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 German 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 biologic(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 not, whereas in the USA the evaluation of interchangeability is considered and a product considered interchangeable can be substituted at the pharmacy.

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) published a 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 Autonomics Committees, and the prescribing physician, who is represented in these Committees.

In Germany, the new law regarding biosimilars came into force on 16 August 2019. Under the GSGA (Gesetz für mehr Sicherheit in der Arzneimittelversorgung), the Federal Joint Committee (G-BA) must develop guidelines for physicians on biosimilar switching before 16 August 2020.

The Italian Medicines Agency (AIFA) published its second position paper in March 2018 stating that biosimilars are interchangeable with the respective reference originator.1 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.1

In the UK, biosimilars are considered interchangeable with their reference product and can be switched by a prescriber after consulting a patient.4

In France, interchangeability was enacted through the social security funding law for 2017. Following the new rules for biosimilars interchangeability, Directorate of Health Care Supply (DGOS) published an instruction in 2017 to promote switching to biosimilars in hospital settings 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 EUS countries, automatic substitution is prohibited by legal regulations in Spain and by recommendations in Italy and the UK.

In Spain, automatic substitution is not allowed.11,12

The AIFA position on automatic substitution was maintained in its second position paper.4

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).1,13

In Germany, according to GSGA Act, a list of substitutable biosimilars for pharmacy is 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 2019.14 Interchangeable products can be automatically substituted based on the Biosimilars 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 subsequent switching, e.g. dispensation of the cheapest product or notification about the substitution, differ across the particular states (Figures 3 & 4).

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


displayed with access restrictions

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Substitution &amp; Switching Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Allowed for off-patent biosimilars for treatment-naive and treatment-experienced patients prescribed the same biological group.10</td>
</tr>
<tr>
<td>Germany</td>
<td>Prohibited by law. Provoked by the pharmacist. Substitution is prohibited.6</td>
</tr>
<tr>
<td>Spain</td>
<td>Prohibited by law. Provoked by the pharmacist. Substitution is prohibited.6</td>
</tr>
<tr>
<td>Italy</td>
<td>Prohibited by law. Provoked by the pharmacist. Substitution is prohibited.6</td>
</tr>
<tr>
<td>UK</td>
<td>Allowed for ex-patent biosimilars, if the prescriber so decides.11</td>
</tr>
</tbody>
</table>

Figure 1. Comparison of the decision making level for biosimilars between the EU and the USA

Figure 2. Definition of interchangeability in the EU and the USA

Figure 3. USA states regarding biosimilar substitution14,16

Figure 4. EU states regarding biosimilar substitution14,16

REFERENCES
2 GSAV. Active substance category (in line with the European Medicines Agency’s position). (2018).
4 The Federal Joint Committee (G-BA) guidelines on biosimilars.
5 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
15 St. Martin, M. New Mexico’s biosimilar substitution policy. The Tablet. (2019).
16 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
17 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
18 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
19 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
20 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Substitution &amp; Switching Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>For treatment-naive and treatment-experienced patients prescribed the same biological group.10</td>
</tr>
<tr>
<td>Germany</td>
<td>Not substituted biosimilar have to be negotiated with the prescriber.6</td>
</tr>
<tr>
<td>Spain</td>
<td>A person whose is a prescriber not allowed to allow switching.6</td>
</tr>
<tr>
<td>Italy</td>
<td>A person whose is a prescriber not allowed to allow switching.6</td>
</tr>
<tr>
<td>UK</td>
<td>For treatment-naive and treatment-experienced patients prescribed the same biological group.</td>
</tr>
<tr>
<td>USA</td>
<td>Not substituted biosimilar have to be negotiated with the prescriber.6</td>
</tr>
</tbody>
</table>

1 The Federal Joint Committee (G-BA) guidelines on biosimilars.
2 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
3 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
4 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
5 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
6 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
7 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
8 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
9 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
10 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
12 GSAV. Guidelines on the use of biosimilars in Germany. (2019).
14 St. Martin, M. New Mexico’s biosimilar substitution policy. The Tablet. (2019).
15 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
16 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
17 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
18 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
19 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).
20 St. Martin, M. Biosimilars and substitution policies in the USA. The Tablet. (2019).