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Pharmacy-mediated substitution of biosimilars – a global survey benchmarking country substitution policies

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Introduction/Study objectives: Between March and May 2017, Pfizer conducted an internal global survey of 82 countries examining biosimilar pharmacy-mediated substitution to understand and benchmark the global policy landscape.

Methods: Pfizer regulatory and corporate affairs colleagues completed a survey:

- Are pharmacists in your country able to substitute a biological with a biosimilar without the physician being involved? Yes, no or situation unclear.
- If pharmacists are able to substitute biologicals with biosimilars, are there any restrictions or conditions?
- Can you provide any additional information on biosimilar substitution policies in your country?

Results: The key finding was in 72% of countries surveyed, substitution of biosimilars at the pharmacy level does not occur, either because it is not permitted or for other reasons. In countries where pharmacy-mediated substitution is permitted, there are often restrictions in place.

Discussion: In Europe, North America and Asia-Pacific, many countries have developed specific policies on pharmacy-mediated substitution relating to biosimilars. Whereas, in Latin America, Africa and the Middle East, there are largely no policies on this matter; the focus appears to remain on the development of general biosimilar regulations and guidances.

Conclusion: Due to the complexity of biologicals, it is our opinion that pharmacy-mediated substitution is not appropriate unless stringent regulatory and legal criteria additional to appropriate biosimilarity requirements can be met, as outlined in the International Federation of Pharmaceutical Manufacturers & Associations' (IFPMA) position paper on pharmacy-mediated substitution. In countries where no additional scientific standard exists for biosimilar substitution, the physician should remain involved in decisions regarding patient treatment.

Keywords: Biosimilars, global, interchangeability, pharmacy, regulation, substitution

Introduction/Study objectives

Biosimilars have the potential to improve access to biologicals by expanding treatment options and offer cost savings to payers through increased competition. They are highly similar but never exact copies of their reference biotherapeutic product (innovator biological) and so should not be viewed in an equivalent fashion as small molecule generics. All biosimilars must demonstrate a high similarity to their reference biotherapeutic product in terms of quality, non-clinical and clinical attributes. However, biosimilars may not always hold all of the same indications as their reference biotherapeutic product either because extrapolation to every indication was not granted based on data considerations or because there are legal or intellectual property reasons why a particular indication may not be granted. This is relevant for pharmacy-mediated substitution where the pharmacist may not have knowledge of a patient's individual health condition and may not be aware that a biosimilar they substitute could potentially be licensed for fewer indications. They may also not always be aware of the indication intended if the prescription does not specify this and prescription practices vary around the world.

Robust regulatory pathways for biosimilars exist in many developed markets underpinned by strong guidance such as the overarching World Health Organization (WHO) guidelines for similar biotherapeutic products [1] and the application of these guidelines ensures the approval of high quality products. However, in some countries surveyed there is also the licensure of non-comparable biotherapeutics. These are biotherapeutic medicinal products that seek to 'copy' another biological product but that have not been approved via a regulatory pathway that is aligned with the WHO similar biotherapeutic product guidelines or directly compared and analysed against an already licensed reference biotherapeutic product [2]. These products are often misattributed as 'biosimilars' or 'similar biotherapeutic products' even though they do not meet WHO scientific and regulatory requirements and will routinely share the same International Nonproprietary Name (INN) as both the original reference product and any biosimilars.

Given the complex global regulatory landscape, there is active global debate on appropriate science driven substitution policy for these products. Substitution describes the practice where a pharmacist elects to change a product, dispensing an equivalent (generic small molecule) or highly similar (biosimilar) product without the prescribing physician's prior consent. This is distinct from switching which describes a decision made by a physician to change a patient's treatment – to another course of therapy, between reference product and a biosimilar, or potentially between biosimilar products. Previous publications have addressed the status of pharmacy-mediated substitution of biosimilars in Europe [3]; however, to the best of the authors'

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knowledge, there is little literature examining pharmacy-mediated substitution of biosimilars on a global basis.

To begin to address this gap, Pfizer conducted an internal global survey between March and May 2017. The primary aim of the survey was to capture and benchmark whether or not pharmacy-mediated substitution of biosimilars could occur and under what policy or legislative frameworks this was regulated in different countries and regions globally. The survey did not seek to capture data or policies relating to physician-directed switching as these decisions are part of usual medical practice and are independent of, and not in any way related to substitution. Where possible, gaps in responses were also supplemented with information from previously available research (both published and unpublished). The aim of the survey was to provide an initial snapshot analysis of pharmacy-level biosimilar substitution throughout Europe, Asia-Pacific, Latin America, Africa and the Middle East and North America. We have been able to present the positions held by 82 countries worldwide. The findings presented in this paper provide the first attempt to benchmark global pharmacy-mediated substitution policies. However, we recognize that this is a rapidly evolving policy area and there will continue to be changes in these countries which may have occurred after this survey was conducted.

Methods

Survey design and dissemination

To benchmark the status of pharmacy-mediated substitution of biosimilars on a global scale, we undertook an internal survey of Pfizer regulatory and corporate affairs colleagues around the world. A questionnaire was sent on 2 March 2017 to internal Pfizer distribution lists of 545 Pfizer colleagues which included regulatory colleagues responsible for Europe, Asia-Pacific, Latin America, Africa and the Middle East and North America.

The questionnaire asked three questions:

1. Are pharmacists in your country able to substitute a biological with a biosimilar without the physician being involved?
   Yes, no or situation unclear
2. If pharmacists are able to substitute biologicals with biosimilars, are there any restrictions or conditions?
3. Can you provide any additional information on biosimilar substitution policies in your country?
   For example, are there any rules/guidances written down? Any other information you have on substitution policies

Survey responses were collected between 2 March 2017 and 31 May 2017. Partial survey responses were not accepted and clarification sought if answers were unclear or contradictory. Responses were received from both in-country and above-country Pfizer colleagues and reflected their understanding of individual country substitution policies and practices to the best of their knowledge. Where a response was not received for a country, where possible, information available through previous internal unpublished research and the second EBE (European Biopharmaceutical Enterprises) Biological Medicines Policy Survey [4] was included, enabling categorization of 82 countries in total, see Appendix 1.

Categorization

Depending on the response received for each of the three questions, each country was then categorized as either 'no substitution', 'restricted substitution', 'unrestricted substitution' or 'unclear'. The process of categorization is detailed in Table 1. Countries were then grouped into the following five geographical regions (Europe, Asia-Pacific, Latin America, Africa and the Middle East, and North America) to report the results.

Table 1: How each country was categorized depending on the combined responses to Questions 1 and 2 from Pfizer country colleagues

Response to Question 1	Response to Question 2	Category assigned
No	N/A	No substitution
Yes	Yes	Restricted substitution
Yes	No	Unrestricted substitution
Unclear	N/A	Unclear

N/A: Not applicable.

Limitations

The authors note that there are limitations to this study:

1. The data presented in this paper refers to the environment at the point in time when the survey was carried out (March–May 2017); the positions held by the regulators and payers in individual countries may have subsequently changed.
2. In addition, there is a gap in the literature examining pharmacy-mediated substitution on a global scale. It is therefore difficult for us to discuss our results in relation to previous research.
3. Many responses were received where Pfizer colleagues answered 'no' to the first question in the questionnaire, however no additional information on regulations or guidances prohibiting pharmacy-mediated substitution was provided. Often this was because regulations or guidances on this topic are not currently in place; we are therefore unable to conclusively state why pharmacy-mediated substitution of biosimilars is not occurring in these countries.
4. The survey sought to examine the country regulations rather than what happens in practice, which may be different; for example, there may be significant INN prescribing taking place. Where we obtained anecdotal comments regarding what happens in practice, these were included in the project findings, where appropriate; however, this was not the focus of this survey.
5. The environment surrounding biosimilar substitution policies is dynamic and individual country healthcare systems vary greatly. It is therefore sometimes difficult to standardize when looking across countries.
6. All of the findings presented in the paper, except for those countries where data from the second EBE Biological Medicines Policy Survey was used, are based on the insights provided by Pfizer colleagues and not country regulatory authorities, payers or healthcare professionals.

Despite the limitations, we believe that the data collected goes some way into addressing the knowledge gap regarding global pharmacy-mediated substitution of biosimilars and providing a baseline to track trends against going forward.

Results

Between 2 March and 31 May 2017, 43 responses were received containing information for 68 countries, see Appendix 1. A further

14 countries were then categorized using data available through internal unpublished research (six countries) and the second EBE Biological Medicines Policy Survey (eight countries) [4]. This gave a total of 82 countries where information on pharmacy-mediated substitution was available. Countries were then grouped into five regions (Europe, Asia-Pacific, Latin America, Africa and the Middle East, and North America) based on geographical location to report the results, see Figure 1A.

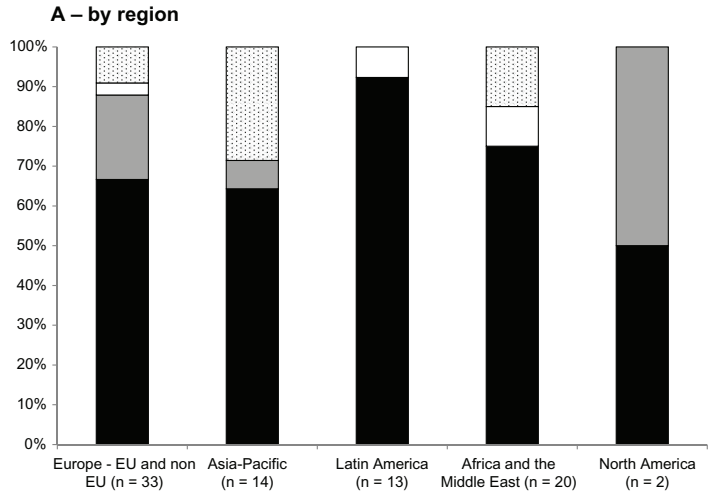
The primary aim of the survey was to capture and benchmark whether or not pharmacy-mediated substitution of biosimilars could occur and under what policy or legislative frameworks this was regulated in different countries and regions globally. In some regions such as Latin America and Africa and the Middle East, most countries reported in the survey that substitution cannot take place, see Figure 1A. Such categorical statements may seem at first sight to be counter-intuitive when there is also an absence of guidance or legislation prohibiting substitution. However, in such cases we speculate that the responses are based on an understanding of usual local pharmacy practice and this is discussed later in the paper.

We found that respondents reported that substitution of biosimilars at the pharmacy level cannot occur in 59 of the 82 (72%) countries, either because it is not permitted or for other reasons. Restricted pharmacy-mediated substitution of biosimilars was reported in only nine of the countries surveyed (11%) whilst unrestricted substitution reported in just four (5%), see Figure 1B.

As noted in the methods, some respondents flagged that in countries where substitution was not technically allowed under existing guidelines or legislation if prescriptions were written by INN (generic name) by the physician it would be impossible for the pharmacist to guarantee they were supplying the correct biological product. In addition, certain countries surveyed purchase these classes of products by bulk tender. In these countries, when the purchased product changes within the healthcare system the pharmacist would only be able to dispense the available product. While both these scenarios are not pharmacy-mediated substitution as per our description, and so are not captured within the formal results of this survey, they reflect the complex environment governing biosimilars usage in practice within these countries, even in the presence of guidelines or legislation.

We believe that the information collected through colleagues' responses to the internal Pfizer survey and the additional information gathered through previous unpublished and published research has enabled us to cover a sufficient number of countries to provide an initial benchmark of global pharmacy-mediated substitution policies. The individual results for the 82 countries are presented within the five regions below.

Figure 1: Proportion of countries, (A) by region; (B) globally, allowing pharmacy-mediated substitution of biosimilars (n = 82)



Europe (EU and non-EU)

The countries in this section include the members of the European Union (EU) and neighbouring non-member countries. Regulations governing pharmacy-mediated substitution of biosimilars are not centralized across EU Member States; therefore, individual countries can adopt their own position [1]. Data were collected for 33 countries in the region, which can be seen categorized in Table 2.

The survey found that pharmacy-mediated substitution of biosimilars cannot occur in the majority of countries in the region (67%), see Figure 1A. Many of these countries have introduced laws or guidances to prevent substitution of innovator biologicals with biosimilars. For example, in Ireland, the Health (Pricing and Supply of Medical Goods) Bill 2012 prohibits pharmacy-mediated substitution of all biologicals, including biosimilars [5]. Similarly in Spain, Orden SCO/2874/2007 states that biologicals may not be substituted by pharmacists [6]. Italy's lower house of parliament passed the 2017 Budget Law, prohibiting biosimilars from being substituted at the pharmacy level [7]. In the UK, National Institute for Health and Care Excellence (NICE) has issued Advice on Biosimilar Medicines stating that all biologicals, including biosimilar medicines, are prescribed by brand name meaning that products cannot be substituted at the pharmacy level [8].

There are several countries in Europe where pharmacy-mediated substitution of biosimilars can occur, see Table 2. However, there are restrictions in place in all of these countries except Turkey. In France, the

Table 2: Pharmacy-mediated substitution of biosimilars in European countries

No substitution		Restricted substitution	Unrestricted substitution	Unclear
Austria Belgium Bulgaria Czech Republic Denmark Germany Greece Hungary Ireland Italy Lithuania	Luxembourg Malta Norway Portugal Romania Slovakia Spain Sweden Switzerland Netherlands UK	Belarus Estonia Finland France Latvia Poland Serbia	Turkey*	Russia Slovenia Ukraine

*See body text of this paper for explanation.

Article L5125-23-3 of the French law (*Code de la santé publique*) states that a pharmacist can substitute the prescribed biological medicinal product with a biosimilar if certain conditions are met [9]. One such condition is that substitution must be carried out at the initiation of treatment. In addition, the prescribing physician must not have excluded the possibility of substitution (the physician is able to handwrite 'non-substitutable' on the prescription). We note however, that substitution does not yet occur in practice in France as at the time of going to press, the mechanisms required to allow substitution are not in place. In Poland also pharmacy-mediated substitution can occur, according to the results of the survey, so long as the prescribing physician has not indicated otherwise using an opt-out provision. Interestingly, Finland, which has a two-channel distribution system, allows substitution by hospital pharmacies, but forbids substitution of biological products by retail pharmacies, an example of a place-based restriction for substituting these products.

The only country surveyed where unrestricted pharmacy-mediated substitution of biosimilars was reported to occur is Turkey. In the absence of any specific biosimilar legislation on substitution, generics substitution legislation developed in the 1980s is being applied. The Budget Guidance, issued on 2 January 1985 and numbered 18623 in the official gazette, allows generics substitution at the pharmacy level. The Budget Guidance states that if products are equivalent to each other, they can be substituted at the pharmacy level. However, our survey respondent indicated that pharmacists normally follow the physician's prescription, so although possible under the existing legislation, unrestricted substitution may not be occurring at high levels in practice.

Russia was categorized as unclear because here biosimilars are treated like generics, being subject to the same interchangeability definition. An interchangeable product is considered one with proven therapeutic equivalence or bioequivalence against the reference drug with equivalent qualitative composition and quantitative composition of active substances, the excipients, dosage form and route of administration [10]. As of July 2017, the reference drugs for the biosimilars have not been designated by the regulatory authority. Until these have been designated, pharmacy-mediated substitution cannot technically occur, however, there is currently a lack of clarity which could be resolved by the development of specific biosimilar guidance, including guidance addressing biosimilar substitution.

Asia-Pacific

Data was collected for 14 countries in the Asia-Pacific region, which can be seen categorized in Table 3.

The survey found that pharmacy-mediated substitution of biosimilars cannot occur in nine of the 14 countries (64%), see Figure 1A; these include Hong Kong, Japan, Korea and Malaysia. As with Europe, several countries in the region have issued guidelines to discourage substitution of biosimilars at the pharmacy level. Hong Kong's Guidance notes for registration of biosimilar products [11] states that *'the Department of Health does not endorse the substitution of reference product with biosimilar product'*. This is therefore applicable to substitution at the pharmacy level. Furthermore, according to the Hong Kong ASP (community pharmacist) Code of Practice, where a prescriber specifies a particular branded product on the prescription, the registered pharmacist is required to dispense that product. In Malaysia, pharmacy-mediated substitution is prohibited by the guidelines for registration of biosimilars (2008) [12].

Pharmacy-mediated substitution of biosimilars can occur under certain conditions in Australia (a-flagged by the Pharmaceutical Benefits Advisory Committee (PBAC)). Currently, there is a box on the prescription that the physician can tick to override pharmacy-mediated substitution. The strategic agreement signed by Medicines Australia and the Australian Government on 9 May 2017 [13] states that prescribing software will use the INN as default (for both small molecule and biological medicines). However, when this is implemented in 2018, physicians will still retain the ability to specify the brand through a new 'opt-in' process. The 'no substitution' dispensing instruction that is currently on the form will remain for physicians to use. The strategic agreement also states that PBAC may, on a case-by-case basis, consider the following biosimilar uptake drivers:

1. *A different prescribing process with a lower level of administrative arrangements required by the physician (Streamlined authority essentially reduces the administrative burden for the physician; they will not have to fill out pages of paperwork)*
2. *For treatment of naïve patients only, the preferred choice will be those biosimilars designated for recommendation by PBAC*

These require legislative changes, which are expected to go through Australian parliament in September 2017. Once again, physicians will be able to override these biosimilar uptake drivers and indicate if substitution is not appropriate for a particular patient.

Table 3: Pharmacy-mediated substitution of biosimilars in Asia-Pacific countries

No substitution		Restricted substitution	Unrestricted substitution	Unclear
Hong Kong Indonesia Japan Korea Malaysia	New Zealand Philippines Taiwan Vietnam	Australia	–	China India Thailand Singapore

Given the response received, India was categorized as unclear. Whilst it appears that medicines are normally dispensed based on the physician's prescription, the pharmacist can substitute for a biosimilar since there is no guidance. Furthermore, advanced discussions on prescription writing took place at the Medical Council of India in February and March 2017, with a subsequent notice being released in April 2017 requesting physicians to write the prescription using the INN. The notice was not specific to any category of drugs and still under discussions for appropriate implementation as the physicians have raised concerns over the notice. As a result, the situation is unclear regarding whether pharmacists can substitute biosimilar products.

It should be noted that numerous non-comparable biotherapeutic products exist in India. Such products are also on the market in other countries surveyed including China, Mexico and Russia. As pharmacists in India have the ability to substitute unrestrictedly, the existence of these non-comparables in the market is of potential concern to patient safety. These products lack comparative data indicating that the products are highly similar to their reference biotherapeutic product; therefore there is the possibility that the safety profile may diverge from the reference product.

Latin America

Data was collected for 13 countries in the Latin American region, which can be seen categorized in Table 4. The responses received indicated that the only country in the region where substitution can occur is Peru, where there are no restrictions. The remaining 12 countries were all categorized as 'no substitution', as per the responses received. However, of the 13 countries surveyed as part of the Latin American region, only Mexico was identified as having laws, regulations or guidance in place; the Mexican Regulation on Health Inputs (Article 31) [14] indicates that the pharmacist must dispense the medicine written on the prescription. Therefore, the majority of responses provided in this region appear to be based on colleagues' knowledge of normal practices for pharmacies, as there are no regulations or guidances in place to allow or prevent biosimilar substitution occurring.

Table 4: Pharmacy-mediated substitution of biosimilars in Latin American countries

No substitution		Restricted substitution	Unrestricted substitution	Unclear
Brazil Colombia Costa Rica Dominican Republic Ecuador El Salvador	Guatemala Honduras Mexico Nicaragua Panama Venezuela	–	Peru	–

Africa and the Middle East

Data was collected for 20 countries in Africa and the Middle East region, which can be seen categorized in Table 5. The countries surveyed in this region follow the same general trend as Europe, Asia-Pacific and Latin America; the majority of countries were categorized as 'no substitution' as indicated by the responses received. Again, this is seemingly based on local pharmacy practice, as there are no guidances or regulations in place to guide the approach that we identified via our survey or additional research.

Table 5: Pharmacy-mediated substitution of biosimilars in African and Middle Eastern countries

No substitution		Restricted substitution	Unrestricted substitution	Unclear
Bahrain Cameroon Egypt Israel Ivory Coast Jordan Kuwait Lebanon	Morocco Oman Qatar Saudi Arabia Senegal Tunisia United Arab Emirates	–	Ghana Kenya	Algeria Nigeria South Africa

North America

The data collected for the US and Canada is displayed in Table 6.

Table 6: Pharmacy-mediated substitution of biosimilars in North American countries

No substitution	Restricted substitution	Unrestricted substitution	Unclear
Canada	USA	–	–

The US has additional legislation that relates to pharmacy-mediated substitution of biosimilars. The term 'interchangeability' is defined by law to mean a biosimilar can be substituted at the pharmacy level without the intervention of the physician who prescribed the reference product. A designation of interchangeability requires that the product meets an additional legal standard beyond biosimilarity. This standard requires the demonstration that the biosimilar '*(1) is expected to have the same result in any given patient, and (2) for products administered more than once, the risk to the patient in terms of safety or diminished efficacy of alternating or switching between use of the originator product and the biosimilar is no greater than the risk of using the originator product without such alternation* [15]'. At present, there are no licensed interchangeable biological products. Although federal law gives the US Food and Drug Administration (FDA) the authority to license biological products as interchangeable, it is state law that governs the substitution of medicines. Currently 35 states have enacted state pharmacy practice acts to address biologicals and biosimilars [16].

Health Canada, the national health authority in Canada, has stated it does not support pharmacy-mediated substitution of biologicals, including biosimilars [17]. No provincial health authority has given pharmacists the ability to automatically substitute biosimilars. Whilst the pharmacist can contact the physician and propose a change to the prescription, the final decision rests with the physician.

Discussion

The study has shown that there is no universal position held worldwide on substitution of biosimilars. The data collected indicates that pharmacy-mediated substitution of biosimilars does not usually occur in 59 of the 82 (72%) countries surveyed. However,

a considerable number of these countries do not have specific regulations, laws or guidances in place to guide policy and practices. Given this, the responses received appear to reflect local pharmacy practices.

For both the Latin American and African and the Middle Eastern regions, where there is an absence of regulations and guidelines on biosimilar substitution in the majority of countries surveyed, we speculate that this is due to a focus on the development of initial general biosimilar regulations and guidelines. In these regions, there is considerable uncertainty surrounding the biosimilar environment and what is occurring in practice. Until these products are more widely available, regulators in these regions have not yet had to address the issue of substitution of biosimilars at the pharmacy level. Given the lack of regulations or guidances, it appears that pharmacy-mediated substitution of biosimilars does not occur because of customs and social norms.

In contrast, Europe, and to some extent the Asian-Pacific region, have well established general biosimilar guidance that recognizes that these are not generic drug products and also have a number of approved biosimilars on the market. As a result, the biosimilars regulatory environment is more mature and many health authorities have turned their attention to advanced/secondary subjects including substitution of biosimilars at the pharmacy level. However, there are still numerous countries in both of these regions where guidances and regulations on substitution are apparently absent, e.g. China, Japan and Norway. We note that European medical societies have provided guidance to physicians on this matter. This survey did not attempt to capture this guidance but we recognize that it can play an important role in steering pharmacy-mediated substitution practices.

It is the opinion of the authors that pharmacy-level substitution of biosimilars is not appropriate unless stringent regulatory and legal criteria additional to scientifically appropriate biosimilarity requirements can be met. For example, the interchangeability designation in the US requires an additional standard for interchangeability and is under-pinned by a strong pharmacovigilance system for all products, together with additional naming measures for suffixes to be appended to the common 'core name' for biologicals to aid traceability of adverse drug reactions (ADRs). The presence of non-comparable biotherapeutics on the market also poses additional potential risks in the context of substitution since such products lack the assurance of even having met the global standard for biosimilarity let alone an additional standard for substitution [18]. In countries where no additional scientific standard exists for substitution of biosimilars and there is a lack of strong pharmacovigilance supported by additional naming measures, substitution is not advisable and the physician should remain at the centre of all decisions regarding patient treatment.

The ability to trace the correct ADR to the correct product is always important for all product types and especially so for biological products due to their increased complexity and variability compared to small molecules. Where pharmacy-mediated substitution does occur for biosimilars, traceability becomes even more critical, particularly in case new or altered frequency of immunogenicity-related ADRs occurs. Globally, we therefore believe all biologicals, not just biosimilars, should carry a unique suffix to the INN; this would ensure biosimilars are readily distinguishable from each other and from their reference product to aid in the accurate reporting of adverse events. This would be extremely valuable in countries where pharmacovigilance systems are still developing and where non-comparable biotherapeutics are available. This would also aid pharmacists in ensuring the correct biological product is dispensed in situations where physician prescriptions are written by the INN (generic name). While this position is still under debate globally, the FDA naming requirement [15] and the proposed WHO Biological Qualifier scheme [19] support the need for distinguishable generic names for biotherapeutic products.

Given the complexity of biologicals, for countries that are looking to develop guidance on pharmacy-mediated substitution for biosimilars we believe that the following principles are core. All of these should be met as these are not generic small molecule products and therefore these additional measures are essential if pharmacy-mediated substitution is to occur in order to safeguard patients:

1. legal frameworks have been established
2. the specific product has received a formal designation enabling substitution based on an additional level of scientific evidence to that shown for biosimilarity
3. a robust pharmacovigilance system should be in place, including measures that the pharmacist or physician can readily access, e.g. via the patient health records, including unique identifiers for the dispensed product to support traceability of adverse drug reactions
4. the biosimilar should be approved for all indications of the reference product not protected by exclusivity
5. the country actively applies stringent regulatory authority approval requirements for biosimilarity, such as those applicable in Canada, EU, Japan and the US, and therefore there are no so called non-comparable biotherapeutic products approved
6. there should be mechanisms in place to ensure that the patient and physician are informed when a product is substituted.

These principles are generally consistent with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) position [18].

Conclusion

This qualitative study provides a first insight into the global landscape of pharmacy-mediated biosimilar substitution, detailing the positions of over 80 countries worldwide.

Our survey identified that a variety of positions on pharmacy-mediated substitution exist in countries across the globe. In the majority of countries for which data was collected, pharmacy-mediated substitution of biosimilars was not reported to occur. Many European and a number of Asian-Pacific countries have regulations or guidances in place to stop or discourage substitution of biosimilars at the pharmacy level. The vast majority of Latin American, and African and the Middle Eastern countries are yet to develop such regulations but despite this it appears in practice substitution is not occurring, although we note these biosimilar markets are still developing and biosimilar availability and usage may not be as widespread as in Europe for example.

It is probable that as biosimilar use increases worldwide, the discussion surrounding pharmacy-mediated substitution will

only intensify. Given the dynamic environment of this topic, there is a need for further research in the future to consolidate and develop on the findings of this initial benchmarking survey.

Appendix 1

Countries where a response was received from Pfizer colleagues: Algeria, Bahrain, Belarus, Bulgaria, Brazil, Cameroon, Canada, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Finland, France, Germany, Ghana, Greece, Guatemala, Honduras, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Ivory Coast, Japan, Jordan, Kenya, Korea, Kuwait, Latvia, Lebanon, Malaysia, Mexico, Morocco, Nicaragua, Nigeria, Norway, Oman, Panama, Peru, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Senegal, Singapore, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, The Netherlands, Tunisia, Turkey, United Arab Emirates, Ukraine, Venezuela, Vietnam.

Countries where data was used from the second EBE Biological Medicines Policy Survey: Austria, Belgium, Estonia, Lithuania, Luxembourg, Malta, Serbia, Slovakia.

Countries where data from internal research was used: Australia, China, New Zealand, Philippines, UK, USA.

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