ROUNDTABLE

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Biosimilars and hospital pharmacists: Addressing misconceptions

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Biosimilars and hospital pharmacists: Addressing misconceptions

The first biosimilar was granted marketing authorisation by the European Commission (EC) in 2006. Since then, the initial uptake has been relatively slow — as was to be expected for a new class of medicine. In recent years, increased stakeholder awareness and education around biosimilars has led to rising usage, but there are still significant improvements to be made.

Contributing to this are a number of misconceptions held by many healthcare professionals, including pharmacists.

Senior hospital pharmacists from seven countries met to identify, explore and address the common misconceptions around biosimilars.

Common misconceptions

The amino acid sequence of the active component of a biosimilar is different to that of its reference biologic.

A biosimilar will not be as efficacious and safe as its reference medicine because they are not identical.

The single confirmatory trial required for EC authorisation is insufficient. More evidence is needed to prove that the biosimilar is as safe and efficacious as its reference medicine for all indications.

Without clinical data for all the indications of the biosimilar, assumptions are being made when extrapolating to all indications of the reference medicine.

The clinical data generated in the development of biosimilars are inadequate. Therefore, post-marketing surveillance is undertaken to compensate.

The most important driver for biosimilar adoption is cost saving.

Biologics are medicines made in living systems or organisms, such as yeast, bacterial or mammalian cells. Vaccines and blood products, as well as recombinant proteins, such as simple replacement hormones or more complex molecules like monoclonal antibodies (mAbs), are all examples of biologics.

Biologics are increasingly well characterised, and their development accounts for approximately 30% of the pharmaceutical industry's investment in research and development.

A biosimilar is defined by the European Medicines Agency (EMA) as 'a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product'.[1]

The earliest biosimilars to come to market were hormones (e.g. somatropin) and growth factors (e.g. filgrastim). Following this so-called 'first generation' of biosimilars came a more complex class of biologics including mAbs and fusion proteins (e.g. infliximab, rituximab and etanercept).

As biologics, biosimilars have revolutionised treatment in a number of therapy areas including growth hormone deficiencies, supportive care in cancer treatment and immune disorders.

Some concerns about the use of biosimilars have been raised, and a number of misconceptions have become commonplace. These need to be addressed in order to enable informed decision making and improve patient access.

Many biosimilars are expected to gain marketing authorisation over the next five years. With the financial strain on European healthcare systems at a critical juncture, now is the time to address these misconceptions.

Challenging the misconceptions

Misconception: The amino acid sequence of the active component of a biosimilar is different to that of its reference biologic.

A prerequisite for biosimilar development is that the amino acid sequence, which defines the primary structure of the protein, of the reference biologic and the biosimilar are identical. There is no difference between them.

This is not to say that the medicines are identical: every biologic exhibits inherent variability between batches of the same product, caused by the biological expression systems and the complex manufacturing processes. The same applies to biosimilars. Critically, the variability of the biosimilar will not be greater than that of the reference medicine.

In addition, the 3D structure of a biosimilar is indistinguishable from that of its reference biologic, as demonstrated by techniques such as X-ray crystallography, despite variations in post-translational modifications such as glycosylation.

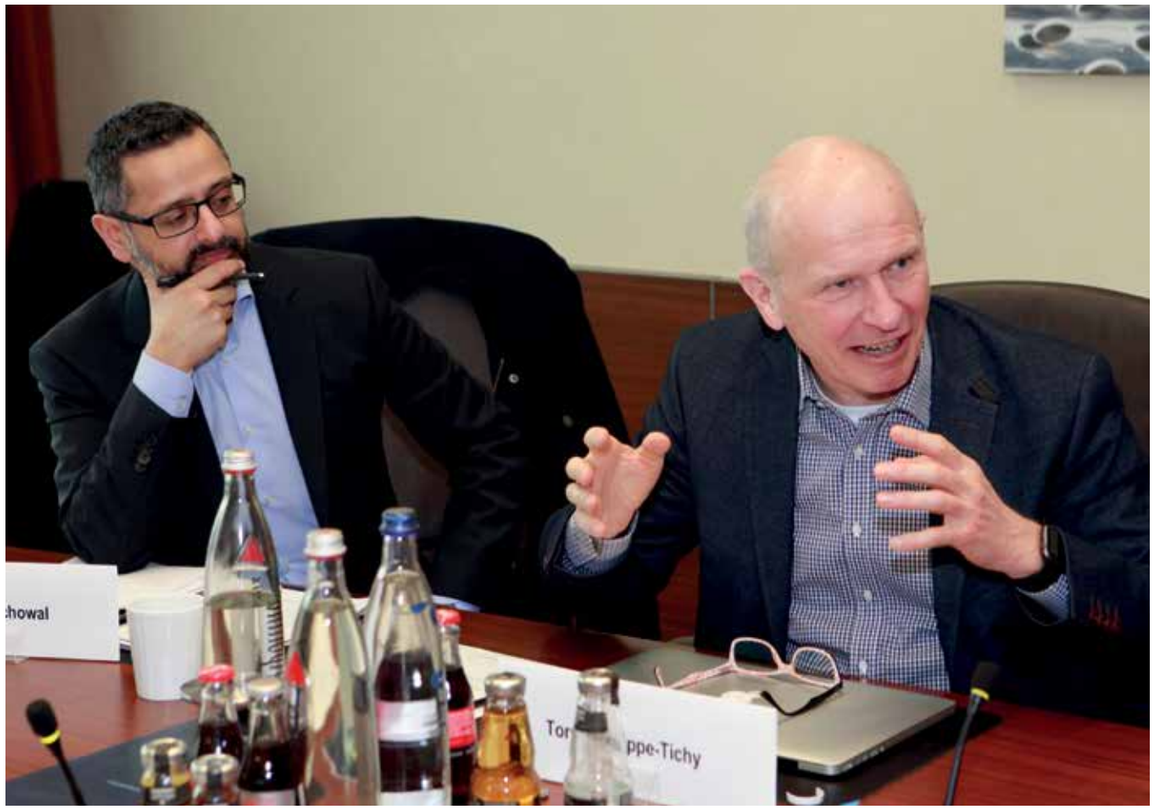
Misconception: A biosimilar will not be as efficacious and safe as its reference medicine because they are not identical.

This misconception sits at the heart of the similar-but-not-identical paradigm.

No biologic will be identical to its reference medicine. As previously noted, all biologics — whether biosimilars or reference medicines — exhibit variability between batches. Regulatory authorities assess biosimilar medicines based on the extent to which the biosimilar matches its reference biologic in terms of safety, efficacy and quality. Comparability exercises are used to demonstrate biosimilarity: the active substance of the biosimilar is, for scientific and regulatory purposes, a version of the active substance of the reference biologic.

'There is a misconception that the only variability that exists is between the reference product and the biosimilar. There is also variability within the reference product.'

– Tim Hanlon



Misconception: The single confirmatory trial required for EMA authorisation is insufficient. More evidence is needed to prove that the biosimilar is as safe and efficacious as its reference medicine for all indications.

The process of EMA marketing authorisation begins with a plethora of analytical tests and measurements to ensure that the biosimilar will match the reference molecule. This includes meticulous analysis of the batch-to-batch variability of the reference medicine, as stated above.

The stepwise comparability exercise follows, involving analytical, preclinical and clinical studies, confirming that the biosimilar matches the reference medicine. The scientific rigour behind the comparison is demonstrating biosimilarity. At least one clinical study will form part of the totality of evidence. This trial is usually in a sensitive indication as agreed between the regulatory authorities and the biosimilar sponsor, so that any potential differences in clinical efficacy, safety and immunogenicity, between the reference medicine and the biosimilar, can be excluded.

'We are trying to pre-empt objections by educating people about biosimilars.'
– Jatinder Harchowal

Misconception: Without clinical data for all the indications of the biosimilar, assumptions are being made when extrapolating to all indications of the reference medicine.

Extrapolation is from the reference medicine molecule to the biosimilar molecule, not from data generated with the biosimilar in one clinical indication to other indications. The totality of evidence exercise proves that the reference medicine and biosimilar molecules match in terms of structural attributes, biological functions, efficacy and safety through data from analytical and preclinical studies as well as clinical studies in at least one sensitive indication. This evidence establishes the scientific bridge to the clinical evidence of the reference medicine, justifying the safe use of the biosimilar in all indications, and in all populations approved for the reference medicine.

For a reference medicine, clinical data must be generated for every indication for which it seeks approval. Evidence is weighted on understanding the clinical performance of that molecule, with pharmacokinetic, pharmacodynamic, preclinical and analytical measurements being of lesser significance.

The focus of biosimilar development is the stepwise comparability exercise that includes analytical, preclinical and clinical evidence, which proves the biosimilar matches the reference medicine with respect to structure and function. To achieve this, analytical measures are the most critical element

of the development process, followed by preclinical and clinical studies. The biosimilar sponsor scientifically proves that the active substances match, and that the biosimilar molecule will behave in the same manner. Therefore, the biosimilar can be approved for indications for which it has not been tested clinically. Extrapolation is not granted automatically; it needs to be scientifically justified and factors including, for example, the mechanism of action must be taken into account.

Data extrapolation is not a concept unique to biosimilars. It is an established principle in the case of major changes in the manufacturing process of reference medicines. Data generated in one indication may be extrapolated to other indications, provided that the totality of evidence gathered from the comparability exercise is supportive. In the case of biosimilars, extrapolation of data from a reference medicine to a biosimilar is considered, provided that biosimilarity to the reference medicine has been demonstrated.

If pharmacists (and prescribers) do not understand this process, seeds of doubt are planted not only about the demonstration of biosimilarity in a clinical study, but also about the validity of extrapolation of data to other indications. The critical fact that needs to be communicated is that extrapolation is based on the scientific principle that the same molecule will behave in the same way. Extrapolation is from molecule to molecule, not from indication to indication.

[Regarding EMA approval requirements] 'the perception is that it is too easy, too simple. Not rigorous enough.'
– Johan Vandenbroucke

Misconception: The clinical data generated in the development of biosimilars are inadequate. Therefore, post-marketing surveillance is mandatory to compensate.

Post-marketing surveillance is vital in monitoring the safety of all biologics. Biosimilars and their reference medicines both have to meet the same strict requirements. The objective of post-marketing surveillance is to collect real-world data, including those on immunogenicity, and to report adverse events should they occur.

The entire body of evidence supporting the proof of similarity between a biosimilar and its reference medicine demonstrates that the same safety profile can be expected.

For a biosimilar, as for any new drug, a comprehensive risk management plan, including a plan for post-authorisation safety surveillance, has to be submitted to the European authorities at the time of the marketing authorisation application.

Misconception: The most important driver for biosimilar adoption is cost saving.

When considering the addition of any medicine to a hospital formulary, the Drug and Therapeutics Committee will consider its efficacy, safety and pharmacoeconomics, as well as the reliability of supply.

'It is about reasonable resource allocation. We have to allocate the resources that we have wisely.'

– Marta Trojniak

Because healthcare systems across Europe are all operating in financially constrained environments, cost will certainly be one of the considerations when making a decision to prescribe a biosimilar, but it will not be the only or the most important driver.

Financial responsibility for the medicines budget does not mean spending less, but rather spending more wisely to provide the best possible outcomes for the greatest number of patients. Choosing a biosimilar increases choice for the patient, while producing the same outcomes.

Greater competition acts as a trigger for companies to get closer to patients' needs, encouraging innovation in what they offer the clinical community.

Addressing misconceptions

Hospital pharmacists are ideally placed to act as agents of change for their colleagues' approach to new medicines. This is because they and the wider clinical team are responsible for the optimal use of resources, including medicines, and because they are the healthcare professionals who will see beyond the medicine to matters of quality, delivery and compliance.

How can pharmacists instil confidence in use of biosimilars in their hospital? It will not be possible to pre-empt all misunderstandings and concerns. Which flags can help them to address misconceptions?

- **Physicians who do not currently prescribe biosimilars present an opportunity for the hospital pharmacist to:**
  - Discuss the rigorous process of head-to-head comparison with the reference medicine, to match in physicochemical and biological characteristics, safety and efficacy.
  - Discuss the nature and rationale of the clinical studies required by the regulatory authorities.
  - Explain to physicians that biosimilar development requires clinical proof of either equivalence or non-inferiority in a sensitive indication.
- **Lack of discussion on biosimilars among physicians and medical staff at a hospital creates an opportunity for the pharmacist to:**
  - Encourage the creation of multidisciplinary teams to discuss biosimilars, where concerns and misconceptions can be addressed in an atmosphere of rational debate, trust and confidence. Colleagues may be keeping their misconceptions to themselves. Some may have received contrary information.
  - Signpost colleagues to key/pivotal biosimilar documents such as:
    - those regarding regulatory matters (for example, EMA European Public Assessment Reports,[2] and the EMA/EC document *Biosimilars in the EU – Information guide for health care professionals*).[3]
    - those on policy (for example, *Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers*).[4]
    - the ECCO position statement: *The use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD)*.[5]
  - Share the information and educational materials they have on biosimilars with colleagues to encourage discussion and debate.
- **When cost is seen as the only reason for prescribing biosimilars, pharmacists have an opportunity to:**
  - Inform their colleagues of the benefits to their patients in terms of choice and best outcomes.
  - Convince their colleagues of the importance of innovation in meeting healthcare demands.
  - Remind their colleagues that they are responsible for making decisions that result in the best possible outcome for the greatest number of people.

Building a sound foundation to educate fellow healthcare professionals about biosimilars takes time, and will require a combination of in-depth knowledge and the negotiation and persuasion skills to communicate it.

The time to advance the argument in favour of biosimilars is now. The sustainability of healthcare budgets and the availability of biologic medicines for patients may depend upon it.

Hospital pharmacists have a responsibility to take full advantage of the development of all biosimilars. The choice to seize the opportunity and to address the misconceptions amongst colleagues about biosimilars is theirs.

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The roundtable 'Exploring misconceptions around the use of biosimilars' convened in Frankfurt on 8 February 2017 with the support of Sandoz, and was attended by senior hospital pharmacists from seven EU countries.

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