Welcome

Welcome to the sixth 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 by the company press releases.

Highlights at a Glance

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Signal Management in Drug and Biosimilars Development

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Signal management in drug development has been ongoing, evolving, and improving for many years. For the European Medicines Agency (EMA), Food and Drug Administration (FDA) and other regulatory bodies immunogenicity is a major area of safety concern for biosimilars as well as for peptide, protein, and drug therapeutics, all of which have the potential to trigger some level of antibody response. Hence, there is the regulatory requirement to conduct immunogenicity testing and safety assessment during pre-clinical and clinical studies, and post-approval, thereafter, usually requiring continued pharmacovigilance monitoring of immunogenicity. During pre-clinical and clinical studies, the critical focus is to decipher the potential for immunotoxicity and allergenicity, supported by appropriate data collection in order to evaluate impact of the pres-
erence of Anti-Drug Antibody (ADA) on pharmacokinetics, pharmacodynamics, efficacy, and safety. While a target focus is to ensure comparable immunogenicity, a biosimilar product with lower immunogenicity than its innovator reference product would not be excluded for biosimilarity approval. As most biosimilars are intended for long-term use to treat chronic diseases, monitoring of safety concerns beyond clinical development will continue to be equally crucial. Therefore, even though pre-clinical and clinical trials are indispensable for determining identified and potential immunogenicity risks, not all such risks (especially those that are rare) can be identified during pre-market phase, and as such, customized risk management, pharmacovigilance, and post market commitments such as Post Authorization Safety Studies (PASS) will continue to be essential.

Iterative signal management process is critical to demonstrate the safety of biosimilars and comparability of their safety profiles to innovator reference products, and overall risk management to ensure that their benefits continue to outweigh their risks. Likewise, post-approval, continued safety monitoring is essential and required. The EMA’s Good Pharmacovigilance Practices guidelines define signal management as follows, “includes the following activities: signal detection, signal validation/confimation, signal analysis and prioritization, signal assessment, and recommendation for action. It therefore is a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks causally associated with an active substance or a medicinal product, or whether known risks have changed.” The initial step in the signal management process is detection of a signal, and the EMA defines a signal as “information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.”

An appropriate signal management process needs to be designed to support both pre- and post-approval phases of biosimilars development, and should also support comparability assessment of safety and immunogenicity profile of the index biosimilar to the innovator reference product. Preceding this process would be the development of Standard Operating Procedures (SOPs) and Work Instructions (WIs), to ensure adequate training (and documentation of such training) of medical and safety pharmacovigilance professionals with relevant pre-requisite education and experience, preferably in the treatment disease indication under investigation. Therefore, the set-up phase of the signal management process should encompass customization of all relevant documents including: strategy document, signal management plan (includes timelines, blinded/unblinded data handling, communication and escalation process), templates, trackers for documentation of medical review; subsequent steps should include, signal detection, validation, confirmation, analysis and prioritization, and recommendation for action. Please note that during the conduct of a blinded study, unblinding of data for signal detection is not necessarily required except in special situations that warrant such action. However, any existing unblinded data such as expedited reports should be reviewed. Situations warranting unblinding should be defined in the protocol. Quality control checks should be part of the quality management system. Overall, a signal management process should define a quality tracking and management system that supports and ensures adequate evaluation of operational quality from “A-to-Z.”

In designing a signal detection and management strategy for a drug or biosimilar in development, a necessary first step is thorough review and understanding of the current non-clinical and clinical safety data, including pharmacokinetics/pharmacodynamics of the innovator reference product, as well as legacy data of the index biosimilar in development. Then, carefully delineating the “assumptions” based on documented scientific and medical evidence on which signal detection will be performed. This should include clearly stating clinical trial study protocols and the safety population to be included in the signal detection and evaluation data. In addition, signal detection strategies should factor in index protocol designs, ensuring that careful data screening is performed on all available safety data, especially during investigational product treatment switch from index biosimilar to comparator as applicable (ie, reference biologic product) and vice versa. Furthermore, well-defined and easy to follow threshold algorithms, both qualitative and quantitative, should be specified, and also ensure that all necessary data output specifications delineated can support the application of the algorithms and the entire signal detection process.

A dynamic and clearly outlined signal management strategy, translated into a plan, should be well-documented and should consider all available data sources and data output, as well as defined assumptions based on pre-clinical and clinical information. Such information includes the current safety and immunogenicity profile (per index innovator reference product) highlighting target medical events such as: adverse events of special interest, safety and medical review guidelines including qualitative and quantitative algorithms to be applied, relevant epidemiology and natural history data, and other peer-reviewed literature to be reviewed as required. A signal management plan should also delineate an appropriate signal validation and confirmation process, in addition to a signal analysis and prioritization process, and signal assessment method. Such a plan should also include an approach to ensure appropriate recommendation for action.

During the pre-approval phase, all signal management activities should be conducted on a compound level, considering the known safety profile of the index innovator reference product per protocol design and indication, as well as relevant approved products of the same class. Overall, a signal detection and management process should be designed to identify and characterize risks during pre- and post-approval phases of development, supporting safety profiling, and description of possible safety issues that may arise with subject/patient exposure to a biosimilar relative to the reference product. Also, a comprehensive and well-designed signal management process feeds into benefit-risk evaluation (BRE) and risk management, as such, should be well-documented, including documentation of qualification and training of all involved medical and safety pharmacovigilance professionals. In the European Union (EU), a Risk Management Plan is mandated to support marketing authorization application, and should include a safety specification encompassing identified and potential risk characterization and safety concerns, as well as pharmacovigilance planning, and planning and implementation of routine and additional (as needed) risk minimization measures and assessment of the effectiveness of such measures.

Overall, the signal management process should be governed by SOPs which should include, signal detection, validation (and confirmation), analysis and prioritization, assessment, and effective communication of significant findings especially validated signals. In addition, there should be appropriate documentation, and tracking of activities and findings. Signal detection and management strategies translated into a plan should be comprehensive in nature, in both planned qualitative and quantitative approaches, as well as tailored to specific biosimilar relative to its innovator reference product and target indication, and taking into account regulatory guidelines and requirements. As the focus on biosimilar development continues to grow, so does the critical need for a comprehensive, efficient and well defined signal management process, continued benefit risk evaluation, and an overall risk management process.

References:


Regulatory Framework Updates

Europe

EMA Issues Finalized Insulin Biosimilars Guideline

The EMA has released its finalized guideline on the non-clinical and clinical development of insulin biosimilars.

The new guideline replaces the “Guidance on similar medicinal products containing recombinant human soluble insulin” (EMEA/CHMP/ BMWP/32775/2005), which came into effect in June 2006. The new guideline lays down the non-clinical and clinical requirements for recombinant insulin-containing biosimilars, including human insulin and insulin analogues (both referred to as insulin).


Date: 26 February 2015
Effective date: 1 September 2015

The non-clinical section addresses the requirements of in vitro pharmacodynamic studies and cases when there is a need for additional in vivo toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, and safety studies, as well as the risk management plan.

In a change from the previously released draft version, EMA has dropped its requirement for ‘manufacturers who are planning comparative clamp studies to consider reports that individuals of African, South Asian, or Hispanic descent have reduced glucose clearance’.

Link to guideline: www.ema.europa.eu

United States

FDA Announces List of Guidance Documents for 2015

The US FDA’s Center for Drug Evaluation and Research (CDER) is planning to release 4 new guidance documents on biosimilars during calendar year 2015.

The guidance documents planned are as follows:
- Biosimilars additional questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009.
- Considerations in demonstrating interchangeability to a reference product.
- Labeling for biosimilar biological products.
- Statistical approaches to evaluation of analytical similarity data to support a demonstration of biosimilarity.

The news of additional biosimilars guidances is seen as a positive development for industry groups who have been calling for FDA to promptly issue appropriate guidance on the issue of naming, as well as to issue, or finalize guidances on other outstanding issues such as establishing interchangeability.


Rest of World

Australia Reviewing Plans For Naming Biosimilars

Following recent international developments in the area of biosimilar naming, the Therapeutic Goods Administration (TGA) will not be continuing with the previously proposed naming convention for biosimilars while a review of the policy is undertaken.

Link to TGA site, 20 Jan 2015: www.tga.gov.au

Mexico Issues Rules On Biolimbos

The Mexican regulatory body for approval of medicines, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS), has issued rules for older non-originator biologicals registered prior to 19 October 2011, when the country’s guidelines for biocomparables were first published, mandating that companies conduct clinical trials to prove biosimilarity. These products, known as “biolimbos”, have not undergone any marketing authorization review consistent with globally accepted standards for the approval of biosimilars.

The companies affected have until 31 December 2015 to present their tests to the agency.

Link to TGA site, 20 Jan 2015: www.tga.gov.au

Link to guideline: www.ema.europa.eu
Biosimilar Applications Approved & Under Review

Europe

EMA Accepts Samsung Bioepis’ Enbrel® Biosimilar Candidate, SB4, for Regulatory Review

Samsung Bioepis’s Marketing Authorization Application (MAA) for its Enbrel (etanercept) biosimilar candidate, SB4, has been validated and accepted for review by the EMA. The acceptance of the MAA marks the first Enbrel biosimilar to advance into regulatory review in the Europe EU. The MAA is based on results from a phase III clinical trial in patients with moderate-to-severe rheumatoid arthritis (RA).

In addition to the European filings, Samsung Bioepis intends to move forward with additional applications for regulatory approvals in other territories worldwide.


United States

FDA Approves First Biosimilar Product Zaxio

The US FDA has approved Zaxio (filgrastim-sndz), the first biosimilar product approved in the US. Zaxio has been approved as biosimilar, not as an interchangeable product.

For this approval, the FDA designated a placeholder non-proprietary name for this product as “filgrastim-sndz.” The FDA have stated that the provision of a placeholder non-proprietary name for this product should not be viewed as reflective of the agency’s decision on a comprehensive naming policy for biosimilar and other biological products. While the FDA has not yet issued draft guidance on how current and future biological products marketed in the US should be named, the agency intends to do so in the near future.

FDA news release 06 Mar 2015: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm

Hospira Submits Application to US FDA for Proposed Epoetin Alfa Biosimilar

Hospira has submitted a Biologics License Application (BLA) to the US FDA for Retacrit™, a proposed biosimilar to Amgen’s EPOGEN® (epoetin alfa) and Janssen’s PROCRIT® (epoetin alfa).

The biosimilar application was submitted on 16 December 2014, under the new 351(k) approval pathway created by the Biologics Price Competition and Innovation Act of 2009 (BPCIA).

Company Press release 12 Jan 2015: phx.corporate-ir.net

US FDA Postpones Celltrion’s Remicade Biosimilar Review Meeting

The FDA has postponed the meeting of the Arthritis Advisory Committee scheduled for 17 March 2015. The postponement is due to information requests pending with the sponsor of the application. A future meeting date is still to be announced in the Federal Register.

The US delay is unlikely to spell a major disruption to Celltrion’s global plans, as Remicade, which brings in roughly $8.4 billion around the world each year, isn’t scheduled to lose US exclusivity until 2018. Celltrion is doing its best to move that date forward, challenging some of Johnson’s and Johnson’s (J&J), the originator company, patents in court but J&J is battling back with legal claims of its own in an ongoing dispute.


Rest of World

None reported.

Regulatory Meetings

Europe/US/Rest of World

None reported.
UK Outlines Process For Developing Biosimilars Guidances

In response to the increasing availability and use of biosimilars by the UK’s National Health Service (NHS), the country’s healthcare watchdog, the National Institute for Health and Care Excellence (NICE), has updated its methods for providing guidance and advice on biosimilars.

NICE is an independent organization, set up by the UK Government in 1999. The agency assesses the clinical and cost-effectiveness of drugs, and decides which drugs and treatments are available on the NHS in England and Wales.

Positive appraisals of biosimilars will use the name of the active drug substance, including the reference product and brand name, to inform clinical decisions.

The decision by NICE to use the name of the active drug substance aligns with the majority of European Union Member States, which have agreed that biosimilars should have the same International Nonproprietary Name (INN) as their reference biological.

Link to full free article: www.amcp.org

Considerations In The Early Development of Biosimilar Products


The widespread use and patent expiration of many biologics have led to global interest in development of biosimilar products. Because the manufacture of biologics, including biosimilars, is a complex process involving living systems, the development of a biosimilar is more rigorous than the development of a generic small molecule drug. Several regulatory agencies have established, or are proposing guidelines, that recommend a stepwise process to ensure the efficacy and safety of a biosimilar. This article also explores the early clinical phase of biosimilar development, which is particularly important to resolving any uncertainties that might remain following in vitro and in vivo evaluations and to enable a selective and targeted approach to phase III clinical efficacy and safety investigation.

Link to purchase site for article: www.ncbi.nlm.nih.gov

The Challenging Definition of Naïve Patient For Biological Drug Use


Biosimilar is defined by the EMA as a biological medicinal product, which is similar, but not identical to the biological drug already authorized. The biosimilar and its reference product are expected to display the same safety and efficacy profile, and are generally used to treat the same conditions. The Italian Medicines Agency considers biosimilars as a valid therapeutic option with an economic advantage, especially in primary naïve patients with no previous exposure to the originator, or with a sufficiently long wash-out period (“secondary naïve”). The identification of “secondary naïve” is not well defined and can be subjected to different variables, mainly the drug biologic effect and its immunogenicity. The first one depends on the type of biologics and on their mechanism of action. The second one is related to the fact that biologicals may be immunogenic and can trigger an anti-drug antibody response (ADA).

In conclusion, the development and use of biosimilars represent a tool for increasing health system sustainability. However, it is of paramount importance to distinguish between the pharmacodynamics of a given drug and its immunogenicity being the 2 aspects unrelated. Thus a detailed definition of “secondary naïve” patients is challenging, and may be related to both the 2 parameters.

Link to court order 19 Mar 2015: www.fdalawblog.net

Assessment of Pharmacists’ Views On Biosimilar Naming Conventions


As the date for the introduction of biosimilars in the US approaches, questions remain regarding the naming, coding, and approval process for these agents that will need to be carefully considered.

To (a) ascertain pharmacists’ awareness of and comfort level with biosimilars and (b) determine the impact of identical or different nonproprietary names on pharmacists’ confidence in

Substituting interchangeable biologics, the Academy of Managed Care Pharmacy, the American Pharmacists Association, and the American Society of Health-System Pharmacists fielded a survey to their membership, or a partial segment of their membership. The survey consisted of 2 sections: (1) current processes for reporting biosimilars being dispensed, and (2) familiarity and preferences regarding biosimilars.

The results of this survey indicate that the ultimate decision on the naming convention for biosimilars may influence dispensing pharmacists, with the majority of respondents being most comfortable with biosimilars having the same nonproprietary name as the reference biologic.

Link to article, 06 Jan 2015: www.nice.org.uk

US District Court Dismisses Amgen’s Petition To Block Launch of Neupogen Biosimilar Zarxio

A district court judge from California has denied an injunction by Amgen meant to stop the launch of the first biosimilar approved by the US FDA - Sandoz’s Zarxio.

“As the twelve-year exclusivity period for Neupogen long ago expired, there exists no substantive bar to market entry for Sandoz’s biosimilar filgrastim and, consequently, no basis on which Amgen is entitled to injunctive relief or other remedies for disadvantages it may suffer due to market competition from Sandoz.”

Amgen originally filed suit when Sandoz failed to provide them with certain information from its biosimilars application, including on the manufacturing processes. However, the judge ruled that in some instances this information does not have to be provided. The judge also dismissed claims of harm by Amgen that would come if Zarxio were to be launched. Questions however, still remain around the pricing of Zarxio, details of which were not included in the latest order.

It appears that Amgen may decide to appeal. The time frame of Amgen’s appeal seems unclear, and Novartis has not specified whether it will launch Zarxio prior to completion of the appeals process.

Link to full free article: www.ncbi.nlm.nih.gov
Company News
(The information provided is sourced directly from the company websites)

**Pfizer To Acquire Hospira**

Pfizer Inc. and Hospira, Inc. have announced that they have entered into a definitive merger agreement under which Pfizer will acquire Hospira for a total enterprise value of approximately $17 billion. This strategically and complementary combination will add a growing revenue stream, and a platform for growth for Pfizer’s Global Established Pharmaceutical (GEP) business.

The transaction is subject to customary closing conditions, including regulatory approvals in several jurisdictions and approval of Hospira’s shareholders, and is expected to close in the second half of 2015.

*Company press release 05 Feb 2015: www.pfizer.com*

**Hospira Launches First Biosimilar Monoclonal Antibody (mAb) Inflectra (infliximab) In Major European Markets**

Hospira announced the launch of the first biosimilar mAb, Inflectra (infliximab), in major European markets. Inflectra is licensed for the treatment of inflammatory conditions including RA, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn’s disease, adult and pediatric ulcerative colitis, and plaque psoriasis.

Inflectra received its license from the EC in September 2013, following adoption of the EMA Committee for Medicinal Products for Human Use (CHMP) positive recommendation for granting marketing authorization. Review by the EMA included detailed analysis of biophysical properties and safety, efficacy, and tolerability data from an extensive pre-clinical and clinical trial program.

*Company press release 16 Feb 2015: phx.corporate-ir.net*

**Oncobiologics ONS-3010 Meets Primary Endpoints**

Oncobiologics, Inc have announced that ONS-3010, its adalimumab (Humira®) biosimilar candidate met the primary endpoints in its first clinical study.

A 3-arm single-dose pharmacokinetic (PK) study was performed in healthy volunteers to compare ONS-3010 to both the US- and EU-sourced Humira® reference products, and the 2 reference products to each other. All of the PK endpoints met the bioequivalence and safety and immunogenicity were similar across the 3 arms.

*Company press release 12 Feb 2015: oncobiologics.com*

**Mabion Submits Registration Dossier in Argentina**

Mabion SA is one step closer to releasing its MabionCD20 drug in Argentina. Together with the intermediary company LKM SA, a petition was submitted in Argentina for approval to start the registration procedure of MabionCD20, a drug used in the treatment of blood cancers and RA.

The data currently available, is only sufficient to initiate the registration procedure. The documentation will be regularly updated with additional data, as it is obtained by the company.

*Company Press release 03 Feb 2015: www.ext.amgen.com*

**Amgen Announces Positive Results From Phase III Study Of Biosimilar Candidate ABP 501**

Amgen have announced a phase III study evaluating the efficacy and safety of biosimilar candidate ABP 501 compared with Humira® (adalimumab) in patients with moderate-to-severe RA, met its primary and key secondary endpoints. The primary endpoint compared the ACR20 measurements (20 percent or greater improvement in ACR assessment) at week 24. The ACR20 was within the pre-specified margin for ABP 501 compared to adalimumab, showing clinical equivalence. Safety and immunogenicity of ABP 501 were comparable to adalimumab. Key secondary endpoints included ACR50, ACR70, and DAS 28-CRP.

ABP 501 is being developed as a biosimilar candidate to adalimumab, an anti-TNF-α monoclonal antibody which is approved in many countries for the treatment of a number of inflammatory diseases.

Amgen has 9 biosimilar molecules in development and expects to launch 5 of these biosimilars between 2017 and 2019.

*Company press release 22 Jan 2015: www.innoventbio.com*

**Next Edition**


**Previous Editions**

Please use the below link to find previous editions of PRA Health Sciences’ Biosimilars Newsletters.

http://prahs.com/therapeutic-expertise/biosimilars/

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