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Authors	O'Callaghan, Joan;Bermingham, Margaret;Leonard, Maurice;Hallinan, Frank;Morris, J. Michael;Moore, Una;Griffin, Brendan T.
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Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland

Joan O'Callaghan [a, b, c, *], Margaret Bermingham [b], Maurice Leonard [d], Frank Hallinan [a, b, e], J. Michael Morris [a], Una Moore [c], Brendan T. Griffin [a, b]

[a] Regulatory Science Ireland, c/o School of Pharmacy, University College Cork, Cork, Ireland
[b] School of Pharmacy, University College Cork, Cork, Ireland
[c] Health Product Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland
[d] AbbVie Limited, 14 Riverwalk, Citywest Business Campus, Dublin 24, Ireland
[e] Jazz Pharmaceuticals, 1 Burlington Road, Dublin 4, Ireland

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ABSTRACT

Increasing numbers of biosimilar medicines are becoming available. The objective of this survey was to assess awareness of and attitudes to biosimilars amongst physicians (medical specialists and General Practitioners (GPs)) and community pharmacists in Ireland. Physicians were invited to complete an online questionnaire during April and May 2016. Community pharmacists received a postal questionnaire in August 2015. Responses from 102 medical specialists, 253 GPs and 125 community pharmacists were analysed. The majority of medical specialists (85%) and pharmacists (77%) claimed to be either very familiar or familiar with the term biosimilar, whereas many GPs (60%) were unable to define or had never heard of the term. One in five (21%) healthcare professionals responded that biosimilars were the same as generic medicines. The majority of medical specialists opposed pharmacist-led substitution of biological medicines but some thought it could be appropriate if agreed with the clinician in advance. Medical specialists who prescribe biosimilars (n = 43) were more likely to do so on treatment initiation (67%), than switch a patient from an originator medicine to a biosimilar (28%). The findings will aid the design of educational initiatives for healthcare professionals and highlight attitudes of healthcare professionals to biosimilars, so informing regulators, policy makers and industry.

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1. Introduction

In 2006 the first biosimilar medicine Omnitrope® (containing somatropin) was approved for use in Europe. At the time of writing (June 2017), there were 28 biosimilars, containing 11 active substances (adalimumab, enoxaparin sodium, epoetin, etanercept, filgrastim, follitropin alfa, infliximab, insulin glargine, rituximab, somatropin and teriparatide), approved in Europe (EMA, 2017c). This number is expected to grow rapidly in the next few years. As of June 2017, there are 22 applications for biosimilars under evaluation at the European Medicines Agency (EMA) or awaiting final approval from the European Commission. Many of these products contain active substances not previously authorised as biosimilars (bevacizumab, insulin lispro, pegfilgrastim, and trastuzumab) (EMA, 2017a, b). In addition, it is estimated that 50 distinct biosimilars are in development (IMS Institute, 2016).

Abbreviations: BSG, British Society of Gastroenterology; EC, European Commission; EMA, European Medicines Agency; EPAR, European Public Assessment Report; Fimea, Finnish Medicines Agency; GP, General Practitioner; HPRA, Health Products Regulatory Authority; HSE, Health Service Executive; INN, International Nonproprietary Name; IPHA, Irish Pharmaceutical Healthcare Association; MEB, Medicines Evaluation Board; MMP, Medicines Management Programme; NMIC, National Medicines Information Centre; RCP, Royal College of Physicians; RSI, Regulatory Science Ireland; SmPC, Summary of Product Characteristics; UCC, University College Cork.

* Corresponding author. Health Product Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
E-mail addresses: joan.ocallaghan@hpra.ie (J. O'Callaghan), margaret.bermingham@ucc.ie (M. Bermingham), maurice.leonard@abbvie.com (M. Leonard), hallinaf@gmail.com (F. Hallinan), mike.morris@ext.hpra.ie (J.M. Morris), una.moore@hpra.ie (U. Moore), brendan.griffin@ucc.ie (B.T. Griffin).

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A biosimilar is a biological medicine that contains a version of the active substance of an already approved original biological medicine (known as the originator or reference medicine) (EMA, 2014). The heterogeneous nature, high molecular weight, batch-to-batch variability and complexity of many biological substances means that it is not possible for a different manufacturer to make an exact copy of the medicine, therefore, generics of biological medicines are not feasible. In the case of chemically synthesised medicines, approval as a generic is possible once an identical chemical structure for the active substance has been confirmed and bioequivalence to the reference product has been demonstrated (Schellekens et al., 2016). Owing to the inherent differences between biological and chemical substances, the abbreviated regulatory pathway used for generics is not suitable for copies of biological substances produced by different manufacturers. Therefore, biosimilar manufacturers are required to demonstrate, by way of a comprehensive comparability exercise, that the biosimilar is similar in quality, safety and efficacy to the reference medicine. Extensive characterisation and comparison of the physiochemical, structural and functional characteristics (e.g., molecular structure, receptor binding and biological activity) of the biosimilar and reference medicine is required. Comparative clinical trials are conducted in key indications where clinically relevant differences are most likely to be revealed. Therefore, a biosimilar may be licensed in therapeutic indications for which no specific clinical trials have been conducted. This is known as indication extrapolation and is only approved by regulators after comprehensive scientific justification, which includes consideration of the mechanism of action in each indication (Weise et al., 2014).

A tailored non-clinical and clinical testing programme means that biosimilars are likely to have reduced development costs in comparison to their reference medicines. A number of budget impact analyses have predicted significant cost savings from the introduction of biosimilar medicines into different healthcare systems (McCarthy et al., 2013; Brodszky et al., 2014; Jha et al., 2015). Subsequent reports, commissioned by the European Commission, have found that the introduction of biosimilar competition can result in lower market prices (IMS Health, 2016; IMS Health, 2017). Such savings, if re-directed appropriately, could be used to increase patient access to expensive biological treatments (Haustein et al., 2012; Gulacsi et al., 2015).

As biosimilars differ from generic medicines it is imperative that healthcare professionals involved in their use are informed of considerations relating to their prescribing practices, traceability and interchangeability (HPRA, 2015). Ongoing pharmacovigilance activities ensures that the safety of all biological medicines, including biosimilars, is monitored on an ongoing basis after approval. Spontaneous reporting of adverse reactions is an important component of pharmacovigilance, despite the fact that underreporting of adverse reactions is a major limitation of such systems (Gonzalez-Gonzalez et al., 2013). Biological medicines have specific pharmacovigilance considerations including immunogenicity, manufacturing variability and stability (EMA, 2016). In order to evaluate the potential impact of any suspected adverse reactions, EU pharmacovigilance legislation requires that brand name and batch number are provided in suspected adverse reaction reports related to biological medicines. As such, robust traceability systems are required to ensure these reports are attributed to the correct medicine. For this reason, physicians are encouraged to prescribe biological medicines by brand name (HPRA, 2015); and batch traceability of biological medicines in clinical use needs to be ensured (EMA, 2016).

In Europe the term 'interchangeability' is generally understood to mean a 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 (EC, 2013). Whilst EMA evaluations do not include recommendations on whether biosimilars can be used interchangeably with their reference medicines, several National Competent Authorities in Europe, including the Irish Health Products Regulatory Authority (HPRA), agree that physicians have the discretion to change their patient's medicine from the reference medicine to a biosimilar once their patient is informed (Fimea, 2015; HPRA, 2015; MEB, 2016). Indeed, there is increasing regulatory opinion that biosimilars in the EU are interchangeable with their reference medicines under prescriber supervision with the caveat that there is appropriate clinical monitoring, and patients have the necessary information about the medicine, including, if necessary, training on its administration (Kurki et al., 2017).

In September 2013, infliximab (marketed as Remsima®/Inflectra®) was approved as the first biosimilar monoclonal antibody (EMA, 2017c). Medical specialists in disciplines who had previously no experience with biosimilar medicines, such as gastroenterology, rheumatology and dermatology, now had a choice over which brand of infliximab they could prescribe to their patients. Surveys conducted around this time indicated that some medical specialists had misconceptions about biosimilars, or were not confident in their use (Danese et al., 2014; Dolinar and Reilly, 2014). A survey of pharmacists, conducted in France in 2015, found that many pharmacists claimed to be not familiar with biosimilars. Notable differences were observed in responses from community and hospital pharmacists, as community pharmacists were more likely to state that they were not at all informed about biosimilars (Beck et al., 2017). Now that biosimilars are becoming more widely available, there is a renewed need to assess the awareness of not only medical specialists but other allied healthcare professionals in relation to their prescribing, dispensing and traceability. Patients often look to healthcare professionals as sources of medicines information (O'Leary et al., 2015). Consequently, medical specialists, GPs and community pharmacists may need to advise their patients about biosimilars. The aforementioned issues are especially pertinent in light of increasing drive to encourage the use of biosimilars in clinical practice (BSG, 2016; MMP, 2016). Therefore we conducted a survey of medical specialists, GPs and community pharmacists in order to assess and compare their awareness of and attitudes to biosimilars.

2. Methods

Questionnaires were developed after reviewing previous surveys on stakeholder views relating to both biosimilar (Zelenetz et al., 2011; Dolinar and Reilly, 2014; Fernandez-Lopez et al., 2015; Grabowski et al., 2015; Hallersten et al., 2016) and generic medicines (O'Leary et al., 2015). Some questions were modified to suit the Irish context and all questions were worded in a neutral manner.

In August 2015, the market research group, Ipsos MRBI, sent a questionnaire to a nationwide community pharmacy sample. Pharmacists who did not respond to the questionnaire received one telephone reminder. A honorarium was provided to the pharmacist respondents.

Questionnaires for physicians (medical specialists and GPs) were designed after distribution of the pharmacist survey. Relevant items on the pharmacist questionnaire were included on the physician questionnaire and in certain cases the questions were developed further so not all questions were identical. Tailored questionnaires for medical specialists and GPs were reviewed and agreed by a panel of 12 experts with clinical, pharmacy, regulatory and academic backgrounds. Medical specialists who practice in areas where biological medicines are prescribed were targeted. The

following groups were invited to participate; dermatologists, endocrinologists, gastroenterologists, haematologists, nephrologists, neurologists, oncologists and rheumatologists. The links to the online questionnaires for medical specialists and GPs (hosted at www.surveymonkey.com) were distributed via email by their national professional societies during April and May 2016. Up to two reminder emails were sent in this time period. No honorarium was provided to the participating physicians.

The pharmacist questionnaire wording was reviewed by the expert panel and it was agreed results from common questions could be compared. The three questionnaires are available in the supplementary material provided. Comparisons between categorical variables were performed using Chi squared test. The research study was approved by the Social Research Ethics Committee (SREC) in University College Cork, Ireland.

3. Results

3.1. Sample characteristics

3.1.1. Pharmacists

A total of 143 responses were received from a panel of 200 community pharmacists (72% response rate). The market research company obtained consent from 125 respondents for their anonymised data to be published. Of this number, 90% practised in independent pharmacies, whereas 10% practised in pharmacy chains. The majority of pharmacists (96%) confirmed that they currently dispense biological medicines to patients in their pharmacy.

3.1.2. Physicians

Responses were received from 268 GPs and 109 medical specialists. The questionnaire for GPs was distributed by the Irish College of General Practitioners. A total of 2917 GP members were sent the email invite, corresponding to a response rate of 9%. The rate of non-participation was not recorded for the medical specialists as some of the societies were unable to provide exact details of physician numbers. Physicians who failed to provide full demographic details and complete the question indicating familiarity with the term biosimilar were eliminated from the analysis. Consequently, responses from 102 medical specialists and 253 GPs were analysed. Not all questions required responses and some respondents chose not to answer every question. The medical specialist respondents were more experienced than GP respondents with 93% having 10 years or more professional experience compared to 66% of GPs having similar experience. The majority of GPs (96%) confirmed that they treated patients who received biological medicines prescribed by a medical specialist. The demographics of the physician respondents are summarised in Table 1.

3.2. Familiarity with the term biosimilar

Survey respondents were asked how familiar they were with the term 'biosimilar' (Fig. 1). The responses differed across the three professions. In comparison to GPs, medical specialists and pharmacists claimed to be more familiar with the term.

Those respondents who answered very familiar or familiar to the question were grouped as 'familiar'. Those who could not define or had never heard of the term biosimilar were grouped as 'unfamiliar'. There was no difference between the rate of pharmacists and medical specialist in terms of reporting that they were 'familiar' with the term (75.2% vs. 85.3%, $p = ns$). However, there was a significant difference between pharmacists and GPs (75.2% vs. 40.3%, $p < 0.001$) and between medical specialists and GPs (85.3% vs. 40.3%, $p < 0.001$) in terms of the 'familiar response'.

3.3. Are biosimilars the same as generics?

To gauge actual awareness regarding their understanding of biosimilars, healthcare professionals were asked if they considered biosimilars to be the same as generic medicines. Of the healthcare professionals who responded ($n = 410$), one in five (21%) thought a biosimilar was the same as a generic medicine. There was no significant difference in the proportion of pharmacists, general practitioners and medical specialists who responded that biosimilars are the same as generic medicines (Fig. 2).

3.4. What's in a name?

Survey respondents were asked how they perceived two biological medicines (e.g. originator and biosimilar) with the same international nonproprietary name (INN) in relation to structure, approved indications and clinical efficacy (Fig. 3). Almost half (47%) of the total respondents incorrectly agreed that biological medicines sharing the same INN were 'structurally identical'. Analysis of the responses by profession revealed that pharmacists (50%) were most likely to agree with this statement whereas medical specialists (31%) were least likely. The majority of healthcare professionals (61%) agreed that two biological medicines with the same INN would be approved for the same therapeutic indications. GPs (75%) were most likely to agree and pharmacists (50%) were least likely to agree with this statement. In relation to clinical outcome, 43% of physicians agreed that two biological medicines with the same INN could be safely received by patients with the same clinical outcome, whilst 34% chose to neither agree nor disagree with this statement and 22% disagreed. In relation to switching between two biological medicines with the same INN, a significant proportion of physicians (42%) were neutral over whether patients could be safely switched and still achieve the same clinical outcome.

3.5. Pharmacovigilance

In order to evaluate pharmacovigilance recording practices, all healthcare professionals were asked how they prescribed, recorded or dispensed biological medicines. It was noted that 7% of medical specialists, 6% of GPs and 1% of pharmacists failed to provide a response to this question. Of those healthcare professionals ($n = 457$) that did respond, most used brand name and INN (36%) or brand name only (43%) to identify biological medicines. The remaining respondents indicated that they used INN only (7%) or responded that their practice in this regard varied by medicine (14%). Many who chose this option explained they would use either brand name or INN depending on their overall familiarity with the medicine. When asked about adverse reaction reporting, 45% of medical specialists ($n = 46$) and 12% of GPs ($n = 29$) indicated that they had previously reported a suspected adverse reaction for a biological medicine. This group of respondents were asked to clarify what type of information they had previously included in such reports. Most (82%) stated that they had included the brand name almost every time or every time. In contrast 57% indicated that they never or almost never included the batch number. In Ireland batch numbers for vaccines administered to patients are routinely recorded in GP surgeries (HSE, 2016). Therefore, in order to minimise bias, the response in relation to batch numbers excluded GPs who had only previously reported suspected adverse reactions for vaccines.

3.6. Prescriber behaviours

Medical specialists, who responded that they were aware of biosimilars in their specific therapeutic area ($n = 73$), were asked

Table 1
Physician sample characteristics (Medical Specialists and General Practitioners).

Characteristic	Medical Specialists [n (%)]	General Practitioners [n (%)]
Years registered as medical practitioner		
<5	0 (0%)	45 (18%)
5–9	7 (7%)	40 (16%)
10–14	20 (20%)	29 (11%)
15–19	25 (25%)	34 (13%)
20–29	35 (34%)	65 (26%)
>30	15 (15%)	40 (16%)
Position		
Hospital based consultant	85 (83%)	
Specialist registrar	10 (10%)	
Other non-consultant hospital doctor	6 (6%)	
Retired consultant	1 (1%)	N/A
Medical speciality		
Nephrology	23 (22%)	
Rheumatology	18 (17%)	
Gastroenterology	16 (16%)	
Endocrinology	10 (10%)	
Neurology	10 (10%)	
Dermatology	7 (7%)	
Haematology	7 (7%)	
Other[a]	3 (3%)	
Oncology	4 (4%)	
Haematology/Oncology	4 (4%)	N/A

[a] Pathology (n = 1), neurosurgery (n = 1), rehabilitation (n = 1).

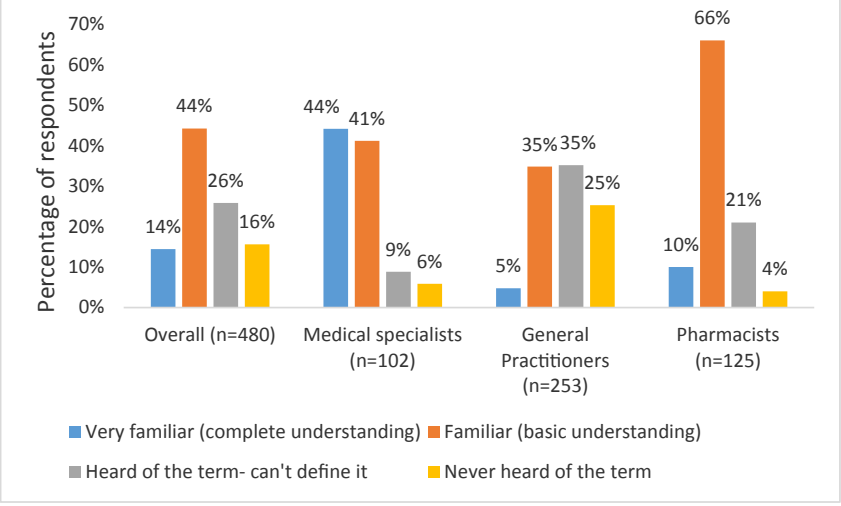


Fig. 1. Familiarity with the term biosimilar. *Survey question: "Which of the following best describes how familiar you are with the term biosimilar?"*

questions in relation to their prescribing behaviours. Amongst this group, 59% indicated that they prescribed biosimilars to patients in their practice, 40% did not and 1% did not know. Those medical specialists who prescribed biosimilars (n = 43) were asked about their prescribing patterns (Fig. 4). The majority (67%) responded that they would be most likely to prescribe a biosimilar on treatment initiation whereas, in the case of clinically stable patients, 28% would be likely to switch from an originator to a biosimilar medicine. Some medical specialists (19%) indicated that they would be likely to switch to a biosimilar if the patient had a poor clinical response to the originator medicine.

3.7. Attitudes to pharmacist led substitution

The questionnaire for medical specialists explored attitudes towards pharmacist-led substitution (Fig. 5). Substitution was defined for respondents as *'a pharmacist dispensing a biosimilar in place of an originator medicine (or vice versa) without consulting the prescriber'*. Very few medical specialists (<5%) believed substitution of a biological medicine by a pharmacist could be appropriate. The majority believed that decisions of this nature should be taken by the prescriber both on treatment initiation (49%) and during a patient's treatment course (61%). However, a significant proportion responded that substitution could be appropriate if agreed with the clinician in advance.

If substitution by a pharmacist did take place, notification of this substitution was considered to be very important or critical by medical specialists both on treatment initiation (84%) and during a patient's treatment course (90%). Pharmacists (n = 125) were asked if substitution of biological medicines was currently permitted in Ireland. Most pharmacists (59%) answered correctly that it was not, some pharmacists (30%) responded that they did not know and 10% believed it was permitted. Pharmacists were then asked how comfortable they would be with substituting a biological medicine

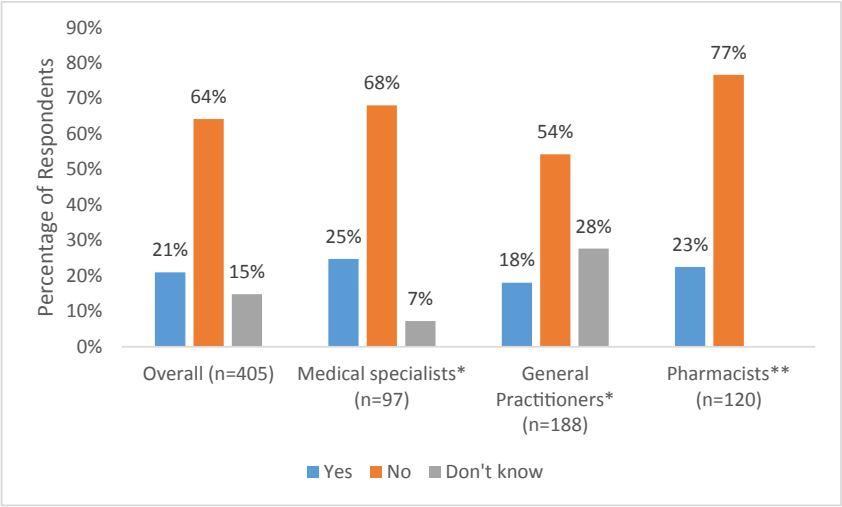


Fig. 2. Understanding of the term biosimilar. *Survey question: Would you consider biosimilars to be the same as generic medicines? The analysis excludes healthcare professionals who previously indicated that they never heard of the term biosimilar.*
**Physicians were offered three options (yes, no and don't know).*
***Pharmacists were only offered two options (yes and no). 1% of pharmacists did not respond.*

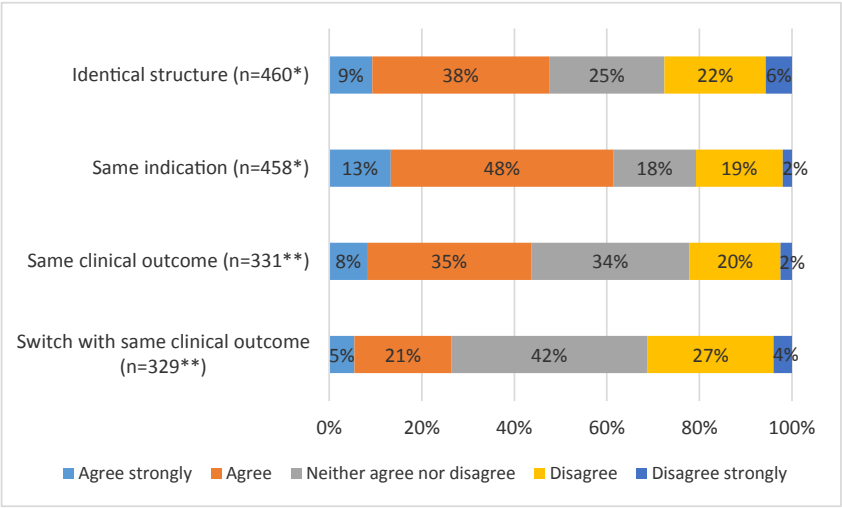


Fig. 3. Perceptions of biological medicines with the same INN. *Survey question: If two biological medicines (e.g. originator and biosimilar) have the same INN do you think this means that: i) the medicines are structurally identical, ii) the medicines are approved for the same indications, iii) patients can safely receive either medicine with the same clinical outcome and iv) patients can be safely switched during treatment with the same clinical outcome.*
**Questions asked to medical specialists, GPs and pharmacists.*
***Questions asked to medical specialists and GPs only.*

in a situation where substitution was permitted. Of the pharmacist respondents, 14% indicated they would be comfortable changing a biologic prescribed by a consultant to a biosimilar. However, the majority of pharmacists (58%) indicated that they would only be comfortable changing a patient's medicine from an originator to a biosimilar with the agreement of the prescriber. A proportion of pharmacists (27%) responded that they were not comfortable with substitution.

3.8. Prescriber concerns

In order to explore perceived concerns on the use of biosimilar medicines, medical specialists were asked to rate their level of concern, relating to six commonly debated topics around biosimilars (Table 2). Medical specialists indicated that they had concerns (ranging from slight to extreme) in relation to: traceability (62%), quality (73%), safety profile (78%), efficacy profile (79%), immunogenicity (81%), and efficacy in extrapolated indications (84%).

3.9. Sourcing medical information

All healthcare professionals (n = 473) were asked how frequently they used certain resources to learn about the details of biological medicines for prescribing, dispensing or monitoring. Frequent use of information resources was assumed when medical specialists and GPs indicated that they used the resource 'a moderate amount' or 'a great deal' on a 5 point Likert scale. Medical specialists (n = 101) reported frequent use of guidelines from professional societies (72%), published literature (68%) and

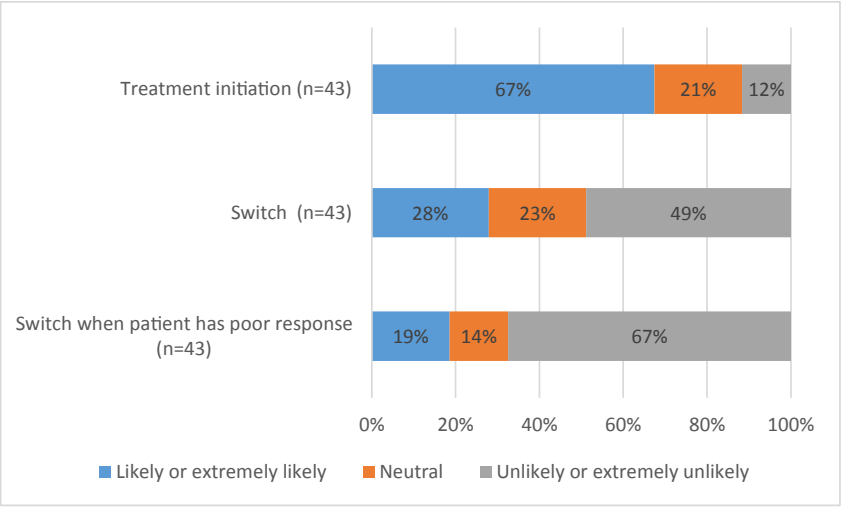


Fig. 4. Prescribing patterns of medical specialists who prescribe biosimilars. *Survey question: If both an originator medicine and a biosimilar were available to you for prescribing how likely would it be that you would carry out the following: (i) prescribe a biosimilar to a patient on treatment initiation, (ii) switch from an originator medicine to a biosimilar when a patient is clinically stable and (iii) switch to a biosimilar when a patient has had a poor clinical response to the originator medicine.*

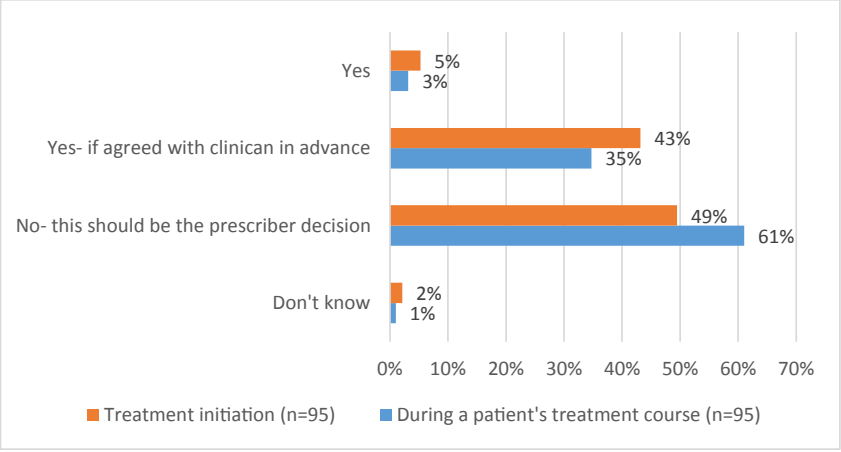


Fig. 5. Attitudes to pharmacist-led substitution held by medical specialists. *Survey question: Do you think substitution of a biological medicine by a pharmacist could be appropriate (i) on treatment initiation and (ii) during a patient's treatment course.*

Table 2
Concerns relating to biosimilars amongst medical specialists (n = 93). *Survey question: In comparison to originator medicines do you have any concerns specifically about biosimilars in each of the following areas?.*

	Not at all concerned	Slightly concerned	Somewhat concerned	Moderately concerned	Extremely concerned	Don't know
Traceability	32%	19%	17%	16%	9%	6%
Quality	24%	24%	15%	24%	11%	3%
Safety profile	20%	31%	15%	22%	10%	2%
Efficacy profile	19%	22%	18%	26%	13%	2%
Immunogenicity	17%	30%	12%	22%	16%	2%
Efficacy in extrapolated indications	9%	23%	22%	22%	19%	6%

educational events (63%). Of the total GP respondents (n = 247) a significant proportion (58%) frequently relied on national or hospital formularies (such as the British National Formulary). A full comparison between pharmacists and physicians cannot be made as the pharmacist questionnaire listed less learning resource options and a different 3 point Likert scale was used. Despite these differences, it was apparent that pharmacists (n = 125) were more likely than other professions to use medical information from the manufacturer/marketing authorisation holder, with 44% of pharmacists reporting that they 'always' used medical information from the manufacturer to learn about details of biological medicines. In contrast, only 13% of medical specialists and 7% of GPs responded that they used this information source frequently. The European Public Assessment Report (EPAR) was the least consulted resource of all the options provided. Most medical specialists (85%) and GPs (94%) indicated that they rarely or never used this resource. A similar pattern was observed for pharmacists with most (90%) indicating that they never consulted the EPAR. However, all

professions reported comparable use of the Summary of Product Characteristics (SmPC) as a learning resource with 52% of medical specialists and 43% of GPs claiming frequent use, whilst 50% of pharmacists indicated that they 'always' used this resource.

4. Discussion

There are 28 biosimilars currently licensed for use in Europe (EMA, 2017c). Impending patent expiry dates of many top selling biological medicines (IMS Institute, 2016) means that more biosimilars are becoming available, offering healthcare professionals wider choices in the brands of biological medicine they choose to treat their patients. Consequently, healthcare professionals need to make informed treatment choices for their patients. A postal survey of community pharmacists was conducted in August 2015. An online survey of medical specialists and GPs was then conducted during April and May 2016. Surveys were carried out in Ireland with the common aim of assessing awareness of and attitudes to biosimilars. The professions were chosen as all are directly involved in the care of patients receiving biological medicines. To the best of our knowledge this is the first published report in which findings from a survey in relation to biosimilars has been presented for 3 healthcare professional groups across primary and secondary care.

In order to explore levels of awareness across the different professions, survey respondents were asked to indicate how familiar they were with the term 'biosimilar'. Many medical specialists claimed to be very familiar with a complete understanding (44%), or familiar with a basic understanding (41%). The same question was asked in a survey of European medical specialists in 2013 and in this instance 22% claimed to have a complete understanding and 54% claimed a basic understanding of the term (Dolinar and Reilly, 2014). Although the results are not directly comparable due to the different sample composition our findings suggest that perceived familiarity with the term 'biosimilar' has increased amongst medical specialists since this time. Indeed, a recent survey of Inflammatory Bowel Disease experts suggests that since 2013 there are fewer concerns about and more confidence in the use of biosimilars in clinical practice (Danese et al., 2016). Although familiarity amongst medical specialists is high, we found that this level of familiarity was not consistent across the 3 professions. Responses from GPs indicated that this group were least familiar with the term, with one in four GPs responding that they had never heard of the term 'biosimilar'. This lack of familiarity may be attributed to the fact that GPs are not directly involved in the prescribing of biological medicines. However, GPs are certainly involved in the treatment of patients receiving biological medicines therefore it is important that GPs are informed about biosimilars. The level of actual understanding amongst some healthcare professionals may also be questionable. The differences between generic and biosimilar medicines is widely communicated in the published literature (Weise et al., 2012; de Mora, 2015). Despite this we found that one in five healthcare professionals who had previously heard of the term 'biosimilar' responded that biosimilars were the same as generic medicines.

In Europe, biosimilars have the same international non-proprietary name (INN) as their reference medicines. Respondents were asked if they agreed with various statements relating to two biological medicines (e.g. originator and biosimilar) with the same INN. The responses revealed some misconceptions. For instance, 47% of all healthcare professional respondents mistakenly agreed that two biological medicines with the same INN would have an identical structure. In relation to clinical outcome, a notable proportion of the physician respondents were either neutral (34%) or disagreed (22%) with the statement that patients could safely receive either an originator or biosimilar medicine with the same INN and still expect the same clinical outcome. Biosimilars are approved on the basis that they have demonstrated comparable efficacy and safety to their reference medicine (EMA, 2014); the high level of neutral answers and disagreement with the statement suggests that this fundamental regulatory principle could be better communicated to healthcare professionals.

The survey findings indicate that the majority of healthcare professionals (79%) practise in line with recommendations by using brand name to identify biological medicines for prescribing, recording or dispensing; however, traceability by batch number appears low. Of the 67 physicians who had previously reported a suspected adverse reaction for a biological medicine (excluding vaccines) many (57%) responded that they had never or rarely included the batch number. This finding echoes conclusions drawn from analyses of EU and national spontaneous reporting systems which indicated traceability to batch level for biological medicines is poor (Vermeer et al., 2013; Klein et al., 2015). Reporting of batch numbers enables links to be established between manufacturing process changes and rare adverse reactions. Ensuring the traceability of batch numbers in clinical practice is not without its challenges (Vermeer et al., 2015). However, education of healthcare professionals around the specific pharmacovigilance considerations applicable to biological medicines, may improve batch number traceability in adverse reaction reports and contribute to ongoing post-marketing surveillance.

In Ireland it is currently recommended that the treating physician is involved in any decisions to change the medicine a patient receives from its reference to a biosimilar medicine or *vice versa* (HPRA, 2015). Changing of a patient's treatment in this manner is often referred to as 'switching' (EC, 2013). When asked about switching many physicians (42%) had no definite opinion on whether biosimilars could be used interchangeably with their originator medicines. Of the 43 medical specialists who currently prescribe biosimilar medicines, more would be likely to prescribe the biosimilar on treatment initiation (67%) than would be likely to switch a patient to a biosimilar after treatment had been initiated with the originator (28%). The differences in responses could reflect the fact that in Ireland there is currently no national guidance in relation to switching. In contrast, some medical societies in the UK have begun to encourage this practice on economic grounds (BSG, 2016; RCP, 2016). One UK hospital has recently highlighted their switching programme which involved consultations with patients, robust traceability systems as well as appropriate clinical monitoring and surveillance (Underhill, 2016). If biosimilar uptake is to be encouraged in Ireland further guidance in relation to switching and how best to manage this practice may be needed. Notably 19% of medical specialists who currently prescribe biosimilars indicated that they would be likely to switch to a biosimilar when a patient's response to the reference medicine was inadequate. Although the sample size is small, this response highlights the need to inform prescribers that biosimilars are equivalent treatments to their reference medicines offering comparable patient outcomes.

A number of countries in Europe, including Ireland, have policies in place to prevent pharmacist-led substitution of biological medicines (Thimmaraju et al., 2015). The results of our survey reflect the national policy with <5% of medical specialists indicating that substitution of a biological medicine by a pharmacist could be appropriate. Interestingly, a notable proportion of medical specialists were supportive of pharmacist led substitution both on treatment initiation (43%) and during a patient's treatment course (35%) if it was agreed with the clinician in advance; though the questionnaire did not probe what level of agreement would be necessary. The majority of medical specialists did, however, believe that decisions of this nature should be prescriber led, which may also reflect some of the challenges associated with the substitution

of biological medicines at pharmacy level (Weise et al., 2012). An additional challenge includes pharmacist attitudes, as this group are ultimately responsible for the implementation of substitution policies at pharmacy level. Only 14% of pharmacist respondents stated they were comfortable with substitution (without prescriber agreement) which echoes findings from previous research indicating pharmacists may have reservations about assuming such responsibilities (Beck et al., 2017).

The EMA has over ten years' experience in the regulation of biosimilars which has led to the approval of 28 safe and effective biosimilar medicines in Europe. Despite this fact there is continued discussion in the published literature suggesting that there are concerns amongst healthcare professionals around the use of biosimilars (Mellstedt et al., 2008; Schimizzi, 2016). Such concerns are likely to be compounded by lack of familiarity with the concept of biosimilarity (Grabowski et al., 2015; Beck et al., 2016, 2017). When asked about such perceived concerns, most medical specialists indicated some level of concern for each of the following commonly debated issues: efficacy in extrapolated indications, traceability, quality, safety profile, efficacy profile and immunogenicity. This is despite the fact that these commonly cited 'concerns' have been addressed and clarified at a regulatory level (Weise et al., 2012, 2014). Although the questionnaire did not probe the specific reasons for each concern, clearly there is a need to address such issues in ongoing educational initiatives on biosimilars. A recent example of such an initiative includes an information guide on biosimilars for healthcare professionals which has been jointly produced by the EMA and European Commission (EMA and EC, 2017).

In order to establish how best to target educational initiatives survey respondents were asked how frequently they used various information sources to learn about the details of biological medicines for prescribing and monitoring. A sizable proportion of those surveyed claimed frequent use of the SmPC which is similar to findings from a recent survey of European medical specialists (Hallersten et al., 2016). In Europe clinical information contained in the SmPC of a biosimilar is generally identical to information contained in the SmPC of the reference medicine; a single statement is included in the prescribing information to indicate that a biological medicine is approved as a biosimilar. In contrast to the SmPC, the EPAR provides more comprehensive information on the evidence submitted to support approval of a biosimilar. The EPAR for a biosimilar medicine is available on the EMA website. The findings of the present study suggest this resource is rarely used by healthcare professionals in Ireland, suggesting that the EPAR which outlines the totality of evidence approach on which the biosimilar philosophy is based, is either not well known or not accessible to healthcare professionals. The survey findings suggest that targeted communication to medical specialists via professional societies, published literature and educational events could help to reduce the information gap on biosimilar medicines. The most appropriate communication channels for GPs and community pharmacists are less clear, but liaison with representative societies may facilitate knowledge transfer to these professions.

The potential for biosimilars to reduce drug expenditure and increase patient access to high cost medicines is recognised by the Irish Health Service Executive - Medicines Management Programme (MMP, 2016). However, the current lack of formal guidance, policies or incentives encouraging the prescribing of biosimilars is likely a factor in Ireland's low uptake of these products (IMS Health, 2016; IMS Health, 2017). It might be expected, that healthcare professional attitudes towards biosimilars would echo their attitudes towards generic medicines. In Ireland, attitudes towards generic medicines have evolved over time. A 1997 survey of Irish GPs found that many were concerned about the quality and reliability of generic medicines (Feely et al., 1997). Pharmacists too, were reported to have concerns about the reliability of generic medicines owing to concerns over bioavailability, quality and patient complaints (Murphy, 1997). Escalating healthcare costs and low generic uptake (Brink et al., 2013) resulted in the introduction of generic substitution and reference pricing in Ireland in 2013. Surveys conducted at this time indicated that attitudes towards generics had changed considerably, with general positive opinions on generics being reported by GPs and pharmacists (Dunne et al., 2014; O'Leary et al., 2015). Stakeholder attitudes are constantly evolving, so it is likely that a combination of policy developments, national guidance on the use of biosimilars and educational initiatives will all contribute to improving healthcare professional perceptions of biosimilars.

The study has some limitations including the fact that the findings cannot be extrapolated to healthcare professionals in countries with high biosimilar uptake or where policies and incentives relating to the prescribing of biosimilars are in place. Owing to the differing response rates, it was not possible for each medical discipline to be equally represented in the sample of medical specialists. Selection biases could also be present as healthcare professionals that are less familiar with biosimilar medicines, may have been less willing to participate in the survey. There are also some minor methodological differences in the collection of survey responses between the pharmacist and physician studies. The provision of a honorarium to pharmacists, and not physicians, and the different methods employed for survey distribution (postal for pharmacists and online for physicians) may have induced participation biases. There was a 9 month time delay in distribution dates of the pharmacist questionnaire (August 2015) and physician questionnaires (April/May 2016). Although, healthcare professional's knowledge and experience may have evolved during this time, the delay is unlikely to have a significant impact in the context of an Irish survey as rates of biosimilar usage in Ireland remain low and did not differ significantly between 2015 and 2016 (IMS Health, 2016; IMS Health, 2017). It should also be acknowledged that hospital pharmacists were not represented in the study. Previous surveys have suggested that hospital pharmacists have an increased awareness of the biosimilar concept (Beck et al., 2017).

While the majority of questions were common to all survey groups, some questions were tailored for either the pharmacist or physician groups. Consequently, only findings from common questions are compared. Community pharmacists, unlike physicians, were not provided with a 'don't know option' when asked 'Would you consider biosimilars to be the same as generic medicines' (Fig. 2). However, it is unlikely that the provision of this extra option to pharmacists would have altered the finding that 1 in 5 healthcare professionals responded that biosimilars were the same as generics. In the case of physicians, survey items were further developed so more in depth information could be assessed. Unlike physicians, pharmacists were not asked if they agreed with statements pertaining to clinical outcome for two biological medicines with the same INN (Fig. 3). Pharmacists were also provided with less learning resource options and a different Likert scale in the question that addressed the sourcing of medical information (section 3.9). The physician questionnaires were tailored for either medical specialists or GPs. Only questions that were directly relevant to GP practice were included on the GP questionnaire, therefore questions relating to prescribing practices and attitudes towards substitution of biological medicines were excluded.

In conclusion this survey was the first study that compared awareness and attitudes to biosimilar medicines amongst medical specialists, GPs and community pharmacists based in Ireland. We found that familiarity with the term biosimilar varied between the three professions, with the highest level of familiarity among medical specialists, followed by community pharmacists and then

GP's. However, 21% of those surveyed responded that a biosimilar was the same as a generic medicine, which could suggest a lack of awareness among some respondents on the differences between generic and biosimilar medicines. Medical specialists who currently prescribe biosimilars were more likely to do so on treatment initiation than switch from an originator to a biosimilar during a patient's treatment course. The majority of medical specialists (>95%) were not supportive of pharmacist-led substitution indicating that they believe decisions to change a patients medicine should be either prescriber led or agreed with the prescriber in advance. The extent of concerns held by medical specialists in relation to biosimilars were highlighted, despite the fact that to date the biosimilars licensed in the EU have proven to be as safe and efficacious as their reference medicines. The development of policy and national treatment guidance on the use of biosimilar medicines may ensure that Ireland benefits directly from their increasing availability. Healthcare professionals may also benefit from targeted educational initiatives to reduce the information gap on biosimilar medicines.

Conflict of interest

Joan O'Callaghan, Margaret Bermingham, J. Michael Morris, Una Moore and Brendan T. Griffin declare that they have no conflict of interest.

Maurice Leonard is an employee of AbbVie and may hold shares in AbbVie. Frank Hallinan is an employee of Jazz Pharmaceuticals.

This paper represents solely the views of the authors and should not be understood or quoted as being made on behalf of or reflecting the position of the Health Products Regulatory Authority, Regulatory Science Ireland, AbbVie Limited or Jazz Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2017.06.013.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2017.06.013.

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