

# BIOSIMILARS: ENSURING CLINICAL EFFICACY & SAFETY

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# DISCLOSURES

David W Holt has reported no conflict of interest



# KEY POINTS



- ◆ **Biological medicines are complex molecules that are difficult to manufacture.**
- ◆ **The regulatory pathway to manufacture them differs from that used for small molecular weight drugs.**
- ◆ **When the patent life expires on biologicals, they can be copied by other manufacturers using a very precise regulatory pathway.**
- ◆ **This pathway ensures quality, efficacy and safety of the resulting product – a biosimilar.**
- ◆ **Because of the complexity of manufacture, a biosimilar is never exactly the same as the originator biologic molecule.**
- ◆ **Any differences in molecular structure between the originator molecule and a biosimilar could compromise clinical efficacy or give rise to adverse effects such as immunogenicity.**
- ◆ **As a result, switching to the use of a biosimilar, or switching between biosimilars of the same drug, requires planned pharmacovigilance to ensure the maintenance of both efficacy and safety.**

# WHAT IS A BIOLOGICAL MEDICINE?

- ◆ **Biological medicines have revolutionised the treatment of several life-threatening diseases and chronic clinical conditions.**

These include:

diabetes

rheumatoid arthritis

inflammatory bowel disease

cancers

- ◆ **In the treatment of cancer several monoclonal antibodies have proved highly effective.**

They include: bevacizumab, rituximab and trastuzumab, among others.

- ◆ **A biological medicine is derived from living organisms.**

These include:

plant or animal cells, bacteria, viruses, yeasts.

Most have been derived from genetically modified cells.

Biologicals are large complex molecules.

# BIOLOGICALS



- ◆ Biologicals are much larger molecules than conventional, chemically derived, small molecular weight drugs, such as aspirin, which has a molecular weight of only ~180 Daltons.
- ◆ Biologicals range in size and complexity from peptides to proteins and glycoproteins.

For example:

Calcitonin ~3,500 Daltons

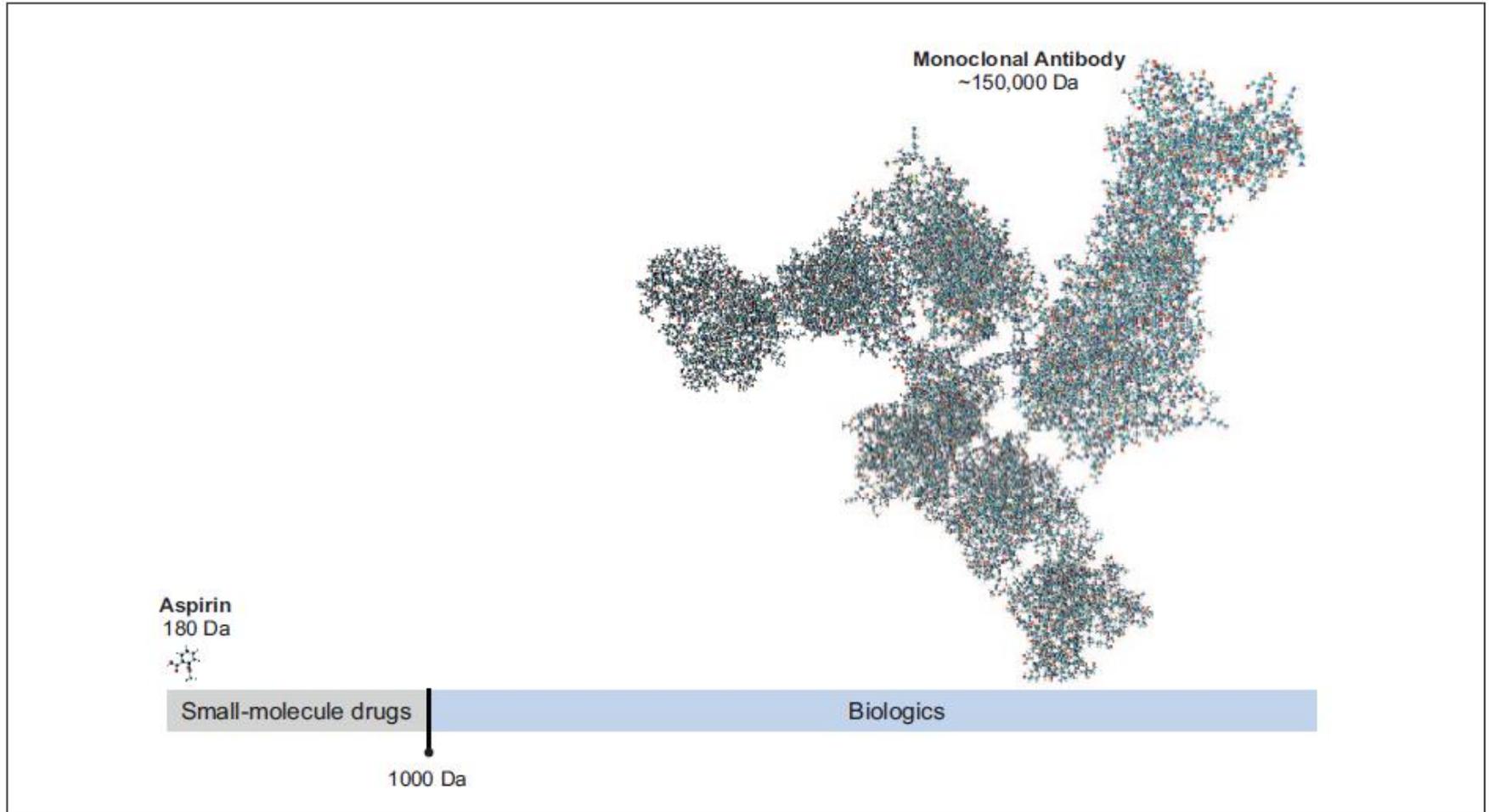
Insulin ~5,800 Daltons

Growth hormone ~22,000 Daltons

Monoclonal antibodies ~150,000 Daltons

The extremes of this range are illustrated in the next slide.

# BIOLOGICALS



Stevenson JG, *et al.* Ann Pharmacother 2017;51(7):590–602, Copyright © 2017 SAGE Publications. Reprinted by Permission of SAGE Publications, Inc..

# BIOLOGICALS



- ◆ **Conventional drugs are:**

Small molecular weight, structurally simple, generally stable, manufactured in a predictable manner and easily characterised.

- ◆ **Biologicals are:**

Large molecular weight, have a complex structure, are unstable, manufactured from a unique cell line which cannot be reproduced exactly and are difficult to characterise.

Biological activity is largely due to the amino acid sequence and folding of the peptide or protein.

# BIOLOGICALS



- ◆ **To produce a biological medicine a manufacturer uses a unique cell line and a unique manufacturing processes.**
  - ◆ When the patent life of a biological expires, other manufacturers can attempt to manufacture a copy of the original biological medicine.
  - ◆ The copy product is known as a biosimilar, a term adopted by several other agencies.
- ◆ **The regulatory authority with the most experience in the field of assessing copies of biologicals is the European Medicines Agency (EMA).**
- ◆ **The EMA approach has had a global impact on the development and testing of biosimilars.**
  - ◆ The first biosimilar approved in the EU was in 2006 - Omnitrop (somatropin).
  - ◆ At August 2018, 46 biosimilars had been approved by the EMA, some of these multiple copies of the same originator drug. <sup>1</sup>

<sup>1</sup><https://www.biosimilarsip.com/2018/08/02/how-the-u-s-compares-to-europe-on-biosimilar-approvals-and-products-in-the-pipeline-2/> (accessed October 27, 2018)

# WHAT IS A BIOSIMILAR?



- ◆ **Biosimilar is a regulatory term introduced by the EMA.**

It is used to denote a biopharmaceutical approved under the biosimilar regulatory pathway.

A biosimilar is a successor to a biopharmaceutical for which the patent has expired and has been approved under the biosimilar regulatory pathway.

- ◆ **It is not a universal term, although it is becoming the most widely accepted for such medicines.**

Other terms that have been used include:

Follow-on Biologic

Subsequent-entry Biologic

Similar Biotherapeutic Product

- ◆ **The EMA defines a biosimilar as:**

A biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (the so-called 'reference medicine').

# BIOSIMILARS



- ◆ Biosimilars manufactured by different manufacturers will differ from the reference medicine and from each other because they use different host cells and manufacturing processes to develop the biosimilar product.
- ◆ The active ingredient of a biosimilar can never reproduce exactly that of the reference biological.
- ◆ As a result, the development, manufacture and testing of biosimilars is more complex and costly than for small molecular weight conventional drugs.
- ◆ Nevertheless, it is anticipated that the entry of biosimilars into the market will reduce healthcare costs for expensive biologicals by introducing competition.

# BIOSIMILARS – SIMILAR DRUGS



- ◆ **A biosimilar is similar, not identical, to the reference medicine.**
  - ◆ The manufacturing process used by the innovator manufacturer can never be duplicated down to the last detail.
- ◆ **The manufacturer of a proposed biosimilar uses a different manufacturing process from that of the innovator, including:**
  - ◆ the cell line
  - ◆ raw materials, including the final excipients and stabilisers
  - ◆ manufacturing equipment
  - ◆ process controls
  - ◆ acceptance criteria
  - ◆ packaging

# BIOSIMILAR APPROVAL PROCESS



- ◆ The complexity of biologicals precludes the use of the generic approach to register biosimilars.
- ◆ **There is no such thing as a generic biologic.**
- ◆ The basis for comparing solid dose formulations of *small molecular weight* drugs is **the bioequivalence process.**
  - ◆ This establishes that two formulations have kinetics for the rate and extent of absorption that are within pre-defined limits.
  - ◆ Excipients do not need to be identical.
  - ◆ Clinical studies are not required.
- ◆ **For biosimilars a more complex system of approval is needed.**
  - ◆ This involves a head-to-head comparison with the reference medicine.

# BIOSIMILAR APPROVAL PROCESS



- ◆ The initial studies centre around a *comprehensive analytical assessment* of the structure of both the reference compound and the proposed biosimilar.
- ◆ **The decision to approve a biosimilar is based on the totality of evidence from the comparative procedure.**
  - ◆ The amino acid sequence must be the same for both molecules and the biosimilar must be highly similar in terms of its three dimensional structure, post-translational modifications (such as glycosylation) and purity.
  - ◆ Purity may also be affected by heterogeneity resulting from changes in protein structure on storage, by processes such as oxidation or deamination. These changes must be documented to exclude any effects on efficacy and safety.
  - ◆ Minor differences in chemical structure of the biosimilar are allowed, but it should possess no clinically meaningful differences in efficacy and safety compared with the originator product.

# BIOSIMILAR APPROVAL PROCESS



- ◆ **Because biological medicines are so complex, they cannot be defined by their chemical structure alone.**
  - ◆ Following the detailed structural and purity comparison it is necessary to undertake pre-clinical and, usually, clinical studies to *demonstrate efficacy and safety*.
- ◆ **The goal of the comparison exercise is to show *similarity* with the originator molecule, not clinical advantage.**
  - ◆ The pre-clinical programme for a biosimilar is abbreviated compared with that of the originator molecule.
  - ◆ The studies include comparison of the pharmacodynamics of the compounds to assure similar binding to target cells and inhibition or activation of pharmacodynamic targets.
  - ◆ The pre-clinical studies are also likely to include studies of sub-chronic toxicology, tolerance, pharmacokinetics and pharmacodynamics, unless adequate *in vitro* models are available.
  - ◆ Clinical studies include a Phase I study comparing the pharmacology (PK/PD) of the two molecules, using the most sensitive biomarkers available.

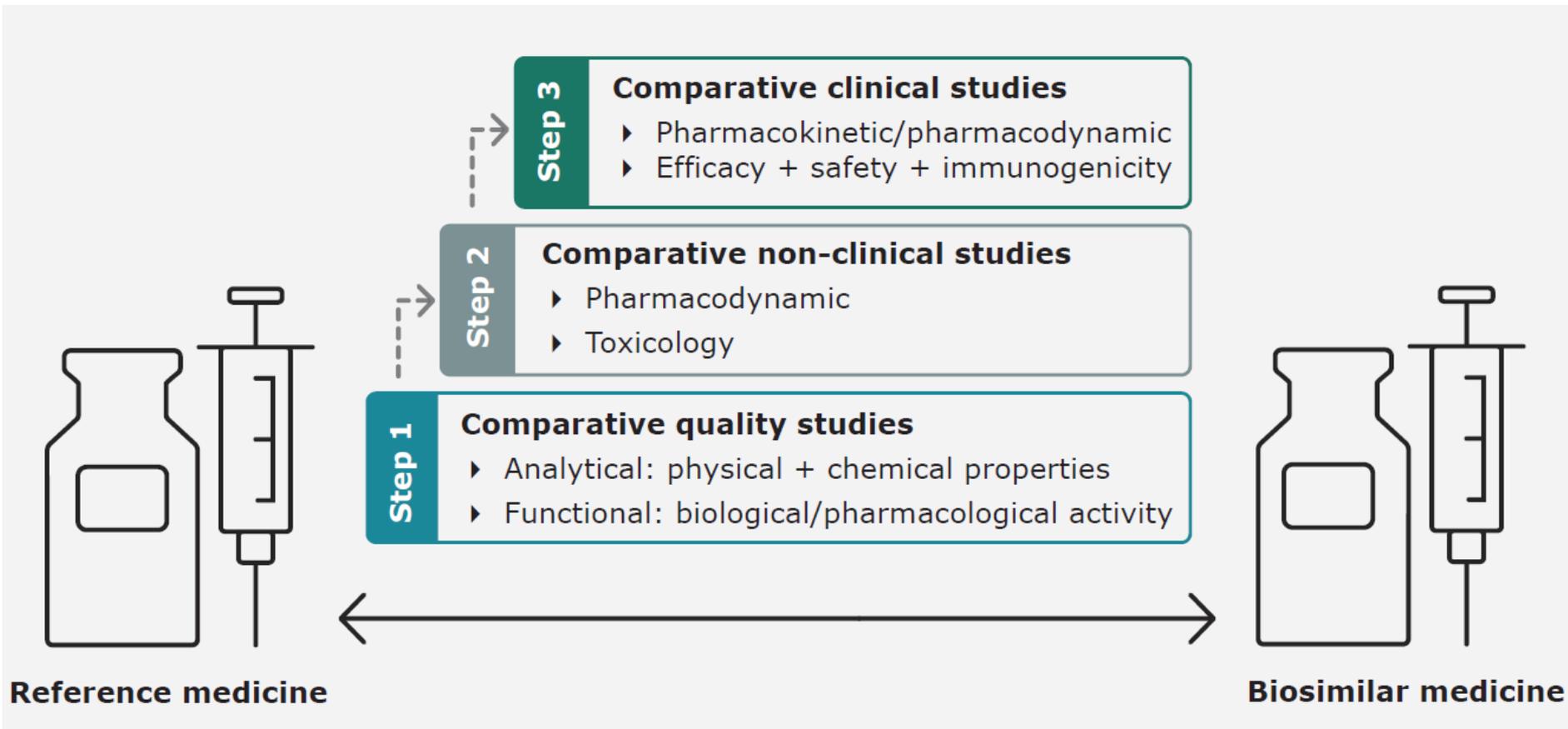
# BIOSIMILAR APPROVAL PROCESS

- ◆ **Clinical studies** are usually required in one clinical indication to ensure comparable efficacy and that key safety issues have been addressed.
  - ◆ A study population most sensitive to efficacy differences between the two formulations is used.
- ◆ **One of the safety issues of particular importance is that of immunogenicity.**
  - ◆ All therapeutic proteins have the potential to illicit an unwanted immune response.
  - ◆ This may result in an adverse drug reaction or loss of efficacy of the medicine due to the formation of anti-drug antibodies.
  - ◆ Immunogenicity can be elicited or made worse by changes in protein structure on storage or by the formation of aggregates.
  - ◆ Immunogenicity may also relate to the route of administration of the drug, disease-related factors or other drug therapy.

# BIOSIMILAR APPROVAL PROCESS

- ◆ **The biosimilar process builds on knowledge gained during the clinical use of the originator medicine. It does not aim to repeat the development programme of the originator.**
  - ◆ Thus, fewer volunteers and patients are exposed to clinical studies and overall development costs for the biosimilar should be lower.
  - ◆ A key aspiration of healthcare providers is that access to biologicals will be cheaper and more widely available as a result of biosimilars entering the market.
- ◆ **The key stages in the development of a biosimilar using the EMA pathway are summarised in the next slide.**

# DEVELOPMENT OF BIOSIMILARS



From: Biosimilars in the EU. Information Guide for Healthcare Professionals.

[https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf) (Accessed 29/11/2018)

# EXTRAPOLATION



- ◆ **Once biosimilarity is established a manufacturer can refer to the extensive safety and efficacy dossier of the originator.**
  - ◆ A biosimilar is usually approved for the same indications as the reference product given that they share the same mode of action.
- ◆ ***Extrapolation to other clinical areas requires scientific justification, generated by data from the comparability studies for the biosimilar and originator drugs.***
  - ◆ Usually, such justification will not require additional clinical studies.
  - ◆ However, additional non-clinical/clinical studies are likely to be requested for additional indications of the biosimilar if the activity of the molecule is mediated via different receptors.
  - ◆ Because immunogenicity is not only related to the physical structure of the molecule and its formulation, extrapolation for immunogenicity is not automatic. It must be justified scientifically.

# INTERCHANGEABILITY SWITCHING & SUBSTITUTION



- ◆ For compounds that have been licenced after going through the complete biosimilar process it is possible to use the drug interchangeably with another registered biological drug for the same indication.
  - ◆ This allows for the use of a biosimilar as an alternative to an innovator biological, or for the use of one biosimilar in place of another.
  - ◆ The rationale for this interchangeability is that the biosimilars have gone through the head-to-head comparison procedure and have been shown to have no significant differences in terms of efficacy and safety.

**Switching** is the process of a clinician making the decision to change a patient from one formulation of an active compound to another for the treatment of the same disease.

**Substitution** is the process of a pharmacist dispensing one medicine which is interchangeable with another, but without consulting the prescribing clinician.

# INTERCHANGEABILITY SWITCHING & SUBSTITUTION



- ◆ In the European Union decisions on switching and substitution are made at the level of the individual member states.
- ◆ Because of their complexity, and the potential for immunogenicity, many consider that switching from one biological to another with the same mode of action is a decision that should always be made by the prescribing clinician.

For instance, the guidelines in the UK are<sup>1</sup>:

*.....switching between a reference product and its biosimilar (and indeed amongst biosimilar medicines) should be managed at the discretion of the individual prescriber in partnership with the patient, with appropriate monitoring in place.*

*Automatic substitution, defined here as the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber, is not appropriate for biological medicines, including biosimilar medicines and is not permitted at this time.*

<sup>1</sup><https://www.england.nhs.uk/wp-content/uploads/2015/09/biosimilar-guide.pdf>

Accessed August 21, 2018

# OTHER REGULATORY PATHWAYS



- ◆ There is broad scientific alignment amongst the highly regulated drug authorities with respect to the assessment of biosimilar medicines.
- ◆ **Three authorities are of particular importance with respect to the assessment of biosimilars:**
  - ◆ The European Medicines Authority, the US Food and Drug Administration and the World Health Organisation.
  - ◆ Because of its breadth of experience, the EMA guidelines continue to play a major role in aligning the highly regulated authorities.
  - ◆ The WHO Guidelines for Similar Biotherapeutic Products are important in assisting global convergence for biosimilars.

# REGULATORY ISSUES



- ◆ Regulatory procedures and intellectual property rights can differ outside those countries with highly regulated drug licencing policies.
- ◆ Biosimilar regulatory practices may fall well below those in the highly regulated areas.
  - ◆ The resulting copy products may be approved by a less-stringent pathway that does not include a head-to-head comparison with the originator drug.
  - ◆ These copy products are known as *intended copies* and do not qualify as biosimilars.
  - ◆ Intended copies may have differences in the formulation or dose compared with the originator, which have not been shown to be without effect on efficacy and safety.
- ◆ **To be called a biosimilar the copy product must undergo the complete biosimilar development pathway.**

# BIOSIMILAR NOMENCLATURE



- ◆ **The naming of biosimilars has important implications for assessing the long-term safety and efficacy of these compounds.**
- ◆ This issue assumes even greater importance as the number of biosimilars with the same active molecule increases, since the scope for multiple switches between different biosimilars and the originator drug increases.
- ◆ **There is no international harmonization on the naming of biosimilars.**
  - ◆ In the EU biosimilars use the same International Non-proprietary Name (INN) as the reference medicine. The recommendation is that, when a biosimilar is prescribed, the trade name and the batch number should be recorded to facilitate identification of any changes in efficacy or safety compared with the reference medicine or another biosimilar.
  - ◆ The FDA use a system involving the INN and a suffix of four randomly allocated lower case letters to distinguish each formulation.
  - ◆ Other systems are in place or evolving.<sup>1</sup>

<sup>1</sup>Mysler E, Pineda C, Horiuchi T, Singh E, Mahgoub E, Coindreau J, Jacobs I.

Clinical and regulatory perspectives on biosimilar therapies and intended copies of biologics in rheumatology. *Rheumatol Int.* 2016;36:613-25

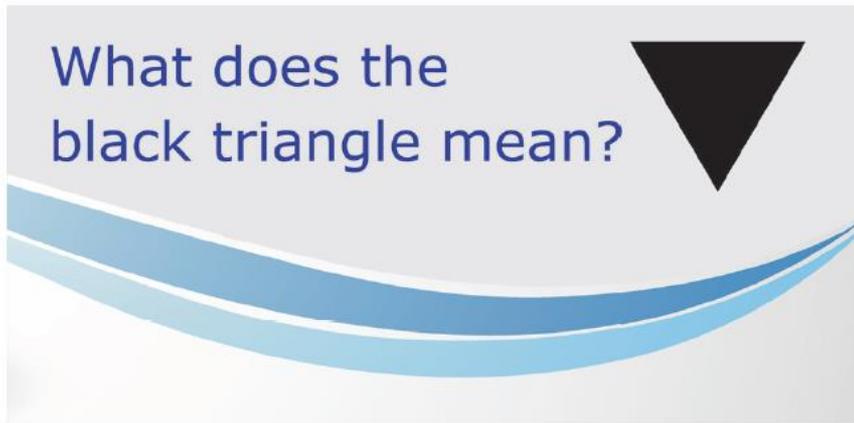
# PHARMACOVIGILANCE



- ◆ **Pharmacovigilance is an essential part of the assessment of both small molecular weight drugs and biologicals.**
- ◆ In the EU all biologicals and biosimilars must follow the requirements of Good Pharmacovigilance Practice (GVP).<sup>1</sup>
  - ◆ GVP requires that the Market Authorisation Holder submits a Risk Management Plan tailored to the individual product.
  - ◆ The Risk Management Plan must include routine pharmacovigilance designed to detect any adverse drug reactions or signals that suggest a negative impact on quality or efficacy.
- ◆ **It is particularly important that pharmacovigilance is in place when patients are switched from one biological to another for non-clinical reasons.**
- ◆ All biologicals approved after January 1, 2011 have been added to a list of drugs subject to additional monitoring, signified by a **black triangle**.

<sup>1</sup>Francescon S, Fornasier G, Baldo P. EU pharmacovigilance regulatory requirements of anticancer biosimilar monoclonal antibodies. Int J Clin Pharm. 2018;40:778-82.

# PHARMACOVIGILANCE



- ◆ The black triangle appears in the Summary of Product Characteristics and the package leaflet.
- ◆ The symbol is used for drugs for which there are limited long-term data on use.
- ◆ It is designed to encourage health professionals and patients to report any possible adverse drug reactions.
- ◆ It does not signify that there are any specific safety concerns.

From: Biosimilars in the EU. Information Guide for Healthcare Professionals.

[https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf) (Accessed 29/11/2018)

# PHARMACOVIGILANCE

- ◆ With more than a decade of experience, the European regulatory authorities have not withdrawn any approved biosimilars as a result of safety or efficacy concerns.
- ◆ However, it should be noted that biosimilars are not tested against each other.
  - ◆ **There is always the potential for, at least, pharmacokinetic differences when switching between biosimilars with the same active molecule.**
- ◆ Accurate pharmacovigilance can only be maintained if there is a careful record of which formulation has been prescribed, and when changes to the prescription have been made.
- ◆ Traceability of the drug used, back to the manufacturer and batch number, is an important part of record keeping.
- ◆ Confidence in the reporting system, and that the regulator will act on information received, is an important contributory factor in clinician and patient acceptance of biosimilars.

# QUALITY AND FALSIFICATION



- ◆ **There is international concern about sub-standard production and falsification (counterfeits) of small molecular weight drugs.<sup>1,2</sup>**
  - ◆ Sub-standard formulations impact on safety and efficacy of medicines.
  - ◆ There is no reason to think that similar problems cannot apply to biological drugs.
  - ◆ There have already been examples of sub-standard<sup>3</sup> and falsified biological medicines.<sup>4</sup>
- ◆ **Preventing these medicines from entering the supply chain requires complex legislation and constant vigilance by the regulatory authorities at manufacturing facilities, at national borders and following prescription of the medicines.**

<sup>1</sup>Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. Br J Clin Pharmacol. 2014;78:218-43.

<sup>2</sup>Abril JL, Holt DW, Wilson RR. Falsified medicines in the European Union and North America: What are we doing to protect public health? J Pharmacovigil 2016;4:213.

<sup>3</sup>Shaltout EL, Al-Ghobashy MA, Fathalla FA, Salem MY. Chromatographic and electrophoretic assessment of Filgrastim biosimilars in pharmaceutical formulations. J Pharm Biomed Anal. 2014;97:72-80.

<sup>4</sup>See following slide.

# COUNTERFEIT BIOLOGICAL

## Improving the Integrity of the Drug Supply in a Global Marketplace

Posted on April 10, 2012 by FDA\_Voice

By: Margaret A. Hamburg, M.D.

Last week FDA announced that a counterfeit version of a cancer drug had surfaced in the United States. It was labeled as Altuzan, a product approved in Turkey and not approved in the United States. The counterfeit did not contain the active ingredient of Altuzan. Unapproved foreign drugs, including the counterfeit, were purchased by medical practices in the U.S. from a foreign supplier.

This discovery comes only a few months after FDA informed 19 medical practices in three states that they had purchased unapproved foreign drugs, which may include the counterfeit version of Roche's Avastin. Roche is the company that manufactures Avastin approved for marketing outside of the United States. This counterfeit was also purchased from foreign suppliers and was also nothing but a sham since it did not contain the active ingredient of Avastin.



For patients with cancer, combating the disease is difficult enough. But to learn that the cancer drug you were taking to save or prolong your life might be nothing but a counterfeit is unthinkable.

The only FDA-approved version of Avastin for use in the United States is marketed by Genentech (a member company of Roche). Genentech's Avastin products are safe and effective for their intended uses, therefore cancer patients that have been receiving these products should not be concerned.

**The anti-cancer drug bevacizumab entered the US supply chain but was a falsified medicine. It was imported as a product approved in Turkey (Altuzan) but not approved in the USA. It was actually made in Syria and contained no pharmacologically active compound.**

<https://blogs.fda.gov/fdavoices/index.php/tag/avastin/> (Accessed 24/09/2018)



# CONCLUSIONS

- ◆ Biological medicines are innovative and are making a significant contribution to the treatment and management of a wide variety of diseases.
- ◆ Their manufacture is difficult, costly and expensive.
- ◆ Potentially, biosimilars could open up patient access to these medicines at a reduced cost, without impacting on quality, efficacy or safety.
- ◆ However, it must be remembered that if a compound has not gone through the recognised biosimilar pathways adopted by the highly regulated licensing authorities, then it is not a biosimilar.
- ◆ Pharmacovigilance is a key element in the acceptance of biosimilars, since the clinical studies required for the biosimilar pathway are abbreviated in comparison with those conducted by the original manufacturer of the drug molecule.
- ◆ When switching between biosimilars or between a biosimilar and the originator formulation decisions should be based on the scientific data available and accurate clinical follow-up observations should be made.
- ◆ Such clinical decisions should be made by a clinician, not a cost-accountant.

# USEFUL REFERENCES

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# ACCESS TO INFORMATION



**EMA:**

<https://www.ema.europa.eu/human-regulatory/overview/biosimilar-medicines>

**FDA:**

<https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm>

**WHO:**

[http://www.who.int/biologicals/biotherapeutics/similar\\_biotherapeutic\\_products/en/](http://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/)

# THANK YOU!

December 2018