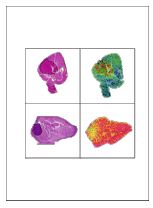

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REPORT

Knowledge, behaviors and practices of community and hospital pharmacists towards biosimilar medicines: Results of a French web-based survey

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ABSTRACT

This study's aims were: 1) to extract a comprehensive overview of the knowledge, experience and opinions of both community pharmacists and hospital pharmacists regarding biosimilar medicines in France; and 2) to identify the perceived problems and solutions to promoting their prescription. A 2015 web-based survey was conducted by the Observatoire des Medicaments, des Dispositifs Medicaux et de l'Innovation Therapeutique of Alsace. A total of 802 pharmacists responded to the survey. Many (536, 66.8%, [95% confidence interval (CI) 63.6–70.1]) indicated that they were not familiar with biosimilars. Half of community pharmacists (95% CI 42.7–57.3) stated that they were not at all informed about biosimilar drugs, compared with 15.7% (95% CI 12.9–18.6) of hospital pharmacists. Almost all respondents (781, 97.4%, [95% CI 96.3–98.5]) had at least one pending question on biosimilars. Most of the questions were related to the manufacturing process, safety, substitution rules and the international non-proprietary name prescription. At the time of the study, 467 pharmacists (58.2%, [95% CI 54.8–61.6]) had already validated a prescription for a biosimilar drug, mainly for filgrastim. These latter were more comfortable in explaining the benefit of biosimilar medicines to the patient. Pharmacists were rather favorable to biosimilar drugs, and about 9 of 10 quoted healthcare cost savings as incentives to their prescription. However, many did not agree with allowing biosimilar substitution. "Patients' wishes to be treated with the originator" and "indication extrapolation" were the two main constraints identified. The survey highlighted the need to provide French pharmacists with accurate and comprehensive information regarding biosimilar medicines.

Abbreviations: ANSM, Agence Nationale de Securite du Medicament et des produits de sante; CNIL, Commission nationale de l'informatique et des libertes; EMA, European Medicines Agency; FDA, Food and Drug Administration; INN, International Non-proprietary Name; US, United States

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Introduction

As of May 31, 2014, 173 biologic medicines were commercialized in France, leading to an expenditure of €5.5 billion/year. Among biotherapies, monoclonal antibodies accounted for the largest budget expense. Of the 10 most expensive drugs in the hospital in 2014 in France, 7 were monoclonal antibodies, namely bevacizumab (Avastin), infliximab (Remicade), tras-tuzumab (Herceptin), rituximab (Mabthera), eculizumab (Soliris), cetuximab (Erbitux) and natalizumab (Tysabri), and these have incurred an expense of about €1.5 billion.[1] Con-sidering this environment, the availability of biosimilar alterna-tives, i.e., versions of reference biological medicinal products, is critical for containing the health care expenses.[2-9]

A biosimilar of infliximab has been on the European market since the beginning of 2015. Subsequently, the availability of the 6 other monoclonal antibodies listed above, in addition to many other reference biological medicinal products, may encourage the production of similar biological medicinal products when patents expire.[10] Biosimilar drugs are available at more affordable costs. These medicines open up the market to competition and induce price reductions for reference biologi-cal medicinal products. Nevertheless, the market of biosimilars is currently limited and is variable among countries. Many fac-tors may influence the biosimilar market uptake, such as pricing and reimbursement, prescription rules, or incentives imple-mented at a national level. Moreover, originator firms develop a range of strategies to compete with biosimilars. This underlines the need for governments to set up coherent biosimilar pol-icy.[11-16] In France, some of these frameworks are already in place, such as a reimbursable drug price difference practice (Ecart medicament indemnisable). When hospitals negotiate prices through tender processes for drugs included on the expensive drug list ("liste en sus," a restricted list enabling the complete drug funding in addition to hospitalization stays),

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the savings, i.e. the difference between the initial price set up by the French Economic Committee for Medicinal Products (Comite Economique des Produits de Sante) and the negotiated price is shared equally between the French Social Insurance and the hospital. Additional initiatives of the French government are also expected to provide strong incentives for physicians to prescribe biosimilar medicines. Similarly to the rules developed for generics, the upcoming initiatives may encompass targets of biosimilar prescription for the hospitals, and an additional bonus aligned with public health objectives (remuneration sur objectifs de sante publique) for office-based physicians, but these approaches are not in place yet.[17]

Compared to generic medicines, biosimilar drugs are more complex and require extensive investigation to obtain a marketing authorization, including preclinical, Phase 1 and Phase 3 clinical studies. The regulatory framework applicable to biosimilar medicines is well-defined both by European Medicines Agency (EMA) and the Food and Drug Administration.[18-22] This framework includes some specific concepts, such as the indication extrapolation rules enabling the approval of a biosimilar medicine for all the clinical indications of the reference medicinal product, solely based on the results of the indication assessed in clinical trials and upon adequate scientific justification. However, the concept of biosimilarity and related issues about the manufacturing process, extrapolation of indications, substitution by the pharmacist, etc., may be questioned by both health professionals and patients.[23-25] This is particularly relevant because some of these biosimilar policies are within the remit of the European Union member states and are therefore not the same in each country.[26] Indeed, the evaluation of biosimilar medicines for authorization purposes by the EMA does not include recommendations related to interchangeability and substitution of a reference biological product with a biosimilar medicine. France was the first European country to specifically authorize the biosimilar substitution in Article 47 of the 2014 French Social Security Financing Law, but only when initiating treatment.[25,27] The primary thoughts of the French National Agency for Medicines and Health Products Safety (Agence Nationale de Securite du Medicament et des Produits de sante, ANSM) on the issues related to biosimilar interchangeability were equally conservative. ANSM excluded the switch of treatment-experienced patients from an originator biologic to biosimilar product. However, the French biosimilar policy has recently evolved. In May 2016, ANSM relaxed its stance on biosimilar interchangeability to state that, while the preference is not to switch treatment from a reference drug to a biosimilar during the course of a treatment, this can be done as long as the patient is made aware, and monitoring and tracking of biosimilars are put in place.[28] Similarly, article 50 of the 2017 Social Security Financing Law Project (PLFSS) now states that French pharmacists can substitute a biosimilar with a prescribed biological product, without making any distinction between naïve and pre-treated patients.[29] Nevertheless, the relevant decrees regarding the specific environment required for biosimilar interchangeability and substitution are still awaited.

Pharmacists could play a valuable role in supporting the uptake of biosimilar medicines by providing accurate information, promoting acceptance among health community and patients and ensuring their safe and proper use. This can only be achieved through pharmacists' confidence in biosimilar drugs prescriptions. We conducted a literature search of the PubMed/MEDLINE database using the search terms "biosimilar" and "pharmacist" that yielded only 18 results, including 3 surveys: 1) a United States (US) survey focusing on biosimilar naming conventions;[30] 2) a qualitative study investigating the barriers to the uptake of biosimilars in Belgium through semi-structured interviews that included a few pharmacists;[31] and 3) a 2015 web-based survey investigating the extent of awareness and understanding of biosimilar products among Japanese physicians and pharmacists.[32] It therefore appeared essential to gather pharmacists' view toward biosimilar medicines. Our study aimed first to produce a comprehensive picture of the knowledge, experience and opinions of both community and hospital pharmacists in France toward biosimilar medicines, and second to identify the barriers and potential actions to promote their prescriptions.

Results

A total of 802 responses to our questionnaire (available as supplementary material) were collected. The demographic information on participating pharmacists is summarized in Table 1. Close to 63% of respondents were women (502 pharmacists) and the pharmacists' average age was 42.1 y (standard deviation (SD), § 11.2). Most respondents worked at hospital (616 hospital pharmacists (76.8%), including 116 pharmacy residents). Hospital pharmacists were involved in numerous activities such as purchasing and logistics (77.2%, [95% con dence interval (CI) 73.5–80.9]), clinical pharmacy (71.8%, [95% CI 67.9–75.7]), quality (68.8%, [95% CI 64.7–72.9]), computerization (64.6%, [95% CI 60.4–68.8]), pharmacovigilance (62.4%, [95% CI 58.2–66.6]), dispensing medicines under temporary authorization (exceptional measures making available medicinal products that have not yet been granted a marketing authorization) and dispensing of hospital drugs to outpatients (51.8%, [95% CI 47.4–56.2]), preparation and control (45.4%, [95% CI 41.0–49.8]), clinical trials (27.4%, [95% CI 23.5–31.3]), sterilization (24.8%, [95% CI 21.0–28.6]) or radiopharmacy (3.2%, [95% CI 1.7–4.7]). All seniority grades were represented. The responses

Table 1. Demographic data of pharmacists respondents (n D 802).

Pharmacists demographics	n (%)	[95% confidence interval]
Gender		
Male	300 (37.4)	[34.1–40.8]
Female	502 (62.6)	[59.2–65.9]
Average age	42.1 (23–72)	SD D 11.2
Professional specialty		
Community pharmacist	178 (22.2)	[19.3–25.1]
Hospital pharmacist (including pharmacy residents)	616 (76.8)	[73.9–79.7]
Other (industrial pharmacist, pharmacologist…)	8 (1.0)	[0.31–1.69]
Seniority grade		
pharmacy student or pharmacy resident	119 (14.8)	[12.4–17.3]
< 10 years	218 (27.2)	[24.1–30.3]
10–20 years	239 (29.8)	[26.6–33.0]
> 20 years	226 (28.2)	[25.1–31.3]

years (range)

standard deviation (SD)

to the survey originated from 94% of all French departments, 93 of 96 departments in metropolitan France and 2 of 5 depart-ments located overseas. To place the response in context, 74,492 pharmacists were working in France and registered by the French national pharmacists association (Conseil National de l'Ordre des Pharmaciens) on January 1, 2015, including 54,924 community pharmacists and 6741 hospital pharmacists. Pharmacists were 46.6 y on average and 67.1% were women.[33]

Pharmacists' knowledge and level of information related to biosimilar medicines

A total of 62.2% (95% CI 58.9–65.6) of the respondents (499 of 802 pharmacists who answered the questionnaire) stated that they had "little knowledge" about biosimilar medicines. Some pharmacists even answered they did not know biosimilar drugs (37 pharmacists, i.e., 4.6%, [95% CI 3.9–5.4]). Community pharmacists were less familiar with biosimilar medicines com-pared with hospital pharmacists. Indeed, 77.0% (95% CI 70.8–83.2) of community pharmacists stated they had "little knowl-edge" and 12.4% (95% CI 7.5–17.2) "no knowledge" related to biosimilar medicines, vs. 57.8% (95% CI 53.9–61.7) and 2.4% (95% CI 1.2–3.7) of hospital pharmacists, respectively ($p < 0.001$, x^2 test). Among hospital pharmacists, nearly 8 of 10 pharmacy residents (81.0%, 95% CI 73.9–88.1) stated they had "no knowledge" or "little knowledge" related to biosimilar medicines.

Nearly 29% (95% CI 25.5–31.8) of respondents felt "well" (188 pharmacists, i.e., 23.4%, [95% CI 20.5–26.4]) or "very well" (42 pharmacists, i.e., 5.2%, [95% CI 3.7–6.8]) informed about biosimilars. However, almost a quarter answered that they were "not at all" informed about biosimilar drugs, includ-ing 50.0% (95% CI 42.7–57.3) of community pharmacists and 15.7% (95% CI 12.9–18.6) of hospital pharmacists who com-pleted the survey ($p<0.001$, x^2 test). Similarly, pharmacy resi-dents felt less informed about biosimilar medicines compared with their older counterparts working at the hospital ($p<0.001$, x2 test). The main sources of information mentioned by respondents were self-study and scientific publications (78.9%, [95% CI 76.1–81.8]), pharmaceutical companies (72.7%, [95% CI 69.6–75.8]), fellow pharmacists (53.7%, [95% CI 50.3– 57.2]), health institutions: ANSM (50.6%, [95% CI 47.2–54.1]) and French National Authority for Health (Haute Autorite de Sante, HAS; 37.7%, [95% CI 34.3–41.0]), and continuous training (44.6%, [95% CI 41.2–48.1]). Notably, the national health insurance was quoted as a source of information about biosimilar drugs by only 42 pharmacists, i.e., 5.2% (95% CI 3.7–6.8) of the survey participants.

Almost all pharmacists (781, i.e., 97.4%, [95% CI 96.3–98.5]) had at least one remaining question on biosimilar drugs. Com-munity pharmacists raised significantly more questions com-pared with hospital pharmacists (5.3 [standard deviation (SD) D 2.4] vs. 4.6 [SD D 2.3] in average, two-sided Student t-test, $p<0.01$). The issues were primarily related to: 1) substitu-tion by a pharmacist of a reference biological medicinal product to its biosimilar equivalent (79.2%, [95% CI 76.4–82.0]); 2) tol-erance and iatrogenic effects (70.6%, [95% CI 67.4–73.7]); and 3) the manufacturing process of biosimilar drugs (54.9%, [95% CI 51.4–58.3]). These were followed by questions about the international non-proprietary name (INN) prescription (49.8%, [95% CI 46.3–53.2]) and criteria to be fulfilled for granting marketing authorization of similar biological medici-nal products (Autorisation de mise sur le marche, AMM; 47.3%, [95% CI 43.8–50.7]). Many pharmacists indicated that they did not feel sufficiently informed to dispense a biosimilar medicine. This lack of confidence in biosimilar drug dispensing was related to the information deficit about drug safety for 43.1% (95% CI 39.7–46.6) of respondents, but also about its quality and efficacy for 36.5% (95% CI 33.2–39.9) and 33.4% (95% CI 30.2–36.7) of pharmacists, respectively.

We asked the pharmacists to indicate whether some state-ments about biosimilar medicines were accurate or not. A min-imum of 59.4% and up to 95.4% of survey respondents gave a correct answer to each of the 9 statements proposed (see Table 2). Overall, an average of 7.1 (SD D 1.5) of 9 correct answers were given.

Pharmacists' experience and practices

At the time of the study, 467 of 802 pharmacists (i.e., 58.2%, [95% CI 54.8–61.6]) had already validated a prescription for at least one of the 9 biosimilar drugs available in France, of which 110 (i.e., 23.6%, [95% CI 19.7–27.4]) did so on an exceptional basis. For 175 pharmacists (37.5%, [95% CI 33.1–41.9]), mini-mal frequency of biosimilar medicine delivery was once a week, and most (169 pharmacists, i.e., 96.6%, [95% CI 93.9–99.3]) worked at the hospital. Biosimilar filgrastim (Ratiograstim , Tevagrastim , Nivestim or Zarzio) was the most commonly

Table 2. Pharmacists' answers to statements about biosimilar medicines (n D 802).

In your opinion, which statements about biosimilar medicines are accurate? A biosimilar medicine:	Adequate answer	Number of adequate answers	
		n (%)	[95% confidence interval]
[is structurally identical to its reference medicinal product]	No	476 (59.4%)	[56.0–62.8]
[is similar to a reference medicinal product that has gone off-patent]	Yes	688 (85.8%)	[83.4–88.2]
[has no meaningful differences from a reference medicinal product in terms of quality]	Yes	754 (94.0%)	[92.4–95.7]
[has no meaningful differences from a reference medicinal product in terms of safety]	Yes	626 (78.1%)	[75.2–80.9]
[has no meaningful differences from a reference medicinal product in terms of efficacy]	Yes	765 (95.4%)	[93.9–96.8]
[has the same dosage and route of administration compared to its reference medicinal product]	Yes	592 (73.8%)	[70.8–76.9]
[is a drug for which marketing authorization is granted on the sole investigation of pharmacokinetic bioequivalence with its reference medicinal product]	No	569 (70.9%)	[67.8–74.1]
[is a drug for which assessment of biosimilarity requires more comprehensive data compared to generic drugs]	Yes	619 (77.2%)	[74.3–80.1]
[requires preclinical and clinical studies]	Yes	596 (74.3%)	[71.3–77.3]

delivered, mentioned by 9 of 10 pharmacists validating prescriptions for biosimilar drugs. Almost half of the pharmacists had already delivered a biosimilar epoetin (Binocrit or Retacrit). Only 50 pharmacists had validated prescriptions for biosimilar infliximab (Inflectra or Remsima), and 20 for biosimilar somatropin (Omnitrope).

Pharmacists were asked if they felt comfortable explaining the benefit of biosimilar medicines to patients, by using a seven-point scale (from 1 D not at all comfortable, to 7 D completely comfortable). They felt less comfortable in explaining the benefit of biosimilars to patients when they had not already validated a prescription for a biosimilar drug. In fact, values 1 to 3 were selected on the scale by 58.9% (95% CI 53.5–64.1) of pharmacists who had not already delivered a biosimilar drug, vs. 31.3% (95% CI 27.1–35.5) of pharmacists already experienced in validating biosimilar prescriptions (x^2 test, $p < 0.001$).

Pharmacists' opinion

"Healthcare cost savings" were identified by close to 92% (95% CI 90.1–93.9) of pharmacists as an incentive to promote the prescription of biosimilar medicines. This was followed by "health policy-makers incentive," "positive impact on patients' access to innovative drugs" and "release of resources allowing treating additional patients," quoted by 72.2% (95% CI 69.1–75.3), 64.8% (95% CI 61.4–68.1) and 62.9% (95% CI 59.6–66.3) of survey respondents, respectively. The "patients' wishes to be treated with biosimilar medicines" was considered as an ele-ment to support the biosimilar drug prescription by 26.1% (95% CI 22.9–29.3) of pharmacists, whereas the opposite sen-tence: "patients' wishes to be treated with the reference biologi-cal medicinal product" was stated by 61.8% (95% CI 58.4–65.2) pharmacists as a barrier to biosimilar prescription. Another item was quoted equally as able to restrain biosimilar prescrip-tion: "extrapolation of efficacy and safety from one therapeutic indication of the biosimilar drug to all indications of the reference biological medicinal product." The issues "lack of information about tolerance" (56.7%, [95% CI 53.2–60.1]) and "risk of increasing patient's worries and concerns" (55.5%, [95% CI 52.0–58.9]) were ranked next in importance, followed by "risk of immunogenicity" (51.6%, [95% CI 48.2–55.1]). Many of these obstacles, e.g., safety issues, were already clearly expressed when asking the pharmacists about their remaining questions related to biosimilar medicines.

Pharmacists were asked whether they agreed to some statements about biosimilar medicines. Their responses are shown in Table 3. They were rather favorable to the widespread prescription of biosimilar drugs. However, slightly more than half of them were in favor of the substitution of a reference biological medicinal product by its biosimilar product (427 pharmacists, i.e., 53.2%, [95% CI 49.8–56.7]). This proportion is relatively small compared with the rate of pharmacists who agreed with the substitution of a reference chemical medicinal product by its generic drug (704 pharmacists, i.e., 87.8%, [95% CI 85.5–90.0]). More than 8 of 10 pharmacists stated that biosimilar prescriptions enable cost savings, and three quarters thought these savings would be "significant" (463 pharmacists, i.e., 57.7%, [95% CI 54.3–61.1]) to "very important" (136 pharmacists, i.e., 17.0%, [95% CI 14.4–19.6]).

Discussion

Our study provided a snapshot of French pharmacists' knowledge, experience and opinion related to biosimilar medicines as of 2015. Very few biosimilar surveys have been conducted, and ours is the first questionnaire survey on the topic performed among pharmacists in a European country.[30-32] Obviously, pharmacists are not the only key stakeholders in biosimilar market uptake, as biosimilar prescription is closely linked to the physicians' confidence and acceptance. To investigate this matter, we conducted a second web-based survey to give an assessment of knowledge, experience and opinions of hospital-based and office-based French rheumatologists toward biosimi-lar medicines and to identify the barriers and possible options to promote their prescription.[34]

The large number of pharmacists who completed our survey combined with their widespread geographical location across the national territory ensured the relevance of the results. We noticed that only a small percentage of the community phar-macists took part in the survey compared with the hospital pharmacists. This difference may be due to a lack of targeted communication, and to the small number of biosimilar drugs now available in community pharmacies. This is further illus-trated by the survey responses, which emphasized that commu-nity pharmacists felt less familiar and raised more questions

Table 3. Pharmacists' level of agreement to some statements about biosimilar medicines (n D 802).

To what extent do you agree or disagree with the following statements? (n D 802)	Strongly disagree n (%) [95% CI]	Disagree n (%) [95% CI]	Neither agree nor disagree n (%) [95% CI]	Agree n (%) [95% CI]	Strongly agree n (%) [95% CI]
[I am in favor with the implementation of biosimilar medicines]	15 (1.9%) [0.9–2.8]	38 (4.7%) [3.3–6.2]	180 (22.4%) [19.6–25.3]	366 (45.6%) [42.2–49.1]	203 (25.3%) [22.3–28.3]
[Biosimilar medicines are tried and tested in terms of efficacy and safety]	6 (0.7%) [0.2–1.3]	56 (7.0%) [5.2–8.7]	210 (26.2%) [23.1–29.2]	396 (49.4%) [45.9–52.8]	134 (16.7%) [14.1–19.3]
[Biosimilar medicines are not only pharmacist's concern]	49 (6.1%) [4.5–7.8]	38 (4.7%) [3.3–6.2]	54 (6.7%) [5.0–8.5]	270 (33.7%) [30.4–36.9]	391 (48.8%) [45.3–52.2]
[I approve the substitution by a pharmacist of a reference biological medicinal product to its biosimilar product]	53 (6.6%) [4.9–8.3]	129 (16.1%) [13.5–18.6]	193 (24.1%) [21.1–27.0]	288 (35.9%) [32.6–39.2]	139 (17.3%) [14.7–20.0]
[I approve the substitution by a pharmacist of a reference chemical medicinal product to its generic product]	17 (2.1%) [1.1–3.1]	25 (3.1%) [1.9–4.3]	56 (7.0%) [5.2–8.7]	262 (32.7%) [29.4–35.9]	442 (55.1%) [51.7–58.6]
[Biosimilar medicines prescription allows for reducing healthcare costs]	4 (0.5%) [0.01–1.0]	22 (2.7%) [1.6–3.9]	106 (13.2%) [10.9–15.6]	369 (46.0%) [42.6–49.5]	301 (37.5%) [34.2–40.9]

CI: confidence interval

related to biosimilar medicines compared with their hospital-based counterparts. Nevertheless, it is essential that they take an active role in enhancing biosimilar drugs uptake and patient acceptance. This is even more critical as new biosimilar drugs, such as subcutaneous anti-tumor necrosis factor biosimilars, will be soon available in community pharmacies. For instance, the first etanercept biosimilar (Benepali) was granted marketing authorization in the European Union in January 2016.

With regard to the first section of the questionnaire, it appeared that communication efforts targeting pharmacists could be developed and spread at a national level, specifically by the national health insurance. Its involvement in promoting prescription of generic drugs is still current, but its incentives toward biosimilar medicines appear to have been somewhat limited so far.

When considering the pharmacists' experience related to biosimilar medicines, we found that very few had already delivered biosimilar infliximab. This is linked to the fact that infliximab is restricted to hospital use in France. Also, biosimilar infliximab was launched very recently, and it is therefore likely to be prescribed to a few patients only, especially as ANSM did not recommend switching patients already treated with originator infliximab to a biosimilar medicine until May 2016.[28,35] Nonetheless, it can already be seen that hospital physicians gradually start prescribing biosimilar infliximab (Inflectra or Remsima) when looking for information on hospital activity in the PMSI (Program de Medicalisation des Systemes d'Information) national database.[1]

We also explored the pharmacists' view on biosimilar drugs. Many were in favor of the implementation of biosimilar medicines. Most also recognized potential cost saving from the use of biosimilar drugs, which could contribute to enhanced access to innovative drugs and to treatment of more patients for a lower price. This topic was already addressed in several studies.[5-8] In a previous analysis, we showed that management of rheumatoid arthritis patients with biosimilar infliximab in France could result in €13.6 million annual cost savings, enabling treatment of 1,141 additional patients if fully reallocated.[8]

Many pharmacists did not feel sufficiently informed about tolerance and iatrogenic effects. However, various clinical trials provided evidence-based information to confirm that there are no meaningful differences in terms of quality, safety and effi-cacy between a reference biological medicinal product and bio-similar drugs.[36,37] Furthermore, numerous changes in the manufacturing process of originator drugs have occurred since their launch. Drugs that are used now are thus, to some extent, biosimilars of what they were at the time of their introduction on the market. This is the case of originator infliximab (Remicade), which underwent more than 35 manufacturing process changes since its marketing authorization in 1999.[38]

The indication extrapolation concept was also widely questioned and perceived by many pharmacists as a limitation to biosimilar prescriptions. Several studies are performed to provide complementary information, especially in investigating biosimilar use in patients suffering from inflammatory bowel diseases, indications that were not evaluated during clinical development of the biosimilar drug, or in supporting interchangeability of the reference biological drug with its biosimilar equivalent in real-life settings.[39-46]

Biosimilar substitution by the pharmacist was another of the main issues raised in our survey. It is important to note that the biosimilar substitution policy is not the same between Euro-pean countries.[26] For instance, France was one of the first coun-tries to allow for biosimilar substitution, under certain conditions that are stated in the article 47 of the 2014 French Social Security Financing Law.[25,27] Substitution by the commu-nity pharmacist of a reference biological medicinal product with a biosimilar equivalent belonging to the same biologic group is currently planned for treatment-na€ıve patients. How-ever, there still exist legal uncertainties. For example, specific measures must be taken in order to ascertain the patient always continues treatment with the same medicine. This raises the questions of INN prescription and traceability of the biological drug that has been delivered. This particular topic was addressed by half of the French pharmacists in our survey. Indeed, with limited exceptions, biosimilars share the same INN as their reference biological medicinal products. Auto-matic substitution of one biologic medicine for another can occur in case of prescription by INN, making clear identifica-tion of the biological drugs and pharmacovigilance monitoring more difficult. Concrete solutions are discussed, such as brand-name prescribing rather than INN-prescribing. The World Health Organization issued guidelines for naming of biosimi-lars, suggesting biosimilar firms could choose to use a Greek letter suffix added to the INN in order to mention differences in terms of glycosylation of their products.[47,48] In addition, electronic patient record systems could help track whether a biological treatment was already dispensed and, if so, which one. Moreover, switch studies assessing the effects of interchanging originator infliximab with its biosimilar equivalent are multiplying, providing additional data about its efficacy and tolerance. In light of these reassuring data, an expansion of interchangeability conditions was addressed by the ANSM in May 2016. ANSM now indicates that interchangeability with a biosimilar drug is possible, even when the patient is already being treated with the reference biological medicinal product.[28] These new recommendations are likely to contribute to some amendments in the French Law that may have a great impact on biosimilar market penetration and on the resulting cost savings.

The findings of our investigation have important implica-tions for pharmaceutical practices and for the uptake of biosi-milar drugs. To date, many pharmacists are in favor of the implementation of biosimilar medicines and convinced of their cost savings potential. Moreover, they are at the heart of the concerns raised by potential regulatory changes and their privileged relationship with patients is a valuable asset to promote a clear understanding and to ensure safe use of these particular drugs. Several issues and possible pitfalls related to biosimilars were identified. Pharmacists, in light of their growing experi-ence and provided they are sufficiently informed and involved, will have the opportunity to take a leadership position to sup-port biosimilar medicines prescription.

Materials and methods

A national web-based self-administered survey was conducted by the Observatoire des MEdicaments, des Dispositifs

medicaux et de l'Innovation Therapeutique of Alsace, which functions within the regional health agency (Agence Regionale de Sante - ARS). The study was conducted for an 8-weeks period, between June 8 and August 2, 2015.

Development of the survey questionnaire

A self-administered questionnaire (available as supplementary material) was created especially for the purpose of the study, and was validated by a task group constituted of 4 pharmacists, 1 rheumatologist and 1 public health physician and epidemiol-ogist. This questionnaire was composed of 22 questions that were divided into four parts, each one dedicated to the collec-tion of data relative to a specific topic: characteristics of respondents, knowledge, experience and opinion with regard to biosimilar medicines, respectively. The main part of the online questionnaire was composed of closed-ended questions since these were more convenient for pharmacists to answer, required less coding and were easier to analyze. A last open-ended question allowed us to gather the pharmacists' com-ments on the topic.

Pilot study

A pilot study was conducted to check for comprehension of the questionnaire, verify its accuracy and completeness with regard to the research topic, identify possible redundancy among the 22 questions, and ensure ergonomics of the data-collecting method.

Target population

Invitations to participate to the web-survey were sent out by e-mail to almost 3000 hospital pharmacists and to more than 6500 community pharmacies with the help of the regional pharmacists' association (Conseil Regional de l'Ordre des Phar-maciens) of 11 of 27 regions of France (22 regions in mainland France and its 5 overseas dependencies) at the time of the sur-vey. Pharmacy residents were also targeted with the help of the National Federation of pharmacy residents trade unions or associations FNSIP-BM (Federation Nationale des Syndicats d'Internes en Pharmacie et Biologie Medicale) and pharmacy resident associations.

Ethical approval

Information strictly required for the purpose of the study was collected in the form of anonymized data. A file containing the electronic addresses of the hospital pharmacists that were con-tacted was created using data from the CNHIM (Centre National Hospitalier d'Information sur le Medicament) website and stored with respect to the approval of the French data pro-tection authority CNIL (Commission nationale de l'informa-tique et des libertes). The study was registered on a data protection register ("Registre informatique et libertes") kept up to date by a CNIL local correspondent as the guarantor of com-pliance with the conditions under which the survey was held.

Statistical analysis

Major changes to the questionnaire were made following the pilot study; thus, questionnaires of the pilot study were not combined with the main study for analysis. Data were gathered and analyzed using Microsoft Excel 2007. Descriptive statis-tics were reported by numbers, averages and standard devia-tions, proportions and 95% confidence intervals. Pearson's Chi-squared tests (χ^2 tests) and Student t-tests were performed using R, version 3.1.0. A p-value below 0.05 was considered to be of statistical significance.

Disclosure of potential conflicts of interest

JS reports financial – received grants (< 10.000 euros) from Roche, Pfizer, AbbVie, UCB and consulting fees or honorarium (< 1.500 euros) from Roche, Chugai, Bristol Myers Squibb, Abbott, UCB, GSK, LFB, Actelion, Pfizer, Merck Sharp, Novartis, Amgen, Hospira and AbbVie. All other authors declare that they have no conflicts of interest.

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References

1. Stats ATIH [Internet]. [cited 2016 Mar 30]. Available from: http://www.scansante.fr/
2. Bocquet F. Les Medicaments Biosimilaires : enjeux economiques et politiques. Paris: Editions de sante; 2015.
3. Gulacsi L, Brodszky V, Baji P, Kim H, Kim SY, Cho YY, Pentek M. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol 2015; 11 Suppl 1:43-52; PMID:26395836; http://dx.doi.org/10.1586/1744666X.2015.1090313
4. Isaacs JD, Cutolo M, Keystone EC, Park W, Braun J. Biosimilars in immune-mediated inflammatory diseases: initial lessons from the first approved biosimilar anti-tumour necrosis factor monoclonal anti-body. J Intern Med 2016; 279(1):41-59; PMID:26403380; http://dx. doi.org/10.1111/joim.12432
5. Haustein R, de Millas C, H€oer A, H€aussler H. Saving money in the European healthcare systems with biosimilars. Generics

Biosimilars Initiat J 2012; 1(3–4):120-6; http://dx.doi.org/10.5639/gabij.2012.0103-4.036
6. Brodszky V, Baji P, Balogh O, Pentek M. Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries. Eur J Health Econ HEPAC Health Econ Prev Care 2014; 15 Suppl 1:S65-71; PMID:24832837; http://dx.doi.org/10.1007/s10198-014-0595-3
7. Jha A, Upton A, Dunlop WC, Akehurst R. The Budget Impact of Biosimilar Infliximab (Remsima( )) for the Treatment of Autoimmune Diseases in Five European Countries. Adv Ther 2015; 32 (8):742-56; PMID:26343027; http://dx.doi.org/10.1007/s12325-015-0233-1
8. Beck M, Michel B, Rybarczyk-Vigouret MC, Sordet C, Sibilia J, Velten M. Biosimilar infliximab for the management of rheumatoid arthritis in France: what are the expected savings? Eur J Hosp Pharm. http:// dx.doi.org/10.1136/ejhpharm-2016-000904
9. Farfan-Portet MI, Gerkens S, Lepage-Nefkens I, Vinck I, Hulstaert F. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? Eur J Health Econ 2014; 15:223-8; PMID:24271016; http://dx.doi.org/10.1007/s10198-013-0538-4
10. DeVries JH, Gough SC, Kiljanski J, Heinemann L. Biosimilar insulins: a European perspective. Diabetes Obes Metab 2015; 17(5):445-51; PMID:25376600; http://dx.doi.org/10.1111/dom.12410
11. Declerck PJ, Simoens S. A European perspective on the market acces-sibility of biosimilars. Biosimilars 2012; 2:33-40; http://dx.doi.org/ 10.2147/BS.S33524
12. Dylst P, Vulto A, Simoens S. Barriers to the uptake of biosimilars and possible solutions: a Belgian case study. Pharmacoeconomics 2014; 32 (7):681-91; PMID:24803078; http://dx.doi.org/10.1007/s40273-014-0163-9
13. Bocquet F, Paubel P, Fusier F, Cordonnier AL, Sinegre M, Le Pen C. Biosimilar versus patented erythropoietins: learning from 5 years of European and Japanese experience. Appl Health Econ Health Policy 2015; 13(1):47-59; PMID:25189295; http://dx.doi.org/10.1007/s40258-014-0125-6
14. Bocquet F, Loubiere A, Fusier I, Cordonnier AL, Paubel P. Competition between biosimilars and patented biologics: learning from European and Japanese experience. Pharmacoeconomics 2016; 34 (11):1173-86; PMID:27412251; http://dx.doi.org/10.1007/s40273-016-0428-6
15. Bocquet F, Paubel P, Fusier I, Cordonnier AL, Le Pen C, Sinegre M. Biosimilar granulocyte colony-stimulating factor uptakes in the EU-5 markets: a descriptive analysis. Appl Health Econ Health Policy 2014; 12(3):315-26; PMID:24578185; http://dx.doi.org/10.1007/s40258-014-0087-8
16. Mestre-Ferrandiz J, Towse A, Berdud M. Biosimilars: how can payers get long-term savings? Pharmacoeconomics 2016; 34(6):609-16; PMID:26792791; http://dx.doi.org/10.1007/s40273-015-0380-x
17. Girault D, Trouvin JH, Blachier-Poisson C, Gary F, Laloye D, participants of round table N 3 of Giens XXX, Bergmann JF, Casadevall N, Delval C, De Sahb Berkovitch R et al. Biosimilars: from Technical to Pharmacoeconomic Considerations. Therapie 2015; 70(1):47-55; PMID:27393396; http://dx.doi.org/10.2515/therapie/2015003
18. Lucio SD, Stevenson JG, Hoffman JM. Biosimilars: Implications for health-system pharmacists. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm 2013; 70(22):2004-17; PMID:24173009; http:// dx.doi.org/10.2146/ajhp130119
19. European Medicines Agency (EMA). Guideline on similar biological medicinal products. [Internet]. 2014 [cited 2015 Apr 21]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
20. European Medicines Agency (EMA). Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues. [Internet]. 2012 [cited 2015 Oct 29]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf
21. Kurki P, Ekman N. Biosimilar regulation in the EU. Expert Rev Clin Pharmacol. 2015; 8(5):649-59; PMID:26294076; http://dx.doi.org/10.1586/17512433.2015.1071188
22. Calvo B, Zuniga~ L. The US approach to biosimilars: the long-awaited FDA approval pathway. BioDrugs Clin Immunother Biopharm Gene Ther 2012; 26(6):357-61; PMID:23030677; http://dx.doi.org/10.2165/ 11635830-000000000-00000
23. Weise M, Bielsky M-C, De Smet K, Ehmann F, Ekman N, Giezen TJ, Gravanis I, Heim HK, Heinonen E, Ho K, et al. Biosimilars: what clinicians should know. Blood 2012; 120(26):5111-7; PMID:23093622; http://dx.doi.org/10.1182/blood-2012-04-425744
24. Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. Blood 2014; 124(22):3191-6; PMID:25298038; http://dx.doi.org/10.1182/blood-2014-06-583617
25. Bocquet F, Paubel P. First monoclonal antibody biosimilars: tackling the challenge of substitution. J Med Econ 2016; 19(6):645-7; PMID:27080815; http://dx.doi.org/10.1080/13696998.2016.1178649
26. Mendoza C, Ionescu D, Radiere G, Remuzat C, Young KE, Toumi M. Biosimilar Substitution Policies: An Overview. Value Health J Int Soc Pharmacoeconomics Outcomes Res 2015; 18(7):A525; PMID:26532944; http://dx.doi.org/10.1016/j.jval.2015.09.1616
27. Legifrance. JORF n 0298 du 24 decembre 2013 page 21034 - texte n 3 - LOI n 2013-1203 du 23 decembre 2013 de financement de la securite sociale pour 2014. [Internet]. [cited 2016 Oct 28]. Available from: https://www.legifrance.gouv.fr/affichTexte.do;jsessionidD451C94702FA3F517186E56A44600EAF7.tpdila16v_2?cidTexteDJORFTEXT000028372809&categorieLienDid
28. Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM). Etat des lieux sur les medicaments biosimilaires - Mai 2016. [Internet]. [cited 2016 May 17]. Available from: http://ansm.sante.fr/ S-informer/Actualite/L-ANSM-publie-une-mise-au-point-sur-les-medicaments-biosimilaires-Point-d-Information
29. Legifrance. PLFSS 2017 - Annexe 10 - Fiches d'evaluation prealable des articles du projet de loi. [Internet]. [cited 2016 Oct 28]. Available from: https://www.legifrance.gouv.fr/content/download/10612/122221/version/2/file/ei_ecfx1623944L_cm_05.10.2016.pdf
30. Fernandez-Lopez S, Kazzaz D, Bashir M, McLaughlin T. Assessment of pharmacists' views on biosimilar naming conventions. J Manag Care Spec Pharm 2015; 21(3):188-95; PMID:25726028; http://dx.doi. org/10.18553/jmcp.2015.21.3.188
31. Alliance for Safe Biologic Medicines (ASBM). ASBM Releases Phar-macist Survey; Findings Show Strong Support for Distinguishable Names for Biologics and Need for Transparency in Labeling. [Inter-net]. [cited 2016 Apr 20]. Available from: http://safebiologics.org/ resources/2015/10/asbm-releases-pharmacist-survey-findings-show-strong-support-for-distinguishable-names-for-biologics-and-need-for-transparency-in-labeling/
32. Tanabe K, Sugimoto N, Fujimoto Y. A Web-Based Survey to Investigate the Extent of Awareness and Understanding for Biosimilar among Japanese Physicians and Pharmacists. Value Health J Int Soc Pharmacoeconomics Outcomes Res 2015; 18(7):A658; PMID:26533689; http://dx.doi.org/10.1016/j.jval.2015.09.2381
33. Ordre National des Pharmaciens. Les Pharmaciens, panorama au 1er janvier 2015. [Internet]. [cited 2016 May 17]. Available from: http://www.ordre.pharmacien.fr/Communications/Elements-demographiques/Les-pharmaciens-Panorama-au-1er-janvier-2015
34. Beck M, Michel B, Rybarczyk-Vigouret MC, Lev^eque D, Sordet C, Sibilia J, Velten M. Rheumatologists' perceptions of biosimilar medicines prescription: findings from a French web-based survey. BioDrugs 2016; 30(6):585-92[epub ahead of print]; PMID:27848166; http://dx.doi.org/10.1007/s40259-016-0202-5
35. Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM). Les medicaments biosimilaires - Etat des lieux Septembre 2013 [Internet]. [cited 2016 Apr 20]. Available from: http://www.ansm.sante.fr/var/ansm_site/storage/original/application/6187b427efca64d2a15e496ff691158e.pdf
36. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, Mikazane H, Gutierrez-Urena~ S, Lim M, Lee YA, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013; 72(10):1605-12;

PMID:23687259; http://dx.doi.org/10.1136/annrheumdis-2012-203091

37. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, Kovalenko V, Prodanovic N, Abello-Banfi M, Gutierrez-Urena~ S, et al. A randomised, double-blind, parallel-group study to demon-strate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013; 72(10):1613-20; PMID:23687260; http://dx.doi.org/10.1136/annrheumdis-2012-203090
38. Schneider CK. Biosimilars in rheumatology: the wind of change. Ann Rheum Dis 2013; 72:315-8; PMID:23390018; http://dx.doi.org/10.1136/annrheumdis-2012-202941
39. ClinicalTrials.gov. "Efficacy and Safety of Infliximab-biosimilar (Inflectra) Compared to Infliximab-innovator (Remicade) in Patients With Inflammatory Bowel Disease in Remission: the SIMILAR Trial.". [Internet]. [cited 2016 Mar 4]. Available from: https://clinicaltrials. gov/ct2/show/NCT02452151
40. Jung YS, Park DI, Kim YH, Lee JH, Seo PJ, Cheon JH, Kang HW, Kim JW. Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study. J Gastroenterol Hepatol 2015; 30:1705-12; PMID:25974251; http://dx.doi.org/10.1111/jgh.12997
41. Park SH, Kim YH, Lee JH, Kwon HJ, Lee SH, Park DI, Kim HK, Cheon JH, Im JP, Kim YS, et al. Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea. Expert Rev Gastroenterol Hepatol 2015; 9 Suppl 1:35-44; PMID:26395533; http://dx.doi.org/10.1586/17474124.2015.1091309
42. British Society of Gastroenterology (BSG). Clinical trials updates - PANTS study. [Internet]. [cited 2016 Mar 4]. Available from: http://www.bsg.org.uk/research/clinical-trials-updates/index.html
43. Nikiphorou E, Kautiainen H, Hannonen P, Asikainen J, Kokko A, Rannio T, Sokka T. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther 2015; 15:1677-83; PMID:26549204; http://dx.doi.org/10.1517/14712598.2015.1103733
44. Sieczkowska J, Jarzebicka¸ D, Banaszkiewicz A, Plocek A, Gawronska A, Toporowska-Kowalska E, Oracz G, Meglicka M, Kierkus J. Switch-ing Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease. Preliminary Observations. J Crohns Colitis 2016; 10:127-32; PMID:26721942; http://dx.doi.org/ 10.1093/ecco-jcc/jjv233
45. ClinicalTrials.gov. The NOR-SWITCH Study. [Internet]. [cited 2016 Mar 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT02148640
46. Nederlands Trial Register. Trial info - The effect of switching treatment from innovator infliximab to infliximab biosimilar on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, spondyloarthritis or psoriatic arthritis in daily clinical care - BIOSWITCH study. [Internet]. [cited 2016 Mar 4]. Available from: http:// www.trialregister.nl/trialreg/admin/rctview.asp?TCD5279
47. Mysler E, Pineda C, Horiuchi T, Singh E, Mahgoub E, Coindreau J, Jacobs I. Clinical and regulatory perspectives on biosimilar therapies and intended copies of biologics in rheumatology. Rheumatol Int 2016; 36(5):613-25; PMID:26920148; http://dx.doi.org/10.1007/s00296-016-3444-0
48. World Health Organization. Programme on International Nonproprietary Names (INN)-2015, Biological qualifier: an INN proposal. [Internet]. [cited 2016 Oct 28]. Available from: http://www.who.int/medicines/services/inn/bq_innproposal201506.pdf.pdf