Considerations IN Pharmacovigilance for Biosimilars

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AGENDA

1. Biosimilar News

2. Biosimilar Safety and Definitions

3. Biosimilar Pharmacovigilance Challenges - Manufacturing & Structure

4. Biosimilar Pharmacovigilance challenges – Product Naming

5. Biosimilarity and Pharmacovigilance Challenges- Interchangeability

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BIOSIMILAR NEW(S)
India’s Central Drugs Standard Control Organization released a new guidance for biosimilars on 28th of March.

Currently several organizations are actively engaged in manufacturing and marketing biosimilars (Similar Biologics according to CDSCO wording) in India. So far, these biosimilars were approved by Review Committee on Genetic Manipulation and CDSCO using an abbreviated version of the pathway applicable to new drugs on a case by case basis. Since there are several such products under development in India, both regulatory agencies considered the need to publish a clear regulatory pathway outlining the requirements to ensure comparable safety, efficacy and quality of a biosimilar to an authorized reference biologic.

According to the new guideline, biosimilars can only be developed against an authorized reference biologic that has been approved using a complete data package in India. In case the reference biologic is not authorized in India, it should have been approved/licensed and marketed in an ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) country.
Latin American deal for infliximab biosimilar

Posted 26/05/2015

US-based Epirus Biopharmaceuticals (Epirus) announced on 14 May 2015 that it had made a deal with biosimilars specialist mAbxience, a subsidiary of Spanish healthcare firm the Chemo Group, for Latin America with respect to the infliximab biosimilar made by Epirus.

The deal covers development and future distribution of BOW015 (infliximab) for Latin American markets, including Argentina, Chile, Ecuador, Paraguay, Uruguay and Venezuela.

Leveraging the Chemo Group’s global infrastructure, mAbxience will be responsible for regulatory submissions, using BOW015’s existing data package, and eventual commercialization in these selected Latin American markets.

BOW015 is a biosimilar of Johnson & Johnson’s blockbuster arthritis treatment Remicade, which was approved by the European Medicines Agency in August 1998. Remicade had worldwide sales of US$5.0 billion in 2014, the patent in the US expired in 2011, in Japan and elsewhere globally the patent expired in 2014 and in the European Union (EU) patent protection on Remicade expired in February 2015.

South Korean biosimilars maker Celltrion and US-based Hospira gained approval for their infliximab biosimilar (Remsima/Inflectra) in the EU in September 2013 [1].

Epirus has also made a licensing agreement for BOW015 with Indian generics maker Ranbaxy Laboratories (Ranbaxy). The terms of that agreement, Epirus will develop and supply BOW015, and upon regulatory approval Ranbaxy will market the ‘similar biologic’ in India and other emerging markets, including South East Asia and North Africa [2].

Epirus received Indian approval for its Infliximab ‘similar biologic’ in September 2014 [3].

Related articles
- Biosimilars of infliximab
- Stada to in-license adalimumab biosimilar
- Epirus and Livzon collaborate on copy biologicals for China

References

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Source: Epirus
Bevacizumab similar biologics launched in India

Generics makers Reliance Life Sciences (Reliance) and Hetero have both launched similar biologics of Roche’s blockbuster cancer therapy Avastin (bevacizumab) in India.

Bevacizumab is a humanized monoclonal antibody. It inhibits angiogenesis (the formation of new blood vessels) by blocking the action of vascular endothelial growth factor A (VEGF-A). Bevacizumab can therefore slow the growth of new blood vessels in tumours and is used to treat various cancers, including colorectal, lung, breast, glioblastoma, kidney and ovarian.

The originator product, Swiss-based Roche’s Avastin had 2015 sales of CHF6.7 billion (US$6.9 billion). The patents on Avastin are set to expire in Europe in January 2022 and in the US in July 2019 [1].

Reliance announced on 10 June 2016 that its similar biologic had been approved for the treatment of colorectal cancer by India’s regulator, the Drug Controller General of India. The product will be marketed by Lupin under the name Bevacirel at a discount of around 25% compared to Avastin.

Hetero announced the approval of its similar biologic on 27 June 2016. Their product is also approved for the treatment of metastatic colorectal cancer and will be sold under the brand name Gizumab. Hetero’s bevacizumab marks the company’s third similar biologic, after darbepoetin alfa and rituximab.

Editor’s comment
It should be noted that ‘similar biologics’ approved in India might not have been authorized following as strict a regulatory process as is required for approval of biosimilars in the European Union. The EMA (European Medicines Agency) regulatory requirements ensure the same high standards of quality, safety and efficacy for biosimilars as for originator biologicals, and also include a rigorous comparability exercise with the reference product.

Related articles
Biosimilars of bevacizumab

‘Similar biologics’ approved and marketed in India

Reference

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Source: Economic Times India, Hetero
Mylan and Biocon submit pegfilgrastim biosimilar to EMA

Posted 19/08/2010

Mylan and Biocon announced on 21 July 2016 that the regulatory submission for their proposed pegfilgrastim biosimilar (MYL-1401H) had been accepted by the European Medicines Agency (EMA).

Pegfilgrastim is a PEGylated form of the recombinant human granulocyte colony-stimulating factor (G-CSF) analogue filgrastim. It serves to stimulate the level of white blood cells (neutrophils). Pegfilgrastim treatment can be used to stimulate bone marrow to produce more neutrophils (white blood cells) to fight infection in patients undergoing chemotherapy.

The originator product, Amgen’s Neulasta (pegfilgrastim), had 2015 sales of US$4.7 billion. The patents on Neulasta expired in the US in October 2015 and will expire in Europe in August 2017 [1].

The application is based on analytical, functional and preclinical data, and includes clinical data from pivotal pharmacokinetic/pharmacodynamic and confirmatory efficacy, safety and immunogenicity studies completed earlier in 2016. This is not the first application for a pegfilgrastim biosimilar to be accepted for review by EMA. The agency is already reviewing three other applications for adalimumab biosimilars [2].

Biocon and Mylan are exclusive partners on a broad portfolio of biosimilars and generic insulin analogues [3]. The proposed biosimilar pegfilgrastim is one of six biologicals being co-developed by Mylan and Biocon for the global marketplace. Mylan has exclusive commercialization rights for the proposed biosimilar pegfilgrastim in Australia, Canada, Japan, New Zealand, the US, and in the European Union and European Free Trade Association countries. Biocon has co-exclusive commercialization rights with Mylan for the product in the rest of the world.

Related article
Biosimilars of pegfilgrastim

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9. Guidelines

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BIOSIMILAR AND SAFETY - DEFINITIONS
BIOSIMILAR OR BIO-SIMILARITY MEANS:

- **Similar biological or biosimilar**
  - A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised reference product in the EEA, and
  - which has shown similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

- **Biosimilar or Biosimilarity**
  - The biological product is highly similar to the reference product
  - not withstanding minor differences in clinically inactive components
  - There are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

- **Pharmacovigilance**
  - Pharmacovigilance is defined by the World Health Organization as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.”
BIOSIMILARITY AND PHARMACOVIGILANCE

Challenges

- **Putting the two together** has yielded a complex regulatory landscape with **wide variations and inconsistencies across countries and markets**.

- Difficult enough to build and maintain a robust PV program to meet regulatory requirements for **small molecule drugs**— and yet **generic PV programs will not satisfy the requirements for Biosimilars**.

- **Evolution is at different speeds and directions**

- **FDA regulations** with respect to biosimilars continue to evolve and continue to improve clarity with respect to pharmacovigilance.

- **European Medicine Agency** has specific requirements for biosimilar pharmacovigilance (PV)—although the PV landscape continues to evolve in Europe, as well.

- **Companies developing biosimilars, need to be aware of several key issues with respect to biosimilars that will impact their PV programs.**
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BIOSIMILARITY AND PHARMACOVIGILANCE

- **Challenges**

  - *Manufacturing methods.*
    1. More complex than for conventional small-molecule drugs.
    2. Small differences between manufacturing methods can significantly impact a biosimilar’s biological properties, purity and clinical activity.
    3. No guarantee that resulting biosimilar will be comparable to its reference product.
Biotherapeutics’ structure & manufacturing underscore the importance of pharmacovigilance (PV)

- A complex production process
  - Intrinsic variability
- A complex structure—difficult to make exact biological copy, hence “biosimilar”
- A potential for generating unwanted immune responses
  - Potential for both rapid and delayed onset adverse reactions
- Potential impact of post-marketing changes

Specifically traceability is of Importance
MANUFACTURED PRODUCT RELATED PROBLEMS

- Microheterogeneity
  - alternative disulfide pairings/disulfide shuffling, deamidation, (methionine) oxidation, crystallization of N-terminal glutamine residues, and partial enzymatic cleavage

- Aggregation

- Glycosylation
  - Only a problem for glycosylated proteins
  - Virtually impossible to replicate glycosylation

- Excipients

- Syringe
  - A known source of problems
GLYCOSYLATION IN BIOLOGICAL DRUGS IS IMPORTANT FOR TWO MAIN REASONS:

• Glycan may affect many of the protein properties: **pharmacokinetics** (uptake and length of time in the body), **bioactivity**, secretion, *in vivo* clearance, solubility, recognition, and **antigenicity**

• Quantitative and qualitative aspects of glycosylation affected by production process in culture, including cell line, method of culture, extracellular environment, and protein itself
The Solution: Characterization

Comprehensive Characterization

- Physicochemical as well as biological
- Against multiple batches of innovator spanning a number of years
- Understand innovator variability
  - Specification changes over life of product
  - No label change
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BIOSIMILARITY AND PHARMACOVIGILANCE

Challenges

- Product names.

- Multiple distinct biosimilars in development, multiple manufacturers may be producing the same biosimilar—names not necessarily distinctive---traceability issues in c/o an ADR.

- Even slight variations in the manufacturing process from one company to another may have untoward consequences. It is critical to record complete batch information as part of the PV program.

- Product identification compromised across healthcare settings.

- Both spontaneous adverse event reporting systems & active surveillance systems depend on accurate identification of the product dispensed or given to patients, yet there is great variability in how health professionals and patients refer to medications in these settings.
Labeling for Biosimilar Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-1042 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2016
Labeling
Labeling for Biosimilar Products

Accordingly, FDA recommends that in the biosimilar product labeling, applicants incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications.

Information and data from a clinical study of a proposed biosimilar product should be described in its labeling only when necessary to inform safe and effective use by a health care practitioner. As a general matter, it is FDA’s view that biosimilar product labeling should not include a description of these data, given that a clinical study supporting the licensure of the biosimilar product generally would not be designed to independently demonstrate the safety and efficacy of the product, but rather to support a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product for the approved indications.
Labeling for Biosimilar Products

1. When to use the biosimilar product name

FDA recommends that the biosimilar product name be used in labeling text that is specific to the biosimilar product or refers solely to the biosimilar product. If a biosimilar product has a proprietary name, FDA recommends that the proprietary name be used in these instances; if a proprietary name is not available for the biosimilar product, the biosimilar product’s proper name should be used.\textsuperscript{13}

2. When to use the reference product name

When clinical studies or data derived from studies with the reference product are described in biosimilar product labeling, the reference product’s proper name should be used. This information would typically be included in sections such as, but not limited to, ADVERSE REACTIONS (Clinical Trials Experience) and CLINICAL STUDIES.
Labeling for Biosimilar Products

3. When to use the core name

The overall risk-benefit profile of the reference product is relevant to the biosimilar product, even if a particular serious adverse reaction or other risk included in the reference product labeling may not have been reported with the biosimilar product at the time of licensure. In

<table>
<thead>
<tr>
<th>Reference Product Labeling</th>
<th>Biosimilar Product Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with JUNEXANT increases the risk of serious infections involving various organ systems and sites that may lead to hospitalization or death.</td>
<td>Treatment with replicamab products increases the risk of serious infections involving various organ systems and sites that may lead to hospitalization or death.</td>
</tr>
</tbody>
</table>

4. When to use more than one product name

There may be text appropriately based on the reference product labeling where more than one of these product identification approaches should be used to accurately convey information.

Replicamab products can cause hepatoxicity and acute hepatic failure. In clinical trials of replicamab-hjxf, 10% of patients developed elevated ALT or AST greater than three times the upper limit of normal and 5% progressed to acute hepatic failure. Evaluate serum transaminases (ALT and AST) and bilirubin at baseline and monthly during treatment with NEXSYMEO . . .
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**Interchangeability** –

Generics and brand name products can be prescribed interchangeably in most cases. Biosimilars—although comparable to the innovator drugs—cannot.

“Automatic” interchangeability would require data showing that a biosimilar produces equivalent clinical result in any given individual.
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Guidelines

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BIOSIMILARITY AND PHARMACOVIGILANCE

- **Challenges - Immunogenicity**
  - *Preapproval immunogenicity in the entire premarketing clinical study population mandatory but not sufficient to rule out rare occurrences*
  - *Post-approval surveillance for immunogenicity and rare adverse events* may be needed and/or required over the long term, once a biosimilar is on the market.
  - Such monitoring is expected across regulatory guidelines varying in conditions from guideline to guideline.
Complexity of immunogenicity: Exaggerated pharmacology

<table>
<thead>
<tr>
<th>Safety Issue</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>tuberculosis</strong> with the use of tumour necrosis factor (TNF)-α inhibitors, especially Infliximab and adalimumab</td>
<td>TNFα has a role in the immune response to the mycobacteria responsible for tuberculosis. <strong>Inhibition of TNFα will lead to an increase of the activity of the bacilli and cause disease</strong></td>
</tr>
<tr>
<td>dramatically increased incidence of pure red cell aplasia in patients treated with one particular formulation of recombinant human epoetin (containing polysorbate)</td>
<td>immunogenic response to endogenous molecules, which occurred following changes in the manufacturing of epoetin alfa</td>
</tr>
</tbody>
</table>

Giezen et al. Drug Safety 2009
Guideline on good pharmacovigilance practices (GVP)
Product- or Population-Specific Considerations II: Biological medicinal products

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft finalised by the Agency in collaboration with Member States</td>
<td>17 November 2015</td>
</tr>
<tr>
<td>Draft agreed by the European Risk Management Strategy Facilitation</td>
<td>24 November 2015</td>
</tr>
<tr>
<td>Group (ERMS FG)</td>
<td></td>
</tr>
<tr>
<td>Draft adopted by Executive Director</td>
<td>8 December 2015</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>15 December 2015</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>29 February 2016</td>
</tr>
<tr>
<td>Revised draft finalised by the Agency in collaboration with Member</td>
<td>9 June 2016</td>
</tr>
<tr>
<td>States</td>
<td></td>
</tr>
<tr>
<td>Revised draft agreed by ERMS FG</td>
<td>26 July 2016</td>
</tr>
<tr>
<td>Revised draft adopted by Executive Director as final</td>
<td>4 August 2016</td>
</tr>
<tr>
<td>Date for coming into effect</td>
<td>16 August 2016</td>
</tr>
</tbody>
</table>
P.II.A.1.1. Immunogenicity

As with any medicinal product, the safety profile of a biological is determined partly by the direct or indirect pharmacological, including immunogenic, properties of the active substance (e.g. exaggerated immunomodulation or immunosuppression), of the excipients and of process-related impurities (e.g. host cell proteins), or by host or disease-related susceptibility (e.g. medicine-induced allergic reactions, auto-immunity, inflammatory events). For biologicals and non-biologicals, the basic principles of benefit-risk assessment of other GVP Modules apply to potential or identified risks.

Sources of immunogenicity for biologicals are multi-factorial and involve one or more product-related factors (e.g. choice of cell line, post-translational changes and alterations to the 3D structure during downstream processing, impurities, choice of product containers), treatment-related factors (e.g. route of administration, dosing frequency) and patient or disease-related factors (e.g. genetic background, concomitant medications, nature of the underlying disease and immune status).

The clinical consequences of immunogenicity may include partial or complete loss of efficacy of the product due to induction of neutralising antibodies, altered pharmacokinetics due to antibody binding, general immune effects such as anaphylaxis, formation of immune complexes and potential induction of cross-reactivity with endogenous proteins or other auto-antibodies.
Specific evaluation of immunogenicity is required during product development and prior to authorisation of biotechnological medicines (see Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins). However, non-clinical models and analytical methods/bioassays can usually not predict immunogenicity in humans. Furthermore, the limited sample size of pre-authorisation studies or the rarity of the disease to be treated may not allow rare consequences of immunogenicity to be evaluated prior to authorisation. Uncertainty in relation to immunogenicity should be reflected in the risk management plan (RMP) (see P.II.B.1.) and requires specific activities or surveillance in the post-authorisation phase as appropriate.

Following on from characterisation of immunogenicity at the time of initial marketing authorisation, the next challenge relevant to any biological relates to changes to manufacturing or quality, and the fact that immunogenicity can potentially be introduced or altered at any time post-authorisation potentially resulting in an altered safety or efficacy profile of a product.

**P.II.B. Structures and processes**

**P.II.B.1. Risk management system**

**Immunogenicity**

If immunogenicity is included in the safety specification (see P.II.B.1.1.2.), relevant strategies for the evaluation of immunogenicity and associated clinical consequences in the post-authorisation setting should be proposed as an additional pharmacovigilance activity. Where applicable, the principles for
Risk Based Approaches to Immunogenicity Testing

Risk = Probability_{harm} \times \text{Severity}_{harm}

- How many patients are likely to mount an immune response?
- What happens to the patient if they mount an immune response?

• Severity outweighs the probability of a risk occurring.

• The overall Risk Score depends on an assessment of the various factors that influence immunogenicity
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Evolving guidelines. As guidelines for biosimilar approvals and PV evolve, pharmaceutical companies will need to stay vigilant so that their PV programs can rapidly adapt to evolving regulatory criteria.
Key Regulatory Countries for Biosimilars

- Europe
- Canada
- Australia
- Japan
- United States (established legal pathway)
- Europe
- India (CDSCO) biosimilar guideline

- 2000-2004
- 2008
- 2009
- 2010, 2016
- 2011, 2015, 2016
- 2012, 2016
P.II.B.1.1.2. RMP module SVI “Additional EU requirements for the safety specification”

For all biologicals, the potential for infections caused by residuals of biological material used in the manufacturing process as well as contaminations introduced by the manufacturing process should be presented in relation to the potential for transmission of infectious agents.

P.II.B.1.1.3. RMP part III “Pharmacovigilance plan”

The need and plans for continuous life-cycle signal detection and pharmacovigilance specific to the product including batch-specific issues, particularly following a significant change to the manufacturing process, should be discussed. In this context, the pharmacovigilance plan should include a discussion around clinical settings of product use and how this may impact on routine product name and batch recording and reporting (e.g. whether used in primary or tertiary care) and what additional activities or risk minimisation measures may be required to support product traceability (e.g. provision of ‘sticky’ labels, bar coding).

P.II.B.1.1.4. RMP part V “Risk minimisation measures”

Evaluation of any new clinical risk associated with a biological product should include a root cause analysis in order to evaluate the ability for risk minimisation or elimination via analytical studies or bioassays (e.g. improved assays, manufacturing steps).

As a general principle in order to improve traceability of biological medicines, all summaries of product characteristics (SmPCs) for biologicals (also with relevant appropriate wording in the package leaflets (PLs)) should include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file. Related wording should also be included in relevant educational material, direct healthcare professional communication (see P.II.B.6.) and product promotional material as applicable. Use of other tools such as sticky/tear-off labels in the product...
P.II.B.2. Management and reporting of adverse reactions

The requirements for the management and reporting of suspected adverse reactions outlined in GVP Module VI apply equally to biologicals and non-biologicals. In addition, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, competent authorities shall ensure that all appropriate measures are taken to identify clearly any biological prescribed, dispensed or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product (see GVP Annex I) and the batch number [DIR Art 102(e)]. When reporting suspected adverse reactions, competent authorities and marketing authorisation holders shall provide all available information on each individual case (see GVP Module VI), including the product name and batch number(s) [IR Art 102(2)]

Competent authorities and marketing authorisation holders should also encourage reporters to record information on product names and batch numbers. A follow-up procedure should be put in place to obtain the batch number where it is not indicated in the initial report.

P.II.B.3. Periodic safety update report (PSUR)

The requirements for signal evaluation as part of the PSUR in GVP Module VII apply equally to biologicals and non-biologicals (see P.II.C.1.2. for the assessment of PSURs for biosimilars).

Post-authorisation safety studies

The most optimal study design should be used considering the objective of the post-authorisation safety study (PASS) (see GVP Module VIII Appendix 1). If an existing registry is to be used or a new registry is to be established, a comparator or non-exposed group should preferably be included. Joint disease registries should be encouraged.
CLINICAL STUDY REQUIREMENTS

Design trials with right endpoints and right population

Difficulty in identifying sites and patients in Phase I and III

Can take a long time and a lot of patients

Phase I
Phase I studies supporting dose(s) for targeted indications

Phase I Study:
• Healthy volunteers vs patients
• Ethics committee considerations
• Part 1 - Initial safety and comparative PK arms (at labeled dose)
• Part 2 - Comparative PK/PD, Immunogenicity and Safety/Efficacy run in parallel to Phase III study submissions
• N>40 for Interim Analysis for PK/PD powering

Difficulties
• Cross-over designs
• Sentinel dosing group for Phase I

Phase III

• Single Pivotal (therapeutic category)
• PK/PD assessments with shorter cycles of therapy
• Immunogenicity determined with full regimen of therapy
• “Interchangeability” not yet addressed by FDA
THANK YOU FOR ATTENTION!