Creativ Ceutical
The enlightened decision

Biosimilar interchangeability, substitution and switching: an overview of 5 European Member States and the United States

Zapała A[1], Kapuśniak A[1], Sroka A[1], Lach S[1], Rémuzat C[2]; Toumi M[3]
[1]Creativ-Ceutical, Krakow, Poland, [2]Creativ-Ceutical, Lyon, France, [3]Faculty of Medicine, Public Health Department, Aix-Marseille University, Marseille, France

OBJECTIVES

- While the European Union (EU) is regarded as the most advanced market and the pioneer in the regulation of biosimilar medicines, the biosimilar market in the United States (USA) remains relatively new.
- The aim of this research was to compare the policies status of the interchangeability, switching and substitution of biosimilars in 5 main EU countries (France, Germany, Italy, Spain and the UK) and the USA.

METHODS

- A comprehensive review of the literature in medical databases (Embase and Medline *via* Ovid), as well as other sources (the Generics and Biosimilars Initiative (GaBi) Journal and website, Food and Drug Agency (FDA) and Medicines for Europe website) was conducted to obtain key publications providing the most recent information on biosimilar policies.
- The following free search terms were used: „biosimilar(s)", „similar biologics(s)/biotech", „off-patent biologic(s)/biotech", „follow-on biologic(s)/biotech", „subsequent entry biologic(s)/biotech", „switching", „substitution", „interchangeability". Search results were screened to select the most relevant publications.

RESULTS

1) Interchangeability

- The level of regulation (Figure 1) and definitions of biosimilars interchangeability (Figure 2) differ between the EU and the USA. European Commission does not recommend on whether the biosimilar is interchangeable with the reference medicine and thus if it can be switched or substituted, whereas in the USA the evaluation of interchangeability is centralized and a product considered interchangeable can be substituted at the pharmacy.[1,2]

2) Switching by a physician

- In all analysed countries physician-led switching is allowed for both treatment-naive and treatment-experienced patients (Table 1), ensuring an accurate monitoring.
  - In 2018, The Spanish Society of Hospital Pharmacy (SEFH) has published its position paper on biosimilar medicines stating that interchangeability in the hospital setting is permitted if it is approved by the Pharmacy and Therapeutics Committees (PTCs) of the hospitals, the regional Autonomic Committees, and the prescribing physician, who is represented in these Committees.[3]
  - In Germany, the new law regarding biosimilars came into force on 16 August 2019. Under the GSAV (Gesetz für mehr Sicherheit in der Arzneimittelversorgung) Act, The Federal Joint Committee (G-BA) must develop guidelines for physicians on biosimilar switching before 16 August 2020.[4,5]
  - The Italian Medicines Agency (AIFA) published its second position paper in March 2018 stating that biosimilars are interchangeable with the respective reference originator.[6] However, AIFA maintained its position, published in the first position paper (May 2013), that the choice of treatment remains a clinical decision entrusted to a prescriber.[7]
  - In the UK, biosimilars are considered interchangeable with their reference product and can be switched by a prescriber after consulting a patient.[8]
  - In France, interchangeability was enacted through the social security funding law for 2017[9]. Following the new rules for biosimilar interchangeability, Directorate of Health Care Supply (DGOS) published an instruction in 2017 to promote switching to biosimilars in hospital sector and supporting competition of the products from the same biological group.[10] In February 2018, the Government introduced financial incentives for healthcare organisations to increase hospital prescription of biosimilars to be dispensed by retail pharmacies.[11]

3) Automatic substitution by a pharmacist

- Among EU5 countries, automatic substitution is prohibited by legal regulations in Spain and by recommendations in Italy and in the UK.
  - In Spain, automatic substitution is not allowed.[12-15]
  - The AIFA position against automatic substitution was maintained in its second position paper.[6]
  - In the UK, the National Health Service (NHS) updated in May 2019 the previous document from 2015 supporting the safe, effective and consistent use of all biological medicines including biosimilars. However, prohibition for automatic substitution was maintained in the updated document.[8]
  - In France, the law allowing automatic substitution of biosimilars, under certain conditions (at the treatment initiation, within the same biosimilar group and until not prohibited by a prescriber), is not yet implemented (pending Decree).[16]
  - In Germany, according to GSAV Act, a list of substitutable biosimilars for pharmacists will be created following assignment of interchangeability by the G-BA. All the provisions will enter into force on 16 August 2022 at the latest.[4,5]
- In the USA, the evaluation of the biosimilar interchangeability is performed by the Food and Drug Agency (FDA) according to the guidance issued in May 2019.[2] Interchangeable products can be automatically substituted based on the Biologics Price Competition and Innovation (BPCI) Act,[17] although no biosimilar has been approved as interchangeable product yet.[18] Majority of states (47/50 and Puerto Rico)[19,20] has already passed the laws allowing the substitution at the pharmacy level. However, conditions and requirements for the substitution, e.g. dispensation of the cheapest product or notification about the substitution, differ across the particular states (Figure 3).[19-22]

Figure 1. Comparison of the decision making level for biosimilars between the EU and the USA[1,2]

Figure 2. Definition of interchangeability in the EU and the USA[1,2]

EU

- *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."*

USA

- *"The biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product".*
- *"Can be expected to produce the same clinical result as the reference product in any given patient."*
- *"For a biological 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 biological product and the reference product is not greater than the risk of using the reference product without alternation or switch."*

Figure 3. USA state law regarding biosimilar substitutions[19-22]

In majority of states (data from 2013-2018)	In some states
• For substitution biosimilar have to be assigned as interchangeable by FDA. • A pharmacist have to inform a prescriber (usually in 3-5 days) and a patient about substitution. • Records of substitution must be retained by a prescriber and a pharmacists (for 1 up to 5 years).	• Pharmacists have to explain the difference in the price of biosimilars medicines. • In South Carolina pharmacists may substitute a reference product with a biosimilar according to their professional judgment. • In West Virginia dispensation of the cheaper product is required unless a pharmacist knows that this it is inappropriate for a patient. • Patient's agreement for the substitution is required.

Table 1. Substitution and switching policy in 5 main EU countries and the USA

Country	Automatic substitution	Switching
France	**Allowed (not yet implemented*)** for treatment-naive patients and with notification to a prescriber, and within the same biosimilars group[13,16]	**Allowed** for treatment-naive and treatment-experienced patients[23]
Germany	**Allowed**** for specific groups of biosimilars (i.e. produced by the same manufacturer)[24,25]	**Allowed** for treatment-naive and treatment-experienced patients[12,13]
Italy	**Prohibited** by guidelines[6,12]	**Allowed** for treatment-naive and treatment-experienced patients[6]
Spain	**Prohibited** by law[12-15]	**Allowed** possible at the physician's discretion, not recommended in general[12]
UK	**Prohibited** by guidelines[8,12,13,23]	**Allowed** for treatment-naive and treatment-experienced patients[8,13]
USA	**Allowed** if not prohibited by a prescriber[19]	**Allowed** for treatment-naive and treatment-experienced patients[26]

* Pending Decree
** Policy is binding until the GSAV provisions enter into force (by 16 August 2022).

CONCLUSIONS

Despite evidence accumulates to support switching of several biosimilars, none of the studied countries formally implemented automatic substitution so far.

REFERENCES
1. European Commission. What you need to know about biosimilar medicinal products. A consensus information document. 2013.
2. US FDA. Considerations in demonstrating interchangeability with a reference product: guidance for industry. 2019.
3. de Castro Martínez- López, N., et al. Spanish Society of Hospital Pharmacy position paper on biosimilar medicines. Farmacia hospitalaria: organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria. 2018 Jul;42(4):180-3.
4. Generics and Biosimilars Initiative, Automatic pharmacist substitution of biosimilars in Germany, Posted 10/05/2019
5. Gesetzfür mehr Sicherheit in der Arzneimittelversorgung, 2019 Aug.
6. AIFA. Secondo Position Paper. Sui Farmaci Biosimilari. 2018.
7. AIFA. Position Paper. I Farmaci Biosimilari. 2013.
8. NHS, What is a Biosimilar Medicine? 2019
9. Social security funding law for 2017 n° 2016-1827. 23 December 2016.
10. Instruction n° DGOS/PF2/DSS/1C/DGS/PP2/CNAMTS/2017/ 244 03 August 2017 related to biosimilars and interchangeability during treatment.
11. Instruction n° DSS/1C/DGOS/PF2/2018/42 19 February 2018 for incentivisation of hospital prescription of biosimilars delivered by retail pharmacies.
12. Rémuzat C. et al. Supply-side and demand-side policies for biosimilars: an overview in 10 European member states. J Mark Access Health Policy. 2017 Jan; 5(1):1307315.
13. DataMonitor Healthcare, Biosimilars Market Access in the EU,Biosimilars Insights, Published on 19 January 2018
14. Macaulay R., Hugon M., Biosimilar market access-comparing the US and European markets, Value in Health. Conference: 23rd Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2018. United States. 21 (Supplement 1) (pp S91), 2018.
15. Agencia Estatal Boletín Oficial del Estado. Spain: Orden SCO/2874/2007 of 28 September
16. Legifrance. France: Code de la santé publique. Article L5125-23-3. 2016 Dec.
17. Biologics Price Competition and Innovation Act of 2009 (BPCIA).
18. FDA. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. 2019.
19. Cauch R. State laws and legislation related to biologic medications and substitution of biosimilars. National Conference of State Legislatures. 2016 Jun.
20. National Conference of State Legislatures. Statewide prescription drug database: 2015-present.
21. Yamauchi, P. S. et al. Biosimilars in Dermatology: Analytical, Regulatory, and Clinical Considerations: A Treatise From the Medical Board of the National Psoriasis Foundation. Journal of Psoriasis and Psoriatic Arthritis. 2019 May 21:2475530319847660.
22. Generics and Biosimilars Initiative, 45 US states have passed biosimilar substitution laws, Posted 15/02/2019.
23. Generics and Biosimilars Initiative, International policies for interchangeability, switching and substitution of biosimilars. Posted 23/11/2018.
24. La Noce A, Ernst M. Switching from Reference to Biosimilar Products: An Overview of the European Approach and Real-World Experience So Far. EMJ. 2018;3(3):74-81.
25. CADTH, International Policies on the Appropriate Use of Biosimilar Drugs 2018.
26. Oskouei S.T. Biosimilar Interchangeability: 9 Things to Consider The Center for Biosimilars. 02 Apr 2018.

ISPOR 2019, Copenhagen, Denmark, November 2-6. PBI37.