the US has centered primarily on questions concerning the safety and efficacy of the products; the percentage reduction in drug prices, which could be affected by the number of biosimilars entering the market and whether the biosimilars were deemed interchangeable with the innovator products; and the effects of biosimilars on incentives to invest in innovative medicinal product research and development.[7,10] However, while the US has been discussing questions, other countries have been generating answers. Regulatory pathways with provisions addressing safety and efficacy have been used to gain marketing approval for biosimilar products, including proteins with complex glycosylation, in the EU as well as other countries. Where approved, biosimilars have been marketed at a lower price compared to innovator products, resulting in at least some savings to health care systems.[7]

To date, few varieties of biosimilars have been approved, and most products were approved only recently (see Part 1, **Table 1**), and so the effect on incentives to produce innovative products cannot be assessed yet. However, the Hatch-Waxman amendments of 1984 were designed to strike a balance between promoting innovation and providing rapid market entry to lower-cost generic products. In the following 25 years, the pharmaceutical and biotechnology industries in the US have generally prospered, and the number of new chemical entities approved by FDA each year has generally remained in the range of 15–30 products

(disregarding the high number of approvals in 1996 and 1997 resulting from provisions of the Prescription Drug User Fee Act of 1992).[11]

One example of the growth and creativity of the biopharmaceutical industry is the rapid expansion of antibody therapeutics available to patients in the US. While there were no marketed mAbs in 1984, and only two by the end of 1996, there were 23 mAbs on the market as of mid-2009, with an additional six undergoing FDA review. Despite the potential new competition, innovator companies will undoubtedly continue to do well by exploiting advances in science, technology and medicine.

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References

1. Dudzinski DM. Reflections on historical, scientific and legal issues relevant to designing approval pathways for generic versions of recombinant protein-based therapeutics and monoclonal antibodies. Food Drug Law J 2005; 60:143-260.
2. Dudzinski DM, Kesselheim AS. Scientific and legal viability of follow-on protein drugs. N Engl J Med 2008; 358:843-9.
3. Woodcock J, Griffin J, Behrman R, Cherney B, Crescenzi T, Fraser B, et al. The FDA's assessment of follow-on protein products: a historical perspective. Nat Rev Drug Discov 2007; 6:437-42.
4. Food and Drug Administration. Guidance for industry: applications covered by section 505(b)(2). Draft guidance 1999; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf.
5. McCabe KW. Guardians at the gate (part 2): Biosimilar and patent reform legislation could fundamentally change the guards for therapeutic monoclonal antibodies. mAbs 2009; 1:415-9.
6. Grabowski H. Follow-on biologics: data exclusivity and the balance between innovation and competition. Nat Rev Drug Discov 2008; 7:479-88.
7. Wroblewski MS, Jex EA, Drennon S, Garmon CJ, Michel ST, Wantman A, et al. Emerging Health Care Issues: Follow-on Biologic Drug Development. Federal Trade Commission Report, 2009; http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.
8. DeParle NA, Orszag P. Letter to Henry A. Waxman 2009; http://www.thepinksheet.com/nr/FDC/SupportingDocs/Pink/2009/Obama_Admin_Reply_to_Waxman_on_FOBs.pdf.
9. Bogaert P. How ill is the European pharmaceutical industry? Scrip 2009; 3437:16-7.
10. Schacht WH, Thomas JR. Follow-on biologics: intellectual property and innovation issues. Congressional Research Service Report to Congress 2008; http://www.biosimilars.com/crs_fobs.pdf.
11. Tufts Center for the Study of Drug Development. Biotechnology trends. Outlook 2007; 4. http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2007.pdf.