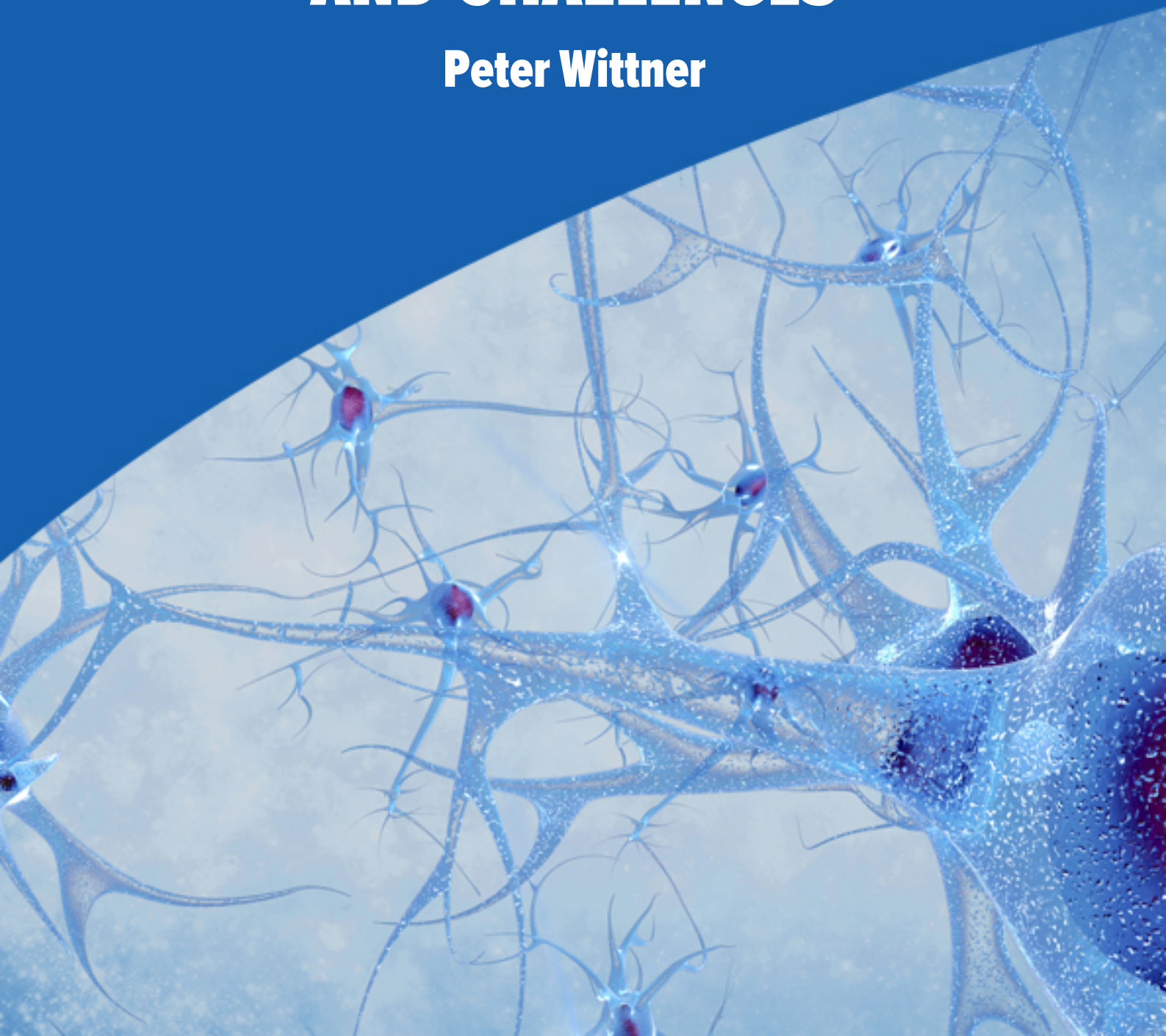
PTI

Biosimilars: The Opportunities and Challenges

Peter Wittner



There is now general acceptance of the definition of a Biosimilar provided by the EMA. The have added to this definition the following comments:

> "Developers of biosimilars are required to demonstrate through comprehensive comparability studies with the 'reference' biological medicine that:
> - their biological medicine is highly similar to the reference medicine notwithstanding natural variability inherent to all biological medicines;
> - there are no clinically meaningful differences between the biosimilar and the reference medicine in terms of safety, quality and efficacy."

This is very useful as it sets out quite clearly and unambiguously what qualifies as a Biosimilar and outlines what developers need to do to convince the regulators.

The EMA has been the trailblazer in regards to setting out a regulatory framework for biosimilars and many other regulators around the world, although not all, have adopted parts of its guidelines. The first of these appeared in 2006 and the EMA has added to these including specific guidelines for classes of biological products such as LMW (Low molecular Weight) heparin, interferon and erythropoietins.

It is important to note that biosimilars are not generics of the original product as they can only be similar, but never identical.

Why the interest in biosimilars?

The interest stems from the fact that the market for biological products is itself enormous and growing. There are therefore many companies that would like to obtain a foothold in the market by copying some of these products and launching biosimilars.

The table below lists the top 10 products by worldwide sales in US$bn in 2016.

	Brand	Generic	Manufacturer	2016 sales US$m
1	Humira	Adalimumab	Abbvie	$16,078
2	Harvoni	Ledipasvir + Sofobusvir	Gilead	$9,081
3	Revilimid	Lenalidomide	Celgene	$6,974
4	Remicade	Infliximab	Janssen	$6,966
5	Avastin	Bevacuzimab	Roche	$6,715
6	Herceptin	Trastuzumab	Roche	$6,714
7	Lantus	Insulin Glargine	Sanofi	$6,057
8	Enbrel	Etanercept	Amgen	$5,965
9	Rituxan	Rituximab	Roche	$5,765
10	Prevnar	Pneumococcal vaccine	Pfizer	$5,718
		Total leading brands		**$76,033**

Six of them are biologicals - Humira, Remicade, Avastin, Herceptin, Enbrel and Rituxan/ Mabthera.

With combined sales of tens of billions of dollars, they make a very attractive target to copy. There are already around 25 biosimilars registered in Europe and the number will grow.

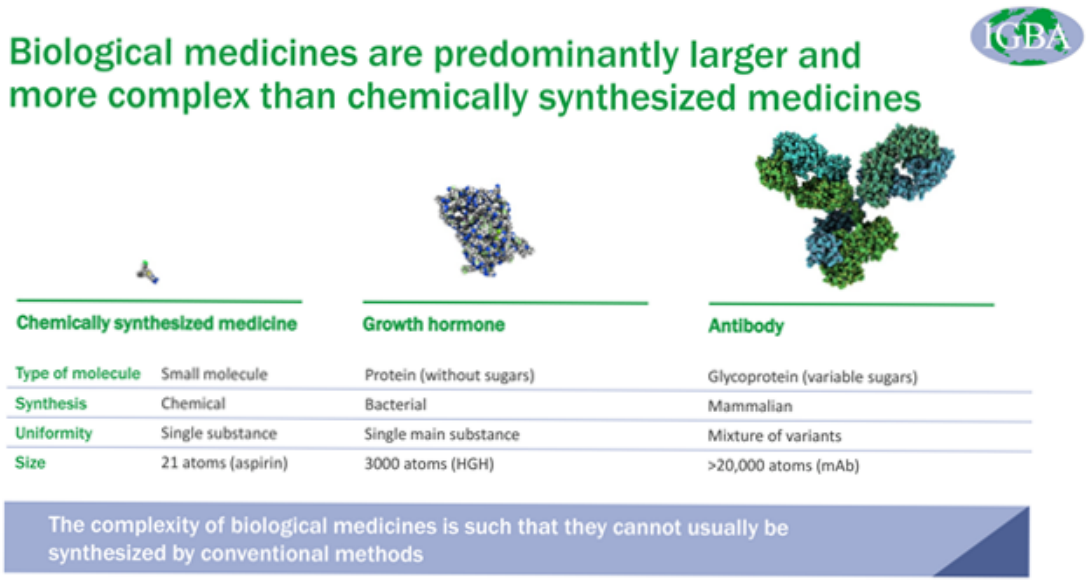
The US authority (FDA), after a later start, is also registering more and more biosimilars and this should give an impetus to the US market, the biggest in the world.

Why are they not generics?

The answer lies in the size and complexity of biological molecules. It is difficult, if not impossible, to copy them 100% without any differences. Even the original manufacturers themselves cannot do it! There are inevitably batch-to-batch variations in the original product even when manufactured using the identical process in the same factory and reaction vessels.

What Biosimilar companies therefore have to do is produce something that they can show by analytical techniques and clinical evidence to be sufficiently “similar” to the original. The illustration below, taken from an IGBA publication “The era of biological medicines” illustrates the enormous differences in size and complexity between Aspirin and a Monoclonal Antibody (MAb).

The complexity of the biological substance means that, as noted earlier, its manufacture is a complex process far removed from the (relatively) simple chemical processes used to product generics.



Interchangeability, substitution and switching

This a critical topic; these terms are often misunderstood as being the same thing, so it is important to explain the different terms that are used

- **Interchangeability: designated by a Regulatory Authority**

(1) The biosimilar is expected to produce the same clinical result as the reference product in any given patient;
(2) Repeated switching between biosimilar and reference product presents no greater safety or efficacy risk than continued use of the reference product

- **Substitution: takes place at the Pharmacist level**

When a pharmacist substitutes a certain prescribed product and replaces it by another equivalent product. If done without the prescribing physician's involvement, it is considered "automatic" or "involuntary" substitution

- **Medical Switching: Decision is made by the treating physician**

When a prescribing physician changes the medication, usually because of efficacy or safety issue(s)

The EMA has stated that it will not categorise a biosimilar as interchangeable: that is left to national authorities.

Barriers to entry

The cost of entry is high due to the need for clinical studies.

A small molecule generic can be copied relatively cheaply – regulators want to see information on topics such as manufacturing, quality of materials used and stability data. The only clinical work needed is a bioequivalence study on a limited number of healthy volunteers. This keeps development costs down to a few hundred thousand Pounds or Euros.

By contrast, the developers of a biosimilar need to provide a huge amount of analytical evidence of the similarity of the biosimilar to the original and conduct extensive clinical studies on patients.

Individual doses of reference product needed for the studies have list prices of several hundred pounds each and clinical studies require investigators to administer multiple doses to hundreds of patients over a long period to assess the efficacy of the biosimilar. This pushes the development costs into the millions

Another major barrier to entry is the complicated process for manufacturing biological products and this is a skill that not many companies possess. The need for expensive processing equipment for manufacture and purification of the finished product adds to the cost, although costs are falling as the market has started to develop and more companies become involved.

Nevertheless, generic companies have dominated the market so far, sometimes by themselves and in others case by entering into cooperation with a partner that possesses biological manufacturing skills.

Early forecasts had anticipated a limited number of competitors with only minimal price competition. However, a higher than anticipated number of competitors and inclusion of biosimilars in tenders has helped to push down prices in some countries and led, unexpectedly, to price wars.

The example below shows quite how significant these discounts can be (*Source*: Steinar Madsen, Norwegian Medicines Agency).

BigPharma companies have now started to catch up, particularly with regard to the MAb (Monoclonal antibody) biosimilars.

Patient	Tender year	Remicade	Remsima	Savings	Discount vs. originator (%)
Rheumatoid arthritis, 70 kg, one year treatment	2014	84 000 NOK 10 500 EUR 14 000 USD	51 000 NOK 6 400 EUR 8 500 USD	33 000 NOK 4 100 EUR 5 500 USD	39%
	2015	83 400 NOK 9 700 EUR 11 000 USD	26 000 NOK 3 000 EUR 3 400 USD	57 400 NOK 6 700 EUR 7 600 USD	69%

About the author

Peter Wittner, B.Sc., is an independent consultant specialising in the commercial aspects of generics with nearly 40 years' pharmaceutical experience. The major part of this has been spent in the generic industry. He was Managing Director for the UK subsidiary of the Indian generic leader Ranbaxy, having joined them to set up the business before returning to consultancy work.

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