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**Knowledge, perceptions, attitude, barriers and facilitators of biosimilars use across specialty physicians and hospital pharmacists: A national survey**

Conocimientos, percepciones, actitud, barreras y facilitadores del uso de biosimilares entre médicos y farmacéuticos de hospital: Una encuesta española

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**Abstract**

**Objective:** To analyze knowledge, perceptions, attitude, barriers and facilitators of biosimilars uptake across physicians managing immune diseases and hospital pharmacists.

**Method:** Two structured and closed anonymous online surveys were designed and sent to 41 physicians (rheumatologists, dermatologists, gastroenterologists) and 32 hospital pharmacists. Sociodemographic and clinical practice related variables were collected. We also gathered information about biosimilars knowledge and importance, access, attitude in clinical practice and perceptions, barriers and facilitators to biosimilars uptake. A descriptive analysis was performed.

**Results:** Surveys response rate was 100% (hospital pharmacists) and 96% (physicians). We found certain lack of biosimilars knowledge about key aspects including switching, extrapolation, interchangeability or substitution. There was a great variability in the types and brands of biosimilars depending on the hospital. We observed several organization preferences, policies, and practices regarding biosimilars. General perception and attitude to biosimilars was positive. If used, biosimilars were predominantly prescribed in biologic treatment-naive patients (this indication was considered adequate and participants felt comfortable with it). Reluctance

**Resumen**

**Objetivo:** Analizar el conocimiento, las percepciones, la actitud, las barreras y los facilitadores sobre el uso de los biosimilares entre los médicos que manejan enfermedades inmunológicas y los farmacéuticos de hospital.

**Método:** Se diseñaron dos encuestas *online* anónimas, estructuradas y cerradas que se enviaron a 41 médicos (reumatólogos, dermatólogos y gastroenterólogos) y 32 farmacéuticos de hospital. Se recogieron variables sociodemográficas y relacionadas con la práctica clínica. También información sobre el nivel de conocimiento e importancia de los biosimilares, el acceso a los mismos, la actitud en la práctica clínica, y las percepciones, barreras y facilitadores con el uso de los mismos. Se realizó un análisis descriptivo.

**Resultados:** La tasa de respuesta fue del 100% (farmacéuticos de hospital) y del 96% (médicos). Encontramos cierta falta de conocimiento sobre los biosimilares en aspectos clave como el cambio de un biológico de referencia a un biosimilar, la extrapolación de indicaciones, la intercambiabilidad o la sustitución. Hubo una gran variabilidad en los tipos y marcas comerciales de biosimilares entre hospitales. Observamos distintas preferencias, políticas y prácticas en los hospitales en relación con el uso de biosimilares. La percepción y actitud general hacia los biosimilares fue positiva. Los biosimilares se prescribían predominantemente en pacientes sin tratamiento biológico.

**KEYWORDS**

Biosimilar Pharmaceuticals; Drug Substitution; Knowledge; Perception; Surveys and Questionnaires; Variability; Spain.

**PALABRAS CLAVE**

Biosimilares; Sustitución; Conocimiento; Percepción; Encuesta; Variabilidad; España.



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to switch in clinical practice was common. The main barriers to biosimilars uptake were the lack of confidence and knowledge. The main facilitators were the development of recommendations from professional associations and societies and the demonstration of interchangeability efficacy. We gathered concerns about biosimilar long term efficacy and safety, lack of real-life data, lack of biosimilars traceability or the risk of biologic reference medicines stock shortages.

**Conclusions:** Biosimilar education and more evidence filling current gaps might help increase prescriber knowledge, comfort and use of biosimilars.

## Introduction

A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine'). The objective of a biosimilar development program is to demonstrate no clinically meaningful differences based on the "totality of evidence" approach which is, a comprehensive comparison of the proposed biosimilar and the reference medicine with respect to structure, function, pharmacokinetics, pharmacodynamics, clinical immunogenicity, efficacy and safety<sup>1</sup>. Biosimilars are approved by regulatory agencies following the same standards applied to all biological medicines<sup>1,2</sup>.

Due to its complex nature and its manufacturing methods, biological medicines (biosimilar or reference medicine) are subject to some degree of natural molecular variability. This inherent variability associated with biological drugs manufacturing make it more challenging to reproduce the exact molecular structure, even among batches of the same product. The variability is subject to a strict control by manufacturers and regulatory authorities<sup>3</sup>. Therefore, biosimilars not only have to comply with Good Manufacturing Practice but also with the same principles of comparability in manufacturing<sup>3</sup>.

Since the approval of the first biosimilar in the European Union in 2006, 63 biosimilars have been licensed as of 31 March 2021<sup>1</sup>. Biosimilars are used in different medical specialties like hematology, oncology, endocrinology, dermatology, rheumatology or nephrology.

However, different surveys have reported a great variability in the uptake of biosimilars across countries that at least in part it cannot be explained by clinical facts<sup>4-9</sup>. Several reasons have been proposed to explain this non clinical variability<sup>4,12</sup>, including organizations policies and practices, economic issues, lack of approval or differences in marketing. Similarly, a number of factors, barriers and facilitators have been highlighted with biosimilars uptake as the lack of knowledge and understanding or the potential risks and benefits surrounding biosimilars that may impact on their acceptance by physicians<sup>4,8,10,11,13-17</sup>.

In Spain there is little or no information about the use and drivers of biosimilars in clinical practice. It has been published that current knowledge about biosimilars among Spanish primary care physicians is low<sup>18</sup>, but there is no evidence in a hospital setting. Therefore, we proposed this project to assess the variability in the uptake of biosimilars and to explore the knowledge, attitude, practice, barriers and facilitators towards them in Spain. For this purpose, and in line with most of the reported articles, we designed and launched a national survey.

## Methods

### Survey design

We conducted between June and November 2020, a nationwide, non-interventional, anonymised, self-administered, one-time web-based survey among dermatologists, rheumatologists, gastroenterologists and hospital pharmacists. These three medical specialties were selected because they treat patients with chronic immunomediated diseases and use similar biologic medicines (currently four biosimilars in Spain). We decided not to include other specialties because their context could be different. We also included hospital pharmacists because they play a relevant role in the use

gico previo (esta indicación se consideraba adecuada y los participantes se sentían cómodos con ella). La reticencia al cambio en la práctica clínica fue común. Los principales obstáculos para el uso de biosimilares fueron la falta de confianza y de conocimientos. Los principales facilitadores el desarrollo de recomendaciones de asociaciones y sociedades científicas y la demostración de la eficacia de la intercambiabilidad. Se recogieron preocupaciones sobre la eficacia y seguridad a largo plazo de los biosimilares, la falta de datos en vida real, la falta de trazabilidad de los biosimilares o el riesgo de escasez de existencias de medicamentos biológicos de referencia.

**Conclusiones:** Actividades formativas en biosimilares y una mayor evidencia podrían ayudar a aumentar el conocimiento, comodidad y el uso de los biosimilares por parte de los prescriptores.

of biosimilars as patient education or taking part in the biological medicines (including biosimilars) committees (BMC).

### Survey procedures

A multidisciplinary steering committee composed by one dermatologist, one rheumatologist, one gastroenterologist and one hospital pharmacist was established. The selection criteria were: 1) Specialized in the use of biosimilars with demonstrated experience; 2) clinical experience  $\geq 8$  years and/or  $\geq 5$  publications; 3) members of relevant health professionals associations.

Then, a comprehensive literature review in PubMed was performed to analyse articles that reported the variability in the use of biosimilars (rates, type of biosimilars, etc.), knowledge, perceptions, attitudes, barriers and facilitators on the use of biosimilars, irrespectively of the drug. We used PubMed's Clinical Queries, and individual searches with Mesh (like Biosimilar Pharmaceuticals) and free text terms (as biosimilar or variability) up to March 2020. The results and other information including the methodology of the studies (most of them surveys) was discussed in a nominal group meeting of the steering committee. In this meeting, an expert methodologist guided the discussion and assisted decisions. The committee agreed to collect data of Spanish health professionals due to the lack of studies. Then, they selected the main points to be explored and decided to design a national survey. For each main point an objective was established and a set of questions proposed. To select the questions, the committee discussed the wording and questions reported in other articles or proposed different ones. The methodologist commented the implications of formulating questions in different ways. Some of the final questions are the same questions of other surveys (adapted to the Spanish context if necessary), others are original (the survey is available by request to the corresponding author).

This resulted in two structured and closed surveys that were generated using the Survey-Monkey online platform and administered by an independent third party. One for the physicians and another for hospital pharmacists. Both shared 55 questions. Physicians answered 6 more specific questions whereas hospital pharmacist another 2. For example, physicians were asked about patients' reaction when a switch was proposed and hospital pharmacists about physicians' reaction when a switch was proposed.

Afterwards, an invitation to participate in this survey was emailed to the survey sample. Reminder emails were sent at 4-6 weeks after the initial mailing. The survey front page included information about the survey, the objectives of the project, and asked for their voluntary participation. By reading and responding, the health professionals gave their consent. All the respondents were able to review and change their responses by scrolling up and down the page before definitive submission. The surveys were first piloted on a small number of health professionals.

### Survey sample

We selected a purposive convenience sampling of 73 health professionals (41 physicians including dermatologists, rheumatologists, gastroenterologists and 32 hospital pharmacists). We looked for health professionals from all Spanish regions that worked in National Health Hospitals with

different characteristics (e.g., general hospitals, county hospitals). We did not apply any criteria regarding to previous knowledge, experience with the use of biosimilars, participation in BMC or other criteria related to the use of biosimilars. To select them, we analysed the type of hospitals in each Spanish region and the steering committee proposed a list of colleagues (using their personal contacts or asking other colleagues).

## Survey questionnaire

The survey was organized in six main sections that included different questions: 1) Sociodemographic and practice related questions, like the presence of a multidisciplinary BMC (a committee in which  $\geq 2$  different health professionals are involved, e.g. hospital pharmacists, dermatologists, rheumatologists, and gastroenterologists). An active involvement in the BMC was defined as an active participation in relevant decisions regarding to biologics such as suggesting which ones can be approved in the hospital; 2) biosimilars knowledge and importance (development, biosimilarity, sensitive indication, approval requirements and processes, efficacy, safety, switching, extrapolation, interchangeability, etc.); 3) access, attitude and perceptions [number and type of biosimilars available in each hospital (all commercial brands of biosimilars available in Spain were included), local policies and coordination, clinical protocols, educational issues, prescription, pharmacy-level substitution, adherence, impact, satisfaction, incentives, etc.]; 4) barriers to biosimilars uptake; 5) facilitators to biosimilars uptake; 6) future with the use of biosimilars and other questions. The survey contained a mixture of checkbox answers and questions asking responders to rank their level of agreement, knowledge, comfort or importance of each statement from 1 to 5 or 10. At the end of most of questions ( $n = 31$ ) a space for comments was provided.

## Statistical analysis

We performed a descriptive analysis. We used the distribution of frequencies, the mean and standard deviation, or the median and interquartile range, depending on the distribution. The survey responses to individual questions were summarized as number and percentage of responding health professionals. Comparisons were performed using the Student's *t*-test or the Chi-square test. The comments are described in the results section in *double quotes in italics*.

## Results

### Surveys response rates and sample characteristics

The surveys response and sample main characteristics are depicted in table 1.

### Biosimilars knowledge and importance

The responder's level of knowledge/understanding of biosimilars is exposed in table 2. We found a medium level of knowledge (scale of 1-5) in key aspects of biosimilars development (means around 3). The reported level of importance (scale of 1-10) of these key aspects and of real-life data was in general high (means around 8). Safety was considered the most important aspect of biosimilars development. Just few differences were observed between hospital pharmacists and physicians.

A total of 23% of hospital pharmacists and 28% of physicians knew what a sensitive indication is. We found that 20-30% of participants did not know the definition of extrapolation, and more than 50% of responders (61% of hospital pharmacists and 54% of physicians), did not have clear understanding of interchangeability, switch or substitution.

**Table 1.** Main characteristics of surveys responders\*

	Hospital pharmacists (n = 32)	Physicians (n = 41)	Differences
Response rate	100%	96%	-
Sex (women)	52%	38%	-
Age (years)			-
$\leq 30$	0.0%	2.0%	
31-40	19.3%	44.0%	
41-50	25.8%	46.0%	
51-60	41.9%	8.0%	
61-70	12.9%	0.0%	
Type of hospital			-
General hospital	95%	90%	
County hospital	5%	10%	
Clinical experience (years) <sup>†</sup>	20.0 $\pm$ 8.5	22.9 $\pm$ 6.7	-
Experience using biosimilars (years) <sup>†</sup>	7.1 $\pm$ 3.4	6.4 $\pm$ 3.9	-
BMC <sup>‡</sup>	55%	51%	-
Multidisciplinary BMC (in hospitals with a BMC) <sup>‡</sup>	93%	93%	-
Active involvement in the BMC <sup>‡</sup>	81%	29%	$p < 0.001$

\*Results are expressed as number (percentage) otherwise is indicated. Only significant differences between groups are numerically depicted. The participants were distributed in the following Spanish regions: Andalucía (18%), Comunidad Valenciana (10%), Murcia (2%), Extremadura (5%), Galicia (12%), Islas Baleares (7%), Cataluña (13%), Castilla-León (9%), Castilla-La Mancha (8%), Comunidad de Madrid (11%), Aragón (2%), Andorra (1%), Asturias (1%).

<sup>†</sup>Mean  $\pm$  standard deviation.

<sup>‡</sup>In some hospitals there is a BMC in which participants discuss different aspects of biosimilars use including the development of protocols. A multidisciplinary BMC was defined as a committee in which  $\geq 2$  different health professionals are involved (e.g. hospital pharmacists, dermatologists, rheumatologists, and gastroenterologists). An active involvement in the BMC was defined as an active participation in relevant decisions regarding to biologics such as suggesting which ones can be approved in the hospital. BMC: biological medicines (including biosimilars) committee.

## Access, attitude in clinical practice and perceptions

There was a great variability in the number, types and brands of biosimilars depending on the hospital. Many participants agreed that there should be more than one brand for two main reasons. First, in order not to run out of stock, and, second, to stimulate competition in the biologicals medicine market. We observed several organization preferences, policies, and practices regarding biosimilars. But most of participants consider economic/efficiency reasons as the main drivers for incorporating biosimilars to the organization. We highlight that 28% of physicians were unaware of procedures and criteria behind the incorporation of biosimilars.

Most participants (85%) were content to initiate biosimilars in biologic treatment-naïve patients. Although 55% of participants have experience with extrapolation, hospital pharmacists were significantly more comfortable than physicians with extrapolation, 74% vs 38% ( $p = 0.039$ ). In this regard, many stated that "Biosimilars might present different results depending on the disease. Therefore, data on each indication should be provided". Around 10% of responders considered appropriate to switch from the reference biological medicine to a biosimilar. Most of participants were reluctant to switch between biosimilars. Some participants commented: "There is little evidence about switching", "I have observed efficacy reductions that cannot be explained solely by nocebo effect", "I would need more time in clinical practice to explain switching to a patient". Finally, compared with hospital pharmacists, significant more number of physicians appeared to have a negative opinion towards the automatic substitution of the reference biological medicine with a biosimilar at the pharmacy level, 16% vs 67% ( $p < 0.001$ ). Besides, 22% of participants indicated this practice in their organizations.

Separate questions assessing details of switching revealed that switching does not modify patients clinical monitoring, at least for 72% of participants. When explaining and proposing a biosimilar to patients, 36% of physicians indicated that in general patients are quite reluctant/mistrustful, though they approve it in the end. When hospital pharmacists were asked about the reaction of physicians if a switch was proposed, 32% stated that they understand and approve the switch, 32% that appear to be quite reluctant /mistrustful, even if they approve in the end and 16% that physicians directly do not accept the switch. A large rate of respondents (more than 90%) believe that adherence to biosimilars is similar to that of reference biologic medicines. Several comments suggested a possible negative influence of pharmaceutical industry and patient associations on biosimilars confidence.

A total of 23% of hospital pharmacists and 34% of physicians indicated their organizations have pre-defined criteria on the use of biosimilars. Some organizations follow regional objectives and criteria others have established some ("mandatory") criteria to start a biosimilar in biologic treatment-naïve patients or to switch all patients on infliximab. We gathered some comments suggesting some kind of pressure to prescribe biosimilars especially in biologic treatment-naïve patients. Others considered that specific or pre-defined criteria on the use of biosimilars are not needed. Almost 60% of participants reported that in their organizations, medical directors or other managers have proposed recommendations to prioritize biosimilars in biologic treatment-naïve patients, and to promote switches.

Finally, 81% of physicians answered that they were quite or very satisfied with the use of biosimilars. Most of responders also considered that the use of biosimilars has a positive impact on costs. Nevertheless, they did not find a clear different impact on efficacy, effectiveness, safety, immunogenicity, adherence, or patient satisfaction.

**Table 2.** Responders level of knowledge and importance of key components of biosimilars development and of real world data\*

	Hospital pharmacists	Physicians	Differences
<b>Level of knowledge of biosimilars (1-5)<sup>†</sup></b>			
Physicochemical issues	3.1 ± 1.3	3.5 ± 0.9	-
<i>In vitro</i> and <i>in vivo</i> studies	3.1 ± 1.3	3.4 ± 0.9	-
Pharmacokinetics and pharmacodynamics	3.1 ± 1.3	3.5 ± 0.9	-
Clinical studies (efficacy)	3.7 ± 1.1	4.1 ± 0.8	-
Clinical studies (safety)	3.8 ± 1.0	4.0 ± 0.8	-
Clinical studies (immunogenicity)	3.3 ± 1.2	3.9 ± 0.8	$p = 0.016$
<b>Level of importance of biosimilars (1-10)</b>			
Physicochemical issues	7.6 ± 2.3	8.0 ± 1.8	-
<i>In vitro</i> and <i>in vivo</i> studies	8.8 ± 1.1	8.3 ± 1.5	-
Pharmacokinetics and pharmacodynamics	8.9 ± 1.1	8.1 ± 1.6	$p = 0.026$
Clinical studies (efficacy)	9.2 ± 1.3	9.1 ± 1.5	-
Clinical studies (safety)	9.3 ± 1.3	9.2 ± 1.1	-
Clinical studies (immunogenicity)	8.9 ± 1.3	8.4 ± 1.5	-
<b>Level of importance of real world data (1-10)<sup>‡</sup></b>			
Effectiveness	8.8 ± 1.7	9.0 ± 1.1	-
Safety	9.1 ± 1.6	9.2 ± 0.9	-
Immunogenicity	8.4 ± 1.7	8.1 ± 1.5	-
Adherence	7.2 ± 2.1	7.7 ± 1.6	-

\*Results are expressed as mean ± standard deviation. Only significant differences between groups are numerically depicted.

<sup>†</sup>1-5 (1 = very low level of knowledge to 5 = very high level of knowledge).

<sup>‡</sup>1-10 (1 = very low level of importance to 10 = very high level of importance).

## Barriers and facilitators to prescribing biosimilars

Tables 3 and 4 depict main barriers and facilitators to biosimilars uptake.

### Future with biosimilars and other questions

When asked if biosimilars might be the first line of treatment, and even replace traditional medicines, the majority answered positively.

We included a specific question for the hospital pharmacists about the importance of different activities related to biosimilars. They graded them from 1 (not important) to 10 (very important) as follows (means): Patients support programs  $7.0 \pm 2.7$ ; Home-Delivery service  $6.4 \pm 2.8$ ; Telepharmacy/telemedicine  $7.2 \pm 2.5$ ; Hospital management educational support  $7.2 \pm 2.4$ .

Finally, we provided the possibility to declare other concerns with the use of biosimilars. Apart from those related to long-term or real-life data, others like the lack of biosimilars traceability or the risk of biologic reference medicines stock shortages due to the line is no longer profitable for the pharmaceutical company emerged.

## Discussion

Our survey examined for the first time the variability in biosimilars uptake in immune diseases like rheumatoid arthritis, inflammatory bowel disease or psoriasis in Spain. In the European Union there are currently more than twenty biosimilars (corresponding for four biologic reference medicines) for the treatment of these diseases<sup>1</sup>. Currently these biosimilars are widely used in Spain<sup>19,22</sup>.

Our analyses revealed that knowledge of the fundamentals of biosimilars and of the regulatory assessment was inadequate, specially taking into account that most of responders have many years of experience using biosimilars and published evidence and information provided by regulatory agencies<sup>1,23-32</sup>. Interestingly, the level of importance of all of these issues was considered high. Other articles have depicted different levels of biosimilars knowledge and understanding<sup>4,7</sup>. This lack of knowledge was further highlighted when specific questions about the definitions of concepts like sensitive indication, or extrapolation were tested. Indeed, more than a half of responders did not have clear understanding of interchangeability, switch or substitution. These results highlight a significant need for evidence-based

**Table 3.** Main barriers to biosimilars uptake and feasibility to overcome them\*

Barrier	Hospital pharmacists	Physicians	Feasibility to overcome <sup>†</sup>
Lack of access	45%	61%	$7.3 \pm 2.6$
Lack of knowledge	81%	89%	$7.1 \pm 2.1$
Lack of robust data from clinical trials	65%	72%	$5.9 \pm 2.4$
Lack of experience	87%	78%	$7.0 \pm 2.0$
Lack of confidence	90%	92%	$6.3 \pm 2.2$
Safety issues	42%	64%	$6.7 \pm 2.5$
Loss of efficacy	42%	64%	$5.8 \pm 2.1$
Administration device	48%	69%	$6.5 \pm 2.3$
Costs	45%	58%	$7.1 \pm 2.6$
Lack of coordination, non-alignment in the organization	77%	89%	$5.3 \pm 2.1$

\*Results are expressed (otherwise is indicated) as number (percentage) of participants who identified the barriers. There were no significant differences between groups. Feasibility to overcome barriers was tested on a scale of 1 (not feasible) to 10 (very feasible).

<sup>†</sup>Mean  $\pm$  standard deviation.

**Table 4.** Main facilitators to biosimilars uptake and feasibility to implement them\*

Facilitator	Hospital pharmacists	Physicians	Differences	Feasibility to implement <sup>†</sup>
Recommended by professional associations and societies	100%	100%	-	$7.9 \pm 1.6$
Supported by key opinion leaders	77%	86%	-	$7.5 \pm 1.7$
Efficacy and safety data from clinical trials and real world evidence (including post-marketing surveillance)	87%	100%	-	$7.6 \pm 2.2$
Efficacy of interchangeability from clinical trials and real world evidence	100%	100%	-	$7.5 \pm 1.8$
Incentives	65%	81%	-	$6.1 \pm 2.8$
Patients opinion	55%	69%	-	$6.2 \pm 2.8$
Organization alignment	90%	89%	-	$6.5 \pm 2.3$
Public transparency involving biosimilar and reference biologic pricing	52%	97%	$p < 0.001$	$6.7 \pm 2.6$
Nursing support	39%	72%	$p = 0.020$	$6.7 \pm 1.8$
Pharmaceutical industry involvement	45%	78%	$p = 0.024$	$6.5 \pm 2.1$

\*Results are expressed (otherwise is indicated) as number (percentage) of participants who identified the facilitators. Only significant differences between groups are numerically depicted. Feasibility to implement facilitators was tested on a scale of 1 (not feasible) to 10 (very feasible).

<sup>†</sup>Mean  $\pm$  standard deviation.



education about biosimilars. Prescribers require an in-depth understanding of biosimilars before they feel comfortable offering these new treatments to their patients.

Despite their experience, physicians were less confident about indication extrapolation and switching patients from biologics reference medicines to biosimilars. As in other studies, they consider that more evidence is needed. Uncertainties have also been reported regarding switching, the decision to administer a biosimilar in a patient previously treated with the reference biologic or vice versa, as well as regarding multiple switching. Similarly to our survey, the risk of nocebo effect, the potential for reduced efficacy or increased immunogenicity, or the "lack of justification" to based switching on cost alone, have been described to explain all of this<sup>4,9,15</sup>.

There was an extraordinary variability in the number, types and brands of biosimilars. We confirmed several organization preferences, policies, and practices regarding biosimilars. Although this project was not designed to explore in detail and measure these aspects, we are confident that they are directly influencing on the prescribers of biosimilars. Further research will be needed. We would also highlight the general lack of a holistic approach, criteria and guidance (based on best evidence) with the use of biosimilars. And in organization where some kind of recommendations were provided, these were basically oriented to increase the use of biosimilars and switches to biosimilars. Financial pressures on organizations are probably generating this situation. It is worth mentioning that one of the main reported barriers was the lack of coordination, and non-alignment in the organization. We also consider that organizations might benefit from engaging health professionals into the design of policies, and protocols to help promote biosimilar properly uptake.

As previously shown<sup>4,7,8,13,15</sup>, the most common barriers reported were the lack of confidence, knowledge and experience. On the other hand, the most important facilitators were the availability of efficacy, safety and interchangeability data (from clinical trials and real world evidence), and the guidance from their professional associations and the experiences of colleagues. These results reinforce the need of educational activities and related projects with biosimilars.

Currently, this study has several limitations. The first one is the sample selection that might limit the representability and reproducibility of the results. Therefore, the results should be interpreted with caution. However, we took into account different factors that might influence on the knowledge or perceptions with the use of biosimilars. We selected a balanced sample of health professionals from different regions and working in different types of hospitals and organizations in order to increase representativeness. Besides, the response rate was very high, and many of this survey findings are in line with the reported in other countries. At this point we would also like to highlight that we did not apply any criteria regarding to the knowledge or the experience with the use of biosimilars to the survey participants in order to avoid selection bias. Another limitation was the extension of the survey that led to a small decrease of response in the last questions. However, we consider that it did not have an impact on the response direction. Finally, due to the sample size, differences among health professionals we might have underestimated differences.

Health professional's hesitations and concerns discourage biosimilars use. Many of them are related to a lack of knowledge and understanding of biosimilars. Thus, biosimilar educational activities are necessary to overcome these barriers. The availability of more supportive evidence on

biosimilars will contribute positively to achieve this goal, and also, taking into account the great variability among organizations connected to the use of biosimilars more efforts are needed to harmonize this use.

Clinicians are also sometimes unwilling to switch between the original and the biosimilar, not only because of a lack of training, but also because the only motivation for switching is economic (e.g. in relation to hospital purchasing policies). More information is needed on the safety and efficacy of these actions based on patient follow-up, registers and clinical practice. It should also be taken into account that the motivations of doctors and pharmacists may be different and that there is sometimes a lack of joint work, with a corporate and collaborative strategy<sup>33</sup>.

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## Conflicts of interest

Ignacio Marín-Jiménez has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Hospira, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Gebro Pharma, Otsuka Pharmaceuticals, AstraZeneca, Sandoz, Fresenius, Amgen and Tillotts Pharma. José Manuel Carrascosa has received honoraria for participation in advisory boards, in clinical trials and/ or as speaker from AbbVie, AMGEN, Biogen, Celgene, Janssen-Cilag, LEO Pharma, Lilly, Novartis Pharma GmbH, Pfizer, UCB, Sandoz, Mylan and Almirall. Marcelo Alejandro Guigini is a full time worker of Fresenius Kabi, España. Emilio Monte-Boquet has received grants/research supports or has participated in educational activities, research projects, scientific meetings (either attendance, speaking and/or delivering presentations) and advisory boards sponsored by Abbott/Abbvie, Amgen, Astellas, AstraZeneca, Baxalta, Bayer, Biogen, Bristol-Myers Squibb, Celgene, Chiesi, Eisai, Fresenius, Gilead, GSK, Ipsen, Janssen, Leo Pharma, Lilly, MSD, Merck-Serono, Novartis, Pfizer, Roche, Shire, UCB and ViiV.

## Contribution to the scientific literature

For the first time, we have depicted a great variability in the use of biosimilars in at least three medical specialties (dermatology, gastroenterology and rheumatology) as well as in hospital pharmacy in Spain. We found a general low degree of knowledge about the most relevant aspects of biosimilars. Likewise, physicians are sometimes reluctant to switch from the original medicine to the biosimilar, not only due to lack of experience, but also because the only find economic justifications for the switch. Recommendations from professional associations and societies, the demonstration of the efficacy of interchangeability, and long-term and real-life safety data would facilitate the use of biosimilars in our country.

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