



PRAHEALTHSCIENCES

Welcome

Welcome to the seventh edition of Biosimilars Newsletter, a quarterly publication dedicated to keeping you updated on current biosimilars news, including the global regulatory landscape, biosimilars articles and reports, and company news as reported via press releases.

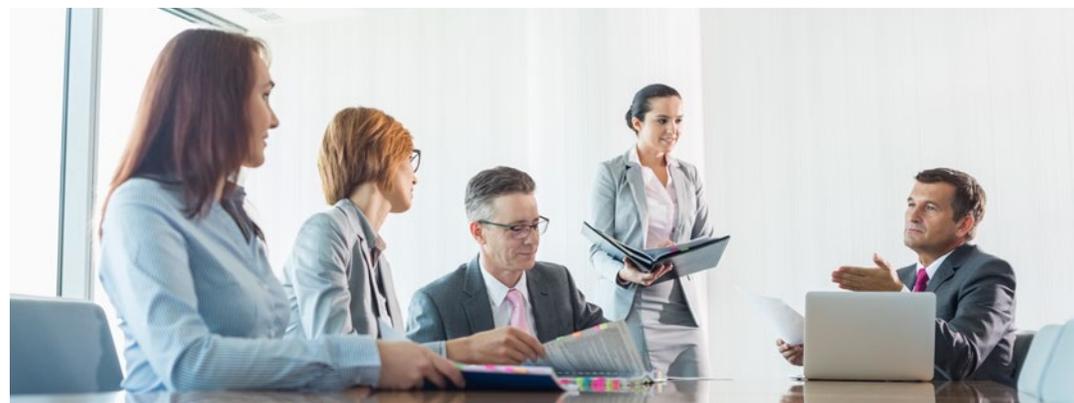
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HOT TOPIC

Scientific Advice in Europe: Roadmap for Product Development Success

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In the second half of the 20th century, rapid progress was made in developing powerful new medicines. More recently, developments in molecular biology and genetics hold great promise for the discovery of new treatments, yet the number of new molecular entities being brought to market has slowed in recent years^{1,2}. The conversion from new discoveries into marketed innovative therapies remains a challenge. Multiple factors contribute to this, including the development of more complex drugs (ie, biologics, advanced therapies) and the

high regulatory demands which are subject to continuous revisions.

The European Medicines Agency (EMA), through its Scientific Advice Working Party (SAWP), has been providing scientific advice (SA) to companies since 1996 to help them develop products and design trials that are scientifically sound and generate adequate data for assessment by the Regulators. SA helps the company to make sure that it performs the appropriate tests and studies, so that no major objections are likely

to be raised during evaluation of the Marketing Authorization Application (MAA). Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal. Following the Agency's advice increases the probability of a positive outcome. The advice can be requested on all aspects of drug development, including quality/Chemistry, Manufacturing, and Controls (CMC), non-clinical and/or clinical issues, either during initial product development, at later stages, and after new data is available.

In a recent publication the EMA commented that adherence to recommendations on trial design results in higher success rates, fewer major objections, and shorter overall assessment time. This conclusion has been drawn from an analysis of MAA outcomes between 2008 and 2012³. During this period, the EMA received 232 MAAs and 143 SA requests. Detailed analysis of MAAs received by the EMA that had an opinion between 2008 and 2012, and of the advice provided to these applicants, shows that:

- 1 out of 3 programs submitted for SA had poor clinical trial designs that were inadequate to generate data for the benefits-risk assessment;
- an acceptable trial design at the time of SA, or a change of a deficient trial design to conform with recommendations, increased the likelihood of a positive outcome with success rates of 84% and 86% respectively, compared with only 41% when a deficient clinical trial design was not adapted;
- compliance with advice on trial design was associated with a reduction in major objections raised during the assessment of the MAA, and on average a 61-day shorter assessment procedure.

A number of medicines fail to obtain a Marketing Authorization (MA) due to deficiencies in the trial design and the inability to demonstrate that the benefits of the medicine outweigh its risks. The outcome of this report supports the importance of advice procedures for future MAAs as an opportunity to initiate a scientific dialogue with the Regulators on all aspects of the development.

In a former analysis of MAAs submitted to the EMA, with an outcome between September 1997 and May 2001, failure to establish clinical efficacy due to lack of adequate randomized controlled trials was the most important predictor of negative MAA outcome⁴. There is evidence that some failures could have been prevented by close communication between applicants and Regulators, and better compliance with the advice obtained.

Routes for Advice in the EU

When considering the request for advice the following key aspects should be taken into account:

- SA is prospective; it focuses on development strategies rather than pre-evaluation of data.
- Advice received is not legally binding on the Agency or the sponsor.
- Provision of advice does not guarantee companies a MA.
- The assessment of the data generated through a company's development program is independent from SA.
- A positive recommendation on a MA is based on a concluding assessment and an overall positive benefit-risk profile.

The detailed analysis of MAA outcomes between 2008 and 2012 clearly demonstrates a greater success rate if the company complies with the advice received. This applies especially for choice of primary endpoint, selection of control, and statistical methods. To meet the requirements of increasing complexities in drug development, various types of advice processes have been established.

a) National or Centralized Scientific Advice

For National SA, the legal basis is according to national legislation, whereas centralized advice provided by EMA/SAWP/Committee for Medicinal Products for Human Use (CHMP) is based on Article 57 (1) of Regulation

(EC) 726/2004. The EMA, acting through its committees, provides advice on the conduct of the various tests and trials necessary to demonstrate quality, safety, and efficacy of medicinal products. National SA can serve as a filter for the centralized advice process in order to fine-tune questions to the level of detail that require a pan-European evaluation, and to enable tight timelines for centralized advice not being hampered by unnecessary questions.

b) Protocol Assistance

Protocol assistance is the special form of advice available for products with an orphan drug designation. In addition to SA, companies developing orphan drugs can ask questions relating to the criteria for authorization of an orphan medicine. These include:

- The demonstration of significant benefit within the scope of the orphan indication.
- Similarity or clinical superiority over other medicines. This is relevant if other orphan drugs exist that might be similar to the product concerned and have market exclusivity in the same indication.

c) Parallel Scientific Advice with the Food & Drug Administration

Since 2005, it has been possible to obtain parallel scientific advice (PSA) with the United States Food and Drug Administration (FDA) and EMA. Requests should ideally coincide with an End-of-Phase 2 or pre-IND meeting with the FDA. Questions are submitted to both Agencies and advice representing the outcome of joint scientific deliberations from the Agencies is received. The Agencies confer prior to meeting with the sponsor. Separate written responses are provided by each Agency at the conclusion of the PSA.

The expected advantages from PSA are increased dialogue between the 2 Agencies and sponsors from the beginning of the new product development, a deeper understanding of the basis of regulatory decisions, and the opportunity to optimize product development, and avoid unnecessary testing replication or diverse testing methodologies.

d) Parallel Scientific Advice with Health Technology Assessment Bodies

The EMA has been working closely with health technology assessment (HTA) bodies since 2008. HTA bodies provide recommendations related to reimbursement by the healthcare system payers in a particular country. Recently, their influence has strengthened due to increased pressure on healthcare budgets. HTA bodies carry out their own assessments of medicines once an MA is approved. HTA bodies compare the relative effectiveness of medicines, in order to assess their usefulness and cost-effectiveness to the healthcare system in their territory. An EMA/HTA pilot project PSA has resulted in a series of improvements to the European Public Assessment Report (EPAR) template. It is the choice of the applicant which HTA bodies to select and approach. There is no obligation for invited HTA bodies to participate in a specific procedure.

e) Pre-submission Meeting

The pre-submission meeting relates to the preparatory steps in advance of submitting a request for MAA. Successful pre-submission meetings should enable applicants to submit applications, which are in conformity with the legal and regulatory requirements, and which can be smoothly evaluated.

For all advice procedures, transparency is the most important rule, ie, if national/central advice has been sought the outcome must be shared in future applications. It is important to check all available guidelines first before issuing the list of questions for SA. The only aspects which are not covered within the guidelines are a suitable subject for questions. The Agency will only respond to the list of questions, it is not the aim of advice to generate the overall product development plan. Questions like "any further recommendation for

toxicology testing?" are not appropriate. To get the best out of the advice procedure, the briefing document must support the list of questions, provide full and accurate documentation, and reflect state of the art development.

While the EMA collects fees for SA, they offer reduced fees to certain products, including orphan drugs, advanced therapeutic medicinal products (ATMPs) and products with a pediatric investigation plan (PIP) in place. Additionally, small- and medium-sized enterprises (SMEs) qualify for reduced fees through the SME office. The Agency believes that providing these incentives and fee reductions can support the development of innovative new products.

The Deerfield Institute-EuropaBio Report on regulatory and HTA body SA for SMEs also concludes that early engagement with Regulators and HTA bodies to be beneficial for SMEs, but that the path to engagement is not always clear⁹. The companies participating in the survey, listed a number of benefits and challenges in obtaining advice from Regulators and HTA bodies. Companies generally found advice toward understanding the perspectives and needs of Regulators helpful, but said they faced internal and external hurdles in obtaining the advice.

Biosimilar Scientific Advice in the EU

Between 2008 and 2011 the EMA reviewed 35 biosimilar monoclonal antibodies (mAbs) in 43 SA procedures (multiple procedures and follow-up advice can be requested). From 2003 to 2011, around 40% of all requests to the EMA for advice on biosimilars were for biosimilar mAbs, reflecting an increase in advice demands for these therapeutics.

Given the value of engagement with Regulators, SA should be considered a key development step and not just a solution for development road blocks or hurdles. In general, the EMA will offer advice on these or any other quality, non-clinical, clinical or methodological issues. For biosimilars, there are

several times when engagement with an Agency may be appropriate, which are listed below:

- While assessing suitability of the biosimilar approach.
- If there are doubts about the appropriateness of the assays for demonstrating in vitro equivalence.
- Determining the acceptability of any planned changes to the biosimilar product when compared to the reference, particularly with regards to strength, pharmaceutical form, formulation, presentation, or excipients; including discuss positive changes such as reducing the impurities in the product.
- The appropriateness of the planned clinical trials for demonstrating similarity to the reference product.
- Extrapolating between indications and the acceptability of the scientific justification for doing so.
- Following unexpected clinical trial results.

It is preferential for questions to be prospective in nature and advice to be sought before taking key decisions which can significantly influence a product's development and certainly prior to undertaking pivotal clinical trials. This allows the Agency to provide constructive input and also provides the company the opportunity to request clarifications, and to amend their development plan to take into account the recommendations that are made.

In conclusion, obtaining early advice during development and at major transition points, as well as compliance with the advice given, can significantly increase the MA success rate. Therefore, companies are strongly encouraged to engage with Regulators regarding the development program via advice procedures. Follow-up advice is strongly recommended when a company deviates from previous recommendations or from existing regulatory guidelines. The final advice letter is often the result of interactive discussion between Regulators and companies, where both parties have learned from each other. Finally, these discussions will improve our regulatory guidelines for future product development.

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Next Edition's Hot Topic - Agency Meetings for Biosimilars in the United States

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Regulatory Framework Updates

Europe

None reported.

United States

After 3-Year Delay, FDA Finalizes Guidance Documents on Biosimilarity

The FDA released a trio of draft guidance documents outlining its expectations for biosimilar products for comment back in February 2012. These were the first policy documents to be released by the FDA after the 2010 passage of the Biologics Price Competition and Innovation Act (BPCI) under the Patient Protection and Affordable Care Act (PPACA/Obamacare).

- Guidance for Industry - Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.
- Guidance for Industry - Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product/Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.
- Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.

The reaction to the finalized guidelines has been fairly muted, perhaps reflecting the feeling that there are no significant changes from the preliminary versions. Moreover, more attention has been on what is not in the guidelines; namely, the FDA's stance on biosimilar interchangeability and labeling.

Link to finalized guidance documents, 28 Apr 2015:
<http://www.fda.gov/Drugs/Guidance-ComplianceRegulatoryInformation/Guidances/ucm290967.htm>

FDA Posts Draft Revised Additional Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; Draft Guidance for Industry

The FDA has posted of a draft guidance for industry entitled "Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009."

The guidance provides new and revised questions and answers. It also includes certain original questions and answers that have not yet been finalized.

One of the new questions, concerns demonstration of interchangeability, which the FDA says will be possible to determine in an original biosimilar application. Although, rather disappointingly, the agency also states that "at this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment". The FDA says that it "is continuing to consider the type of information sufficient to enable the FDA to determine that a biological product is interchangeable with the reference product".

Link to draft revised Q&A document, 12 May 2015:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery

Rest of World

None reported.



Biosimilars Applications Approved & Under Review

Europe

Applications For New Human Medicines Under Evaluation By The Committee For Medicinal Products For Human

According to the EMA's list of applications for new human medicines under evaluation by the CHMP posted on 22 May 2015, the Agency is reviewing 4 biosimilar applications.

Common Name	Therapeutic Area	Number of Applications
Enoxaparin sodium	Antithrombotic (blood-clot prevention)	1
Etanercept	Immunosuppressant	1
Human insulin	Diabetes	1
Infliximab	Immunosuppressant	1
Total		4

Link to applications for new human medicines under evaluation by the CHMP, 22 May 2015: www.ema.europa.eu

United States

None reported.

Rest of World

Australian Approval for Biosimilar Insulin

Australia's Pharmaceutical Benefits Advisory Committee (PBAC) has given a positive recommendation for the listing of Eli Lilly's biosimilar insulin glargine, Basaglar in the country's Pharmaceutical Benefits Scheme (PBS). Basaglar is the first biosimilar insulin to be approved in Australia, providing an alternative, affordable treatment option for patients suffering from diabetes.

Basaglar is a biosimilar of the PBS listed insulin glargine, Lantus, made by French drugmaker Sanofi. PBAC recommended the listing of insulin glargine Basaglar for the treatment

of type 1 and 2 diabetes mellitus on a cost-minimization basis with Lantus. Interestingly the PBAC also said it will consider marking the biosimilar as equivalent, ie, 'a' flagging. Medicines deemed substitutable at a pharmacy level by PBAC include a notation in the official Pharmaceutical Benefits Schedule known as an 'a' flag.

Link Recommendations made by the PBAC, Mar 2015: www.pbs.gov.au

Iran Approves its First Rituximab Biogeneric

In May 2015, Iran's National Regulatory Authority, the Food and Drug Organization (FDO), approved its first rituximab biogeneric (Zytux). The medicine received its MA based on the previously published national guideline for marketing of biogenics in Iran.

GaBI Online, Posted 15 May 2015: www.gabionline.net

Approval of the First Biosimilar Monoclonal Antibody in Brazil

The National Sanitary Vigilance Agency (ANVISA) granted MA to Celltrion Healthcare Distribuidora de Produtos Farmaceuticos dos Brasil Ltda's (the Brazilian subsidiary of Celltrion, Inc. for the monoclonal antibody Remsima, a copy of Janssen's Remicade (infliximab). The approved indications include rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, adult and pediatric Crohn's disease, fistulizing Crohn's disease, and adult and pediatric ulcerative colitis or rectocolitis.

GaBI Online, Posted 4 May 2015: www.gabionline.net

Venezuelan Approval for Celltrion's Remsima

Celltrion announced on 29 April 2015 that it received approval to sell Remsima from the Instituto Nacional de Higiene Rafael Rangel (INHRR), the National Institute of Health in Venezuela. Accordingly, the company can now sell the product in 13 out of the 22 countries in South America.

GaBI Online, Posted 8 May 2015: www.gabionline.net



Articles & Reports of Interest

Australia's PBAC Recommends Substitution of Biosimilars

Australia's PBAC has recommended that biosimilars are suitable for substitution at the pharmacy level.

Medicines deemed substitutable at the pharmacy level by the PBAC include a notation in the official Pharmaceutical Benefits Schedule known as an 'a' flag. The PBAC has recommended marking biosimilars as equivalent, ie, 'a' flagging, and therefore suitable for substitution at the pharmacy level, where the data is supportive of this conclusion.

The PBAC advised that the following would be relevant considerations in establishing that a biosimilar could be 'a' flagged with the originator biological:

- absence of data to suggest significant differences in clinical effectiveness or safety compared with the originator;
- absence of identified populations where the risks of using the biosimilar are disproportionately high;
- availability of data to support switching between the originator and the biosimilar;
- availability of data for treatment-naïve patients initiating on the biosimilar;
- whether the Therapeutic Goods Administration has deemed a product to be biosimilar with the originator biological

The PBAC also stated that where a biosimilar could not be 'a' flagged at the time of listing in the PBS, data should be collected to support 'a' flagging at a later point.

This position is in line with the recent PBAC recommendation to list the biosimilar insulin glargine Basaglar, where the committee also said that it would consider marking the biosimilar as equivalent, ie, 'a' flagging (see

section Biosimilars Applications Approved & Under Review - Australian approval for biosimilar insulin).

In addition, to try and put patients' minds at ease, the PBAC has placed a statement on their website to try to put this issue into perspective backed by scientific evidence.

Both the Australian Government and the PBAC are concerned that the introduction of biosimilars may lead to the spread of misinformation, as has happened in other countries, which will slow the progress of the development of these medicines.

Recommendations made by the PBAC - April 2015 PBAC Special meeting:
www.pbs.gov.au

Statement by the PBAC - Safety of Biosimilar Medicines:
www.pbs.gov.au

New Forum Launches to Expand Access to Biosimilar Medicines, Improve Health-care

A coalition of 11 leading companies involved in the development and manufacturing of biopharmaceuticals and "biosimilar" medicines today announced the formation of the Biosimilars Forum – the first non-profit organization solely dedicated to expanding patient access to biosimilars in the United States (US).

The founding members of the Biosimilars Forum represent the majority of companies with the most significant US biosimilars development portfolios, including: Actavis, Amgen, Boehringer Ingelheim, Coherus BioSciences, EMD Serono, Hospira, Merck, Pfizer, Samsung, Sandoz, and Teva. Many of these same companies provide branded biologic products, and together have extensive expertise and experience in the science, development, manufacturing, regulation, and clinical applications of

biological medicines. The Forum will provide evidence-based information to educate and advocate for public policies and practices that encourage access, awareness, and adoption of biosimilars.

Link to Biosimilars Forum Website:
www.biosimilarsforum.org

Dutch & Finnish Agencies Approve Switching of Biosimilars, and How Price Does Matter

Biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products, but the decision lies outside the remit of the EMA/CHMP. A number of countries have legal, regulatory, and political provisions to prevent substitution and others have introduced policies for switching. However the Dutch Medicines Evaluation Board (MEB) has recently updated its position on biosimilars¹, stating that "biosimilars have been proven to have no relevant differences compared to an innovator biological medicinal product as far as quality, safety and efficacy are concerned", a change from its position in 2010 which recommended to avoid switching. The Agency's decision to change this position was based on "a careful study of the most recent literature and experiences in the evaluation of biosimilars". This states MEB led it to the conclusion that "this strict condition is no longer valid".

In May 2015 the Finnish Medicine Agency recommended switching² and stated that there is no evidence for adverse effects due to a switch from a reference product to an approved biosimilar and the "theoretical basis of such adverse effects" is weak.

Biosimilars in the EU are usually priced 15-30% below their reference products, but they have achieved little market share because of lack

of interchangeability. There is reluctance to switch for a small cost saving in particular where the originator company is offering high level of patient support. However as recently shown a significant price decrease could turn the tide. The Finnish drug company Orion Oyj, which licenses the biosimilar Remsima from South Korea's Celltrion, started with a 39% discount in February 2014 for the drug. The biosimilar captured about 6% to 7% of the market. By February 2015, the discount reached 69% and the biosimilar moved on to grab 50% of the market. In France the Assistance Publique - Hôpitaux de Paris has just reported that it has decided to buy Hospira's biosimilar version of infliximab Inflectra at an estimated 45% discount, proving that price does matter³.

¹ **Communication from MEB, Posted 20 Mar 2015:**
<http://english.cbq-meb.nl>

² **Communication from fimea, dated 22 May 2015:**
www.fimea.fi

³ **Communication from the Assistance Publique - Hôpitaux de Paris (in French), Posted 03 Jul 2015:**
www.aphp.fr

Senate Health Committee Republicans Urge FDA to Provide Clarity, Certainty on Biosimilar Drug Approval Process

Senator Lamar Alexander has led a group of 9 Republicans on the Senate Health Committee in urging the FDA to immediately finalize all guidance regarding the approval of biosimilar drugs.

In a letter to the FDA Acting Commissioner Stephen Ostroff, MD, the senators wrote, "Earlier this week, FDA released the first final guidance on the biosimilar pathway, and we are encouraged by this positive

Articles & Reports of Interest

Continued

development. Yet FDA still has not provided guidance on many fundamental issues, and much of the guidance it has provided is in draft form. Resolving unsettled questions about the biosimilar approval pathway is critical to ensuring that patients have access to safe and effective biosimilars.”

“It is important to us that this pathway becomes a successfully functioning one, as Americans will benefit from greater competition and more treatment options,” they continued. “FDA has not provided sufficient guidance on important issues relating to the review and approval of license applications for biosimilar products, such as naming, interchangeability, and production of patent information.”

The senators said the FDA’s failure to answer “fundamental science and policy questions” through final guidance before approving the first biosimilar raises serious concerns. Specifically, the “FDA still has not announced a policy on nonproprietary names for biosimilar products,” instead relying on a “placeholder” nonproprietary name that provides little clarity to hospitals, consumers, patients, doctors, and others. The senators also expressed concern about the lack of final guidance for the FDA staff reviewing biosimilar applications, saying, “it is not clear what agency policies, if any, have been governing the process.”

The senators continued, “The Biologics Price Competition and Innovation Act, passed over 5 years ago, was meant to foster competition and improve choices for American patients, and all of us want the biosimilars pathway it established to succeed. However, the FDA’s opaque implementation process is creating a troubling degree of uncertainty for patients, doctors, manufacturers, and other stakeholders who are invested in the success of this pathway.”

Link to Letter from the US Senate Committee on Health, Education, Labor and Pensions to the FDA, 30 Apr 2015:
www.help.senate.gov

AbbVie Petitions FDA to Require Biosimilar Labeling to Include Disclaimers and a Description of Data Differences

AbbVie requests the FDA to require the approved labeling for biological products licensed under PHS Act § 351(k) to contain (if applicable) certain statements and descriptions that would differentiate biosimilars from their reference product counterparts. Specifically, AbbVie wants biosimilar labeling to include:

- a clear statement that the product is a biosimilar, that the biosimilar is licensed for fewer than all the reference product’s conditions of use (if applicable), and that the biosimilar’s licensed conditions of use were based on extrapolation (if applicable);
- a clear statement that the FDA has not determined that the biosimilar product is interchangeable with the reference product (if applicable); and
- a concise description of the pertinent data developed to support licensure of the biosimilar, along with information adequate to enable prescribers to distinguish data derived from studies of the biosimilar from data derived from studies of the reference product.

In AbbVie’s Citizen Petition to the FDA, the company argues biosimilar products should bear “a clear statement that the product is a biosimilar,” and, if necessary, that the product may not be licensed for all indications for which the original drug has obtained approval and may not be interchangeable with the reference product.

In March 2015, the FDA approved the US’ first biosimilar product, Zarxio (filgrastim-sndz), a copy of

Amgen’s Neupogen. Zarxio’s label does not make any mention of the term “biosimilar,” and is nearly identical to the label for Neupogen.

For AbbVie, that approach indicates the FDA is adopting a “same labeling” approach for biosimilars—an approach that is “legally unsound,” AbbVie claims in its Citizen Petition.

Another interesting argument contained within the petition relates to pediatric labeling.

Link to Citizen Petition Form AbbVie Inc, 02 Jun 2015:
www.regulations.gov

AbbVie Media statement, 03 Jun 2015:
www.abbvie.com

Clinical Trial Development for Biosimilars

Alten R and Cronstein B N; Seminars in Arthritis and Rheumatism 44 (2015) S2–S8

The objective of this article is to discuss issues regarding clinical trial design for the development of biosimilars in the EU and the US, with special focus on monoclonal antibodies used in the treatment of inflammatory diseases.

A search of the Internet as well as PubMed was conducted through June 2014 for information related to the clinical development of biosimilars using the keywords biosimilar, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, and ankylosing spondylitis. The EMA and the FDA websites were searched for biosimilar guidelines.

Results showed that the EMA began issuing draft guidelines for the development of biosimilars almost a decade ago and has approved numerous biosimilars. The FDA has issued draft guidance providing stepwise considerations for the nonclinical and

clinical development of biosimilars but has yet to approve a biosimilar under this pathway.

Clinical trials aim to resolve uncertainties that may remain following nonclinical development regarding the similarity of the proposed biosimilar with the reference product. Pharmacokinetic and pharmacodynamic studies form the backbone of early clinical development, and serve to inform phase 3 clinical development. Factors to be considered in clinical development include study population, design, end points, sample size, duration, and analytical methods.

Link to paper:
www.semaphrthritisrheumatism.com

Company News

(The following information comes directly from company websites)

EPIRUS Biopharmaceuticals & mAbxience Sign Latin America Distribution Deal for Infliximab Biosimilar, BOW015

Epirus and mAbxience, have entered into a development and future distribution deal for EPIRUS' lead program, BOW015 (infliximab, reference biologic Remicade®), for Latin American markets, including Argentina, Chile, Ecuador, Paraguay, Uruguay, and Venezuela.

mAbxience will be responsible for regulatory submissions, using BOW015's existing data package, and eventual commercialization in these select Latin American markets.

Company press release, 14 May 2015:
<http://ir.epirusbiopharma.com>

Merck and Samsung Bioepis Announce Pivotal Phase 3 Studies for Investigational Biosimilars SB4, Enbrel (Etanercept), and SB2, Remicade (Infliximab), Met Primary Endpoints

Merck and Samsung Bioepis Co have announced that pivotal Phase 3 clinical studies of SB4, an investigational biosimilar of Enbrel (etanercept), and SB2, an investigational biosimilar of Remicade (infliximab), met their primary endpoints, demonstrating equivalence to the originator medicine in patients with moderate to severe rheumatoid arthritis (RA) despite methotrexate therapy. The primary endpoint in the two studies was the American College of Rheumatology 20 percent response criteria (ACR20), at week 24 and at week 30 of treatment, respectively. In these studies, SB4 and SB2 demonstrated a safety profile equivalent to the originator medicines.

Company press release, 10 Jun 2015:
<http://www.fdanews.com>

CMS Announces Pricing, Policies for Biosimilars Use

The Centers for Medicare & Medicaid Services has announced that it plans to begin paying for biosimilars through its Part B, Part D, and state coverage policies.

As with standard drugs, coverage determinations will be based on the manufacturer's wholesale acquisition cost and the average sales price of the biosimilar, according to a question-and-answer sheet on how biosimilars will be reimbursed under Medicare Part B.

Medicare will pay 106 percent of the wholesale cost of the product until the average sale price can be determined. Once that information is available, coverage will be set at the average sale price plus 6% of the average price for the reference product, CMS says in a Q&A document released last week.

Biosimilars will have different reimbursement codes than those used to denote their reference products. CMS expects to come up with those codes by July 1, with reimbursements applying retroactively to the biosimilar's FDA approval date — the first of which came last month when the FDA approved Sandoz's Zarxio (filgrastim-sndz).

The distinct codes are a positive step, as they recognize that biosimilars are not inherently identical to their reference products and will ensure CMS reimburses for them properly.

CMS plans to encourage use of biosimilars and is also encouraging state programs to work biosimilars into their preferred drugs lists as a means of saving money and expanding access to expensive treatments.

Link to Medicaid Drug Rebate Program Notice Release No. 169, 30 Mar 2015:
www.medicaid.gov

Biocon-Mylan Programs Make Progress

Biocon has made clinical progress in its partnered programs with Mylan.

Two molecules Pegfilgrastim (PEG-G-CSF) and Adalimumab have entered global Phase 3 clinical trials. While the PEG-G-CSF trial is well underway the Adalimumab trial has been recently initiated.

In addition, the Phase 3 global clinical trial for Trastuzumab is progressing in more than 100 sites around the world. An initial rest of world (ROW) focused Phase 3 trial for Bevacizumab is also underway.

Two global clinical trials for generic Insulin Glargine initiated in 2014, have also made significant progress. The patient recruitment for type 1 diabetes study has been completed ahead of schedule, while the recruitment for type 2 diabetes study is expected to be completed by July 2015.

Company press release, 07 May 2015:
www.biocon.com

amp Biosimilars AG Successfully Out-licenses First Biosimilar

amp biosimilars AG has announced its first successful out-licensing of a biosimilar. The first biosimilar to be out-licensed from the product pipeline is ABY-018, a humanized monoclonal antibody. At present, there are 4 biosimilars in the amp product pipeline.

amp biosimilars licensed the biosimilar to a leading mid-sized Chinese pharmaceutical corporation, with a portfolio of more than 50 pharmaceutical products, a GMP-certified production capacity of 2 billion tablets and 1 billion capsules per year as well as a national sales network that will

put it in a position to pursue commercialization in China.

Under the agreement the Chinese company will assume all financing for the development and market approval processes starting from Clinical Phase 1 through to production and marketing of the biosimilar in China. The partner will have the right to unlimited marketing in China and will pay a percentage of the proceeds to amp biosimilars (royalties). amp biosimilars retains the global rights outside of China. This arrangement allows amp biosimilars to conclude additional out-licensing agreements for the biosimilar, for example in the US, Europe, and other Asian countries, or to develop the relevant markets independently and thus generate greater potential revenues. By way of reciprocation, amp will pay the Chinese partner royalties in the same amount.

Company press release, 28 May 2015:
www.ampbiosimilars.com

Second Biosimilar Product Successfully Out-licensed

amp biosimilars has reported a second successful out-licensing of another one of their biosimilar products; ABY-021 is a humanized monoclonal antibody for treating immunological symptoms.

The out-licensing partner is once again a leading medium-sized Chinese pharmaceuticals company, which has thus secured the rights to market ABY-021 in China. The licensing helps amp biosimilars to secure complete financing for the development and approval processes starting from Clinical Phase 1 on through to production and marketing of the biosimilar in China. The global rights outside of China remain with amp biosimilars and allow the issuance of further licenses to other pharmaceutical companies around the world, creating potential for additional earnings.

Company News

Continued

In addition to the financing of product development up to the approval process, amp biosimilars will receive royalties starting from the marketing launch of the biosimilar, which may be worth hundreds of millions of Euros.

Company press release, 10 Jun 2015:
www.ampbiosimilars.com

JHL Biotech Successfully Raises US\$45.6 Million Series C Financing

JHL has closed a Series C fundraising of \$45.6 million.

The company intends to utilize the proceeds toward continuing development of its biosimilar programs through clinical trials, enabling the construction of a fill-finish facility in Wuhan's commercial manufacturing plant, expanding its pre-clinical novel therapeutic portfolio, and applying the rest towards working capital. With this round of financing, JHL has now secured capital necessary to complete the full development and BLA filing of at least two of its proprietary biosimilar compounds.

Company press release, 12 May 2015:
www.jhlbiotech.com

Ligand Acquires Rights to More Than 15 Fully-Funded Development Programs from Selexis SA

Ligand has acquired a portfolio of potential future milestone and royalty payments for more than 15 biologic development programs from Selexis SA for \$4 million in cash.

Highlights of the transaction include the following:

- The basis for the development programs and economic rights is a proprietary technology for manufacturing stable and high performing mammalian cell lines for biologic therapeutics.
- The acquired assets include a mix of novel biologics and biosimilars.
- The programs are in various stages of development ranging from preclinical through Phase 3.
- Each acquired program is fully funded by a development partner.

Company press release, 11 May 2015:
<http://investor.ligand.com>

Coherus BioSciences and Baxter Announce Amendment to Etanercept Biosimilar Collaboration Agreement

Coherus and Baxter have amended certain financial terms of their collaboration agreement established in August 2013 regarding the development and commercialization of CHS-0214, an etanercept biosimilar product candidate for Europe, Canada, Brazil, and certain other markets. Under the terms of the amended agreement, certain existing milestones and funding obligations have been revised, and the collaboration has been expanded to include select pre-commercialization activities. In aggregate, the revised milestone payments may exceed the previous Baxter funding obligations by approximately \$12 million. Additionally, Baxter has agreed to purchase Coherus common stock in a private placement transaction. All other contractual provisions remain materially unchanged.

Company press release, 15 Apr 2015:
<http://globenewswire.com>



Next Edition

Look out for the next edition of the Biosimilars Newsletter due out in October 2015.

Previous Editions

Please use the below link to find previous editions of our Biosimilars Newsletters.

<http://prahs.com>

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