SPECIAL REPORT

USA and Europe differ in interchangeability of biosimilars

This paper highlights differences between USA and Europe when it comes to the interchangeability of biosimilars. The lack of harmonization between USA and Europe may introduce confusion for stakeholders and biosimilars makers and could be delaying access to life-saving treatments.

Keywords: Biosimilar, EMA, interchangeability

There are some major differences between USA and Europe regarding how they view interchangeability of biologicals/biosimilars. In fact, there is a lack of harmonization around the world when it comes to how different countries or regions approach interchangeability of biosimilars [1].

USA

In the US, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with a Food and Drug Administration (FDA) licensed reference product. Interchangeability is defined in law as part of the BPCI Act as:

'the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product'.

FDA defines interchangeability as:

- the biological product is **biosimilar** to the reference product;
- it can be expected to produce the **same clinical result** as the reference product **in any given patient;** and
- for a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

FDA may approve a biological product as interchangeable, see

Table 1: Interchangeability and substitution of biolgoicals/biosimilars in USA and Europe

Country/region	USA 	Europe 
Legal basis	Defined in BPCI Act	Defined in consensus document
Interchangeabilty	**Interchangeable or interchangeability** – The biological product is biosimilar to the reference product – It can be expected to produce the same clinical result as the reference product in any given patient – For a product administered more than once to an individual, the risk in safety and diminished efficacy of alternating or switching between use of product is not greater than the risk of using the reference product without such alternation or switch	**Interchangeability** – A scientific and medical term – 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	An interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product	– An administrative measure – Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber
Agency role	FDA may approve a product as interchangeable	EMA does not have authority to designate interchangeability
State/Member State role	Individual states control the act of pharmacy-level substitution	Interchangeability decisions reside within EU Member States
Policies/Guidance	FDA issued draft guidance in January 2017	Some regulatory agencies issued statements in 2015 clarifying support for prescriber-supervised switching between a reference product and a biosimilar
Result	35 US states have passed legislation addressing biosimilar substitution	Pharmacy-level substitution for biosimilars is not widely practised in any EU country

BPCI Act: Biologics Price Competition and Innovation Act of 2009; FDA: US Food and Drug Administration; EMA: European Medicines Agency; EU: European Union.

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Table 1. Although individual states control the act of pharmacy-level substitution. The agency issued draft guidance on interchangeability in January 2017 [2] and more recently extended the comment period on the guidance [3].

As of 1 July 2017, 35 states and Puerto Rico have passed laws allowing substitution by a pharmacist if the biosimilar is considered interchangeable and is covered under an insurer's pharmacy benefit [4]. However, despite issuing draft guidance on interchangeability in January 2017 [2], to date FDA has yet to approve a biosimilar as interchangeable with its reference biological.

European Union

The European Commission (EC) has defined interchangeability in a consensus information document on biosimilars [5] as:

> *'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 is considered to be:

- An administrative measure
- The practice of dispensing one medicine instead of **another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber**

In the EU, decisions on the interchangeability or substitution of biosimilars and originator biologicals are not made by the European Medicines Agency (EMA), but at the national level, see Table 1. This is the case, despite the fact that biosimilars developed in line with EU requirements are considered by EMA to be therapeutic alternatives to their reference biologicals [6].

Automatic substitution of biosimilars is therefore not routinely practised in Europe, although in some Member States the use of biosimilars has been actively facilitated by national and local tender systems.

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