Biosimilar Medicines: Recent Developments

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Issue 19 of the HPN featured an article entitled 'Biosimilar Medicines: Opportunities and Challenges in the clinical use and supply of Biosimilars'. Further to this the following update discusses some interesting developments in the world of biosimilar medicines.

2015 has been a significant year for biosimilars. The emergence of new biosimilar products onto the marketplace may result in significant healthcare savings. However increased availability of biosimilars poses challenges for pharmacists and healthcare professionals in terms of pharmacovigilance practices, interchangeability and divergent global naming policies.

1.0 BIOSIMILARS IN THE PIPELINE

In November 2015 the European Medicines Agency (EMA) recommended the granting of a marketing authorisation to Samsung Bioepis UK Limited for the etanercept biosimilar Benepali®. Etanercept is a fusion protein which binds to TNFα and so inhibits its biological activity. Benepali® has been shown to have a comparable quality, safety and efficacy profile to its reference medicine Enbrel®. Like Enbrel®, Benepali® will be indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis and plaque psoriasis. However unlike Enbrel®, Benepali® will not be approved for the treatment of juvenile idiopathic arthritis or paediatric plaque psoriasis. Final approval from the European Commission is expected in February 2016 and the SmPC will be available on the EMA website from this date. Other biosimilar applications currently under evaluation at the EMA are listed in Table 1.

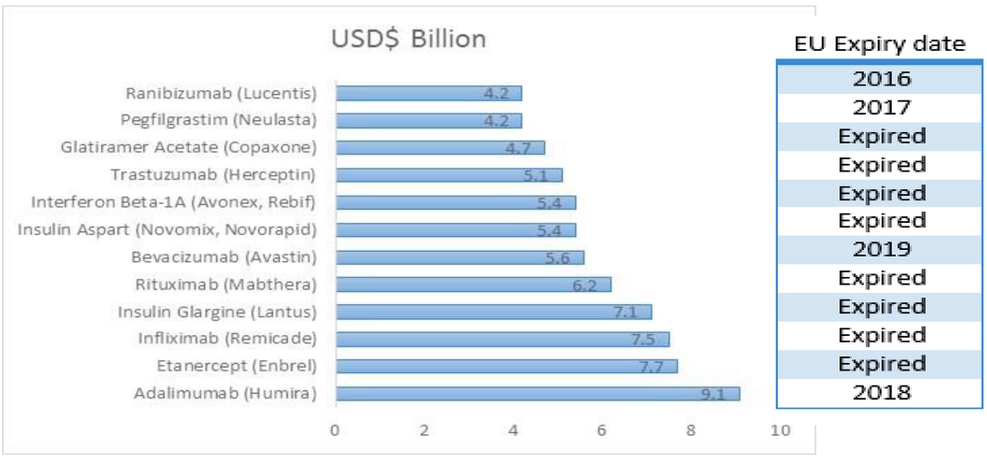
The impending patent expiry of many top selling biological medicines (see Figure 1) will likely result in more biosimilars coming to market over the next few years.

Table 1: Marketing authorisation applications for biosimilars currently under evaluation at EMA (5 January 2016)

INN	Reference product	Nature of active substance	Therapeutic area	Number of applications
Adalimumab	Humira®	Monoclonal antibody	Immunosuppressant	2
Enoxaparin sodium*	Clexane®	Low molecular weight heparin	Antithrombotic medicines	2
Etanercept**	Enbrel®	Fusion protein	Immunosuppressant	1
Infliximab	Remicade®	Monoclonal antibody	Immunosuppressant	1
Insulin glargine	Lantus®	Long acting insulin analogue	Medicines used in diabetes	1
Pegfilgrastim	Neulasta®	Pegylated glycoprotein	Immunostimulant	2
Rituximab	Mabthera®	Monoclonal antibody	Antineoplastic medicines	1

** Classified by EMA as a biosimilar as the starting material is of biological origin and the manufacturing process defines the characteristics of the drug substance*
*** Benepali® received positive opinion in Nov 2015*

Figure 1: Biological Medicinal Products - sales and patent expiry



2.0 PHARMACOVIGILANCE

EU and national legislation requires that in the case of suspected adverse reaction reports for biological medicines, the brand name and batch number of the medicine should be included in the relevant report. In addition new biological medicines including biosimilars are subject to additional monitoring in the first few years after approval. This monitoring is necessary as the medicine is new to the market and there is limited data on its long term use. Medicines subject to this additional monitoring contain a black inverted triangle on their package leaflet and SmPC. Pharmacists and other healthcare professionals should be aware of this status and report any suspected adverse reactions promptly so emerging information can be analysed efficiently.

A draft guideline on good pharmacovigilance practices for biological products is currently undergoing a public consultation process on the EMA website. This guideline applies to all biological medicines including biosimilars and will be open for comment until the 29th February 2016. The purpose of the guideline is not to replace or amend existing pharmacovigilance requirements but rather to address the main challenges associated with pharmacovigilance for biological medicines. The guideline provides an insight into the importance of traceability for all biological medicines and recommends that traceability should be fully integrated across different healthcare settings and infrastructure.

Biological medicines typically contain heterogeneous mixtures of large molecular weight structurally complex protein molecules. Living systems (e.g. animal or bacterial cells) are used in the production of these proteins which results in inherent variability even amongst different batches of the same medicine be it the originator or the biosimilar. In addition the complex manufacturing process required for production of a biological medicine is specific to each manufacturer and so this will shape the overall quality, safety and efficacy profile of the medicine. For these reasons traceability to product and batch level needs to be assured.

The draft guidance discusses pharmacovigilance considerations applicable to biological medicines namely; immunogenicity, manufacturing variability, stability and cold chain as well as product traceability. Some of the main points addressed in the guidance are outlined in Table 2.

Pharmacovigilance: Key Learning Points

- Pharmacists should be aware of medicines subject to additional monitoring. This status applies to all newly authorised biological medicines including biosimilars. Suspected adverse reactions for medicines with this status should be reported promptly.
- To ensure traceability, product **brand name** and **batch number** of biological medicines should be recorded at all levels of supply including dispensing and patient administration.

Table 2: Specific issues and challenges relating to biological medicines outlined in draft GVP guideline[1]

Specific issues and challenges	Summary of main points from draft guideline
Immunogenicity	• Biologicals pose greater risk of immunogenicity than chemical medicines • Sources of immunogenicity include product related factors (e.g. changes to 3D structure of protein during processing), treatment related factors (e.g. route of administration) and patient/disease related factors • Immunogenicity can be introduced at any stage in the lifecycle of the medicine due to changes in manufacturing processes and/or quality
Manufacturing variability	• Changes in manufacturing processes are often required for biological medicines (e.g. change in source materials, purification processes etc.) • Changes are supported by a quality comparability exercise, where batches of the medicine produced before the change are rigorously compared to those manufactured after the change. The need for non-clinical and clinical comparability studies is determined on a case by case basis • Manufacturing changes may impact product quality and subsequently affect efficacy and safety. It may not always be possible to predict immunogenicity as a result of a manufacturing change • Biological medicines are considered to have a 'dynamic quality profile'. The 'drift' in quality specifications over time may eventually result in medicines with the same INN exhibiting different safety profiles
Stability and cold-chain	• Once a medicine is released from the manufacturer the stability of the medicine is assured by appropriate storage/handling, cold chain and good distribution practices • Non adherence can affect the medicines quality and stability and may introduce immunogenicity or contamination
Product traceability	• Due to the aforementioned manufacturing variability and associated 'dynamic quality profile' traceability to the individual batch number is essential in order to consider the potential impact of any suspected adverse reactions observed • Consequently product **brand name** and **batch number** should be recorded at all levels in the supply chain from manufacturer release, prescription, dispensing and patient administration

3.0 INTERCHANGEABILITY OF BIOLOGICAL MEDICINES

Currently there is much debate over whether originator and biosimilar medicines can be considered interchangeable and whether switching or substitution of biological medicines is appropriate. The use of different terms such as 'interchangeability', 'switching' and 'substitution' can also be a source of confusion. Useful definitions are provided in the European Commission Consensus Information Document 'What you need to know about biosimilar medicinal products' (see Table 3).

3.1 IRELAND

Although the EMA is involved in the approval process of a biosimilar, decisions about interchangeability are subject to the discretion of each Member State. In Ireland biological medicines cannot be substituted at a pharmacy level without prescriber consent as such medicines are outside the scope of the Health (Pricing and Supply of Medical Goods) Act 2013. This Act allows for pharmacy led 'substitution' of specific chemical medicines. In order to avoid inadvertent substitution, the brand name of the biological medicine or if appropriate the INN plus name of the marketing authorisation holder should be recorded when prescribing and dispensing a biological medicine. The HPRA guide to Biosimilars for Healthcare Professionals and Patients advises that the treating physician be consulted regarding decisions around interchangeability/switching of originators and biosimilars. In addition the guide states that switching back and forth is not recommended due to current lack of clinical studies to support this practice.

3.2 INTERNATIONAL POLICIES

Policies relating to interchangeability, switching and substitution differ across the globe. In Australia the body involved with listing medicines for reimbursement the 'Pharmaceutical Benefits Advisory Committee' (PBAC) have taken the decision to award an 'a' flag to the infliximab biosimilar 'Inflectra™'. A 'flagged' brand can be considered for substitution by the pharmacist at the point of dispensing. The awarding of this flag means that Inflectra™ and the innovator Remicade® are now substitutable at pharmacy level once the pharmacist has consulted with the patient. However prescribers retain the right to indicate that 'substitution is not permitted'.

The first biosimilar medicine in the United States, Zarxio (filgrastim-sndz), was approved by the FDA in March 2015. In contrast to the situation in Australia decisions concerning pharmacist led substitution of biological medicines in the US are made by the medicines regulator and not bodies responsible for reimbursement. In addition to the biosimilar classification the FDA also makes provision for an 'interchangeable biological product' category. According to the FDA website 'interchangeable biological products' are biosimilars which meet additional requirements for interchangeability. If a medicine is classified as such then the interchangeable medicine may be substituted for the originator without the intervention of the prescriber. The FDA has yet to publish guidance on what the requirements for interchangeability are and to date no biosimilars have been placed in this category.

3.3 CLINICAL STUDIES TO SUPPORT INTERCHANGEABILITY

A number of hospital sponsored clinical studies are ongoing throughout Europe in order to evaluate the safety and efficacy of switching from originator infliximab to biosimilar infliximab. Preliminary results from the NOR-SWITCH study are expected in July 2016. This is a randomised, double blind, parallel group study which is evaluating safety and efficacy associated with switching from Remicade® to Remsima® in comparison to continued treatment with Remicade®. An estimated 500 adult patients are enrolled in the trial which is being conducted in Norway. The trial covers all the current adult indications approved for the originator and biosimilar medicines in Europe. The BIO-SWITCH study in the Netherlands is an open parallel group study which is examining the effect of switching treatment from originator infliximab to biosimilar infliximab on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, spondyloarthritis or psoriatic arthritis. The target number of participants is 200 and expected completion date of the trial is April 2017.

Table 3: Definitions of interchangeability, substitution and switching taken from EC Consensus Information document 'What you need to know about biosimilar medicinal products'.

Interchangeability	The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.
Substitution	Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber
Switching	Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

4.0 NAMING OF BIOSIMILARS

In Europe biosimilars share the same INN with the originator once similarity between the two medicines has been established. However this approach to naming varies across different global regions. For instance WHO and FDA proposals on the naming of biosimilars differ to the approach used in Europe.

The WHO have proposed a voluntary scheme where a biological qualifier (BQ) can be used to differentiate biological drug substances with the same INN that been manufactured by different processes. The BQ is a random code, which according to the WHO, will prevent the proliferation of distinct national qualifier systems. A separate naming scheme has been proposed in the United States. Draft FDA guidance proposes that the non-proprietary name of an originator and biosimilar share the same core drug substance name but also contain a differentiating FDA-designated suffix. A hypothetical example given on the FDA website is replicamab-cznm (innovator) and replicamab-hixf (biosimilar). According to the FDA website the naming convention will serve to prevent inadvertent substitution and support safety monitoring of all biological medicines once they are on the market.

In Europe the naming situation is less complex as biosimilars simply use the same INN as the originator and no qualifier is required. However different approaches taken to naming of biosimilars in different regions could cause confusion amongst healthcare professionals. Pharmacists should be aware that the appropriate naming of biosimilars in other regions is currently under debate and this may need to be considered when dealing with patients from different jurisdictions.

5.0 IMS REPORT ON BIOSIMILAR UPTAKE IN EUROPE

In November 2015 IMS Health published a report entitled 'The Impact of Biosimilar Competition'[2]. The report describes the effect of biosimilar competition on price, volume and market share in each European country in 2014. The report illustrates that biosimilar competition drives down the price not only of the originator but also of other medicines in the same therapeutic category. In the cases of established biosimilar products (e.g. epoetin medicines) EU average savings of up to 28% can be seen across the entire product class. Such savings have significant implications for healthcare budgets and serve to increase patient access to biological medicines.

6.0 REGULATORY SCIENCE IRELAND BIOSIMILARS RESEARCH PROJECT'

Regulatory Science Ireland (RSI) is a voluntary network of interested parties from Academia, HPRA, Industry and Government Agencies. RSI is conducting a research project which aims to enhance understanding of biosimilars amongst stakeholders and so encourage best practice in the use of these medicines. Areas of focus include safety concerns with inter-changing biosimilar substances, enhanced pharmacovigilance and traceability requirements, and the need for procurement/ purchasing procedures to take due account of the differences in biosimilars relative to originator medicines. One of the initial objectives will be to survey knowledge of biosimilars amongst healthcare professionals. It is planned to disseminate the results of the research findings via peer-reviewed scientific articles, relevant training materials and outreach activities. The research project outcomes will serve as an impartial independent resource which will support effective knowledge transfer regarding biosimilars to pharmacists and other healthcare professionals.

References

[1] Draft guideline on good pharmacovigilance practices (GVP): Product – or population specific considerations II: biological medicinal products (December 2015), available on the European Medicines Agency website.

[2] The Impact of Biosimilar Competition, IMS Health Report, November 2015, available on the European Commission website.

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