IPHA SUBMISSION TO THE NATIONAL BIOSIMILAR MEDICINES POLICY CONSULTATION

SEPTEMBER 2017

Executive Summary

The Irish Pharmaceutical Healthcare Association (IPHA) represents the **international research-based pharmaceutical companies** who are responsible for developing, manufacturing and bringing innovative medicines to the Irish market. It is worthwhile noting that **IPHA members manufacturer both originator biologic medicines and biosimilars.** IPHA supports bringing new technology and science to the market and believes that biosimilars have a vital role to play in healthcare. Availability of safe, effective and quality biologic medicines for patients is critical and so we welcome the development of an informed, evidence based National Biosimilars Medicine Policy.

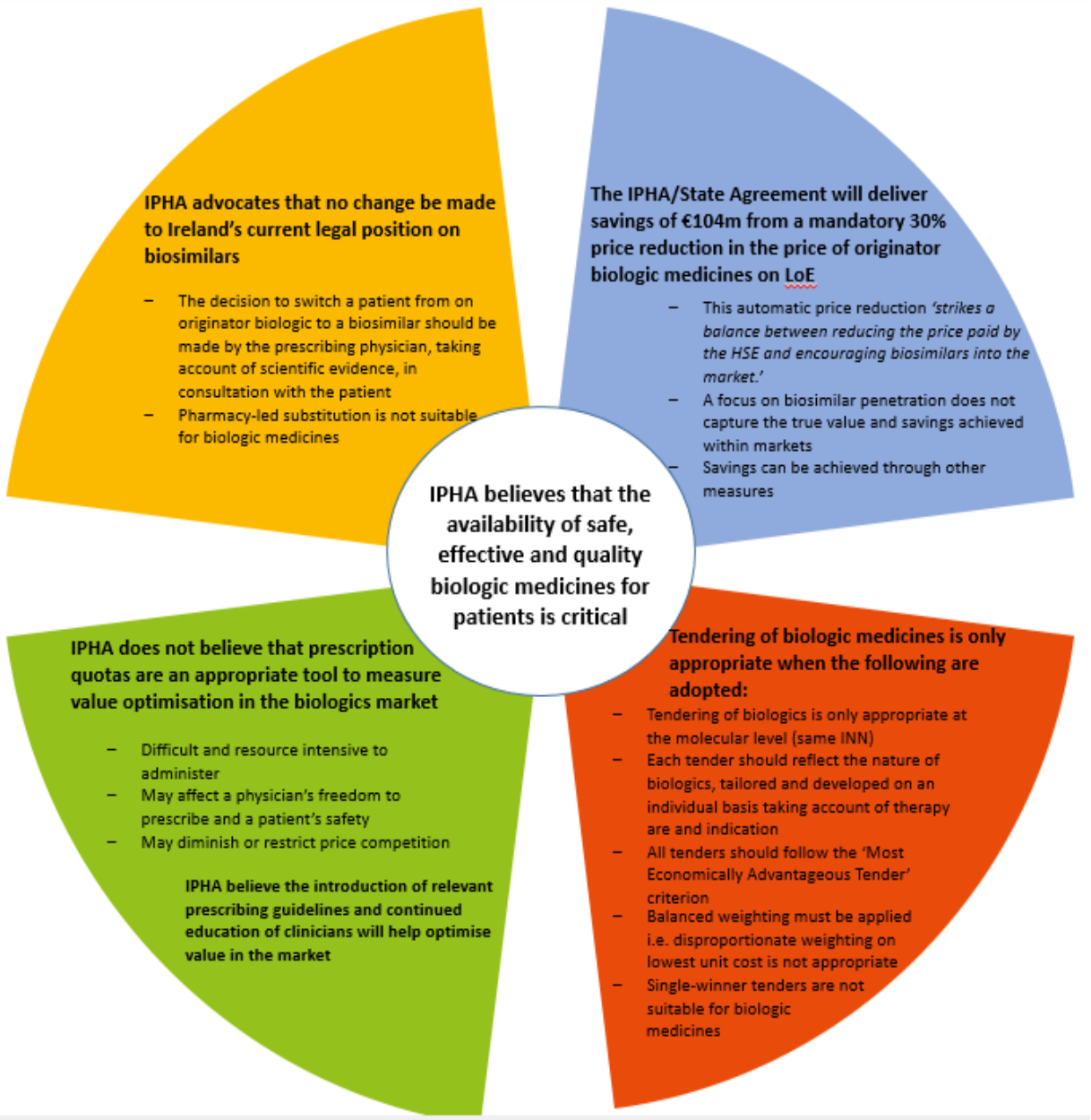
IPHA strongly believes that **the choice of biologic treatment for an individual patient should be made by their physician in consultation with the patient themselves.** The law already provides for this in that physicians are free to choose which product to prescribe for the patient at any time, be that an originator biologic or a biosimilar, but it is prohibited for this choice to be changed without the knowledge of the physician, thus **pharmacy substitution is prohibited**. Section 5 (7) (d) of the Health (Pricing and Supply of Medical Goods) Act, 2013 excludes biologic medicines from being considered interchangeable; **similar exclusion provisions are common across Europe** as there is insufficient evidence to support interchangeability at this time. As a result IPHA is **strongly opposed to any change in the current legislation and believes it is unnecessary** as physicians are already permitted to choose to prescribe any product for a patient which they deem clinically appropriate. Similarly any change to the legislation which would allow pharmacy substitution would mean that it would be impossible to preclude multiple switches between products and the **HPRA and the EMA are both opposed to patients being "switched back and forth"**. IPHA however **fully endorses the provision of more education about biologics and biosimilars for physicians** which would ensure that they have all of the requisite information to make an informed decision and so feel empowered to prescribe appropriately for each individual patient.

IPHA would like to reiterate that it is **fully supportive of competition in the biologics market as a means of delivering value to be re-invested in innovative products**. This is a relatively new dynamic as some of the biologic molecules reach their patent expiration, thus it is important to make well informed and evidence-based policy decisions grounded in real information. For example it has been claimed that Ireland doesn't have the full range of EMA approved biosimilars available, however this is not relevant as Ireland has at least one biosimilar available for each of the approved molecules which are commonly available in Europe, which is sufficient to create competition.

Biosimilars do indeed have a positive impact on competition and cost reduction, but it is important to ensure that this impact is measured appropriately. For example, a measure of biosimilar uptake would not reveal the full extent of savings delivered for a particular molecule, since savings do accrue from the reduced cost of the originator biologic. The **cost per treatment day is a more holistic and specific measure which gives an accurate measure of the extent of the cost reduction across all patients**. Any other measures to monitor competition or other aspects such as prescribing activity need to be developed in a way that is appropriate for the Irish healthcare system and which don't inadvertently distort the market or have a negative impact on patients.

IPHA was cognisant of the changing market dynamic and so **biologic medicines were included as a discreet element of the 2016 Agreement** for the first time as it was acknowledged that biosimilars were becoming more readily available and since they are not like generics there was a need to make specific provisions for them. Clause eight of the Agreement refers specifically to biologic medicines

and **provides for a mandatory reduction in cost of 30% net to the originator biologic as soon as a biosimilar becomes available**; this is conservatively **estimated to generate €100 million** in savings over the lifetime of the Agreement. In addition the nature of the provision ensures an **immediate and risk-free saving to the State with minimal administrative burden** and also applies to the treatment of all patients, not just those starting treatment *de novo*. Framework agreements between the industry and the State are common across Europe, their purpose is to outline a mechanism to reduce costs on the one hand while also outlining how new medicines will be made available, with the underlying principle that the savings made help the State to fund the newer innovative medicines. IPHA looks forward to the publication of the National Biosimilar Medicines Policy which together with the Framework Agreement will **ensure that there is value optimisation in the biologics market creating scope for investment in better innovative products for Irish patients.**



Section A – Introduction

1. Before reading this consultation paper, were you aware of biosimilar medicines?

Yes, as representatives of both the manufacturers of originator biologic medicines and biosimilars, the IPHA was aware of biosimilar medicines before reading this consultation paper.

2. Before reading this consultation paper, what was your understanding of Ireland's legal and regulatory position on biosimilars? Has this understanding changed from reading this paper? Please explain your answer.

Before reading this consultation paper, IPHA had a comprehensive understanding of Ireland's legal and regulatory position on biosimilars. Our understanding has not changed following our review of this paper.

Legal Position

The legal position on biosimilars in Ireland has been set out under Section 5 (7) (d) the Health (Pricing and Supply of Medical Goods) Act 2013[1] which deems that biologic medicines are not interchangeable and thus prohibits the substitution of biologic medicines by pharmacists.

a. In the interest of patient safety, IPHA advocates that **no change be made to the current legislation** and that the decision to switch a patient from an originator biologic to a biosimilar should be made by the prescribing physician, taking account of scientific evidence, in consultation with the patient and not by any third party.
b. As it stands, any prescribing physician is allowed to either initiate a new patient or switch an existing patient to a biosimilar based on their clinical judgement for each individual patient.
c. Any **decision to switch a patient should not be based on cost factors** alone but on the best treatment option for individual patients.
d. IPHA fully **supports the position that biologic medicines cannot be substituted at pharmacy level.**

Regulatory Position

The regulatory position on biosimilars in Ireland has been set out by the Health Products Regulatory Authority (HPRA) in their 'Guide to Biosimilars for Healthcare Professionals and Patients', Dec 2015[2].

a. IPHA fully supports the HPRA's position that physician-led interchangeability, i.e. switching, of originator biologics and biosimilar medicines is appropriate.
    - *"If it is planned to change the medicine a patient receives from a reference to a biosimilar medicine or vice versa, the treating physician should be involved…[2]"*
b. IPHA further supports the HPRA position that patients should not be switched back and forth between a biosimilar and an originator biologic.
    - *"It is not recommended that patients switch back and forth between a biosimilar and reference medicine…[2]"*

[1] Health (Pricing and Supply of Medical Goods) Act 2013, http://www.irishstatutebook.ie/eli/2013/act/14/enacted/en/html

[2] HPRA, Guide to Biosimilars for Healthcare Professionals and Patients, 2015 http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare-professionals-and-patients-v2.pdf

3.	**Before reading this consultation paper, were you aware of the low uptake of biosimilars in Ireland? What, in your view, are the primary reasons behind this?**

Yes, before reading this consultation paper, IPHA was aware of the low uptake of biosimilars in Ireland. IPHA fully supports competition at Loss of Exclusivity (LoE) to ensure expenditure headroom is provided for innovative products with a view to:

a. **Reducing costs** to the payer and providing better value for money.
b. **Increasing options** for patients and physicians and increasing patient access and/or numbers.
c. **Generating savings** to create expenditure headroom for investment in new innovative medicines.

However, IPHA believes it is important to recognise that a **focus on biosimilar penetration does not capture the true value and savings achieved** within markets. A report by QuintilesIMS which was commissioned by the European Commission and released in May 2017 'The Impact of Biosimilar Competition in Europe' found that EU Member States were saving money in markets even where biosimilar market share was low. The following points provide an outline of the key results of the study[3]:

a. The **entrance of a biosimilar is the catalyst for competition** and drives down the price of the whole class including the originator, this happens **even if there is just one biosimilar** competitor available.
b. Fundamentally, a weak correlation exists between biosimilar market share and total market price reduction i.e. **high savings can be achieved even if the biosimilar market share is low**.
c. In analysing the impact of competition the **timing** of patent expiry and biosimilar launches has a direct impact on results and **can distort statistics**, e.g. if a biosimilar is only launched half way through the year you will only achieve half the impact.
d. The **size and dynamics of individual markets can influence launch timings** and it may not be commercially feasible in a small market for all licenced biosimilars to launch.

Biosimilar uptake provides insight into just one relevant parameter and overlooks the savings from the originator biologic price change and impact of increasing competition in the market. IPHA recommends that the following should be considered when interpreting biosimilar uptake rates:

a. **Savings** delivered by the originator biologic are **prompted by the entry of just one biosimilar** to the market.
b. The **reduction in the cost per treatment day should be measured** following the introduction of a biosimilar. This would provide a more accurate measurement of the true value realised and would take account of any discounts.
c. Savings can be used to treat more patients. **Overall spend may remain constant but with more patients benefiting**.

At the time of writing, the EMA had granted market authorisation for 35 biosimilar medicines across 12 molecules ***(Note: one of these molecules is currently patent protected in Ireland and therefore biosimilar entry is not legal at this time)***. Of the 11 molecules where biosimilar entry is possible in

[3] 2017 QuintilesIMS Biosimilar report - The Impact of Biosimilar Competition in Europe. http://ec.europa.eu/DocsRoom/documents/23102

Ireland, 8 are available and reimbursed by the State (see Table 1) and are delivering savings to the payer in the following ways:

a. The **2016 IPHA/State Agreement provides for a mandatory 30% reduction in the price** of originator biologic medicines on LoE. This ensures an **immediate and risk-free saving** to the State with **minimal administrative burden**.
b. Further savings are generated from the price point of the biosimilar and subsequent market competition which can lead to further price reductions in both the originator biologic and biosimilars i.e. **30% is the minimum price reduction and greater discounts may be applied by the supplier**.
c. Evidence indicates that some European models apply to treatment naïve patients only thus offering less savings opportunities than a mandatory price reduction across all patient cohorts as is current practice in Ireland.

Of the three molecules where biosimilars are currently not available in Ireland, our research shows that while enoxaparin sodium and teriparatide have EMA approval there also appears to be no sales in other European countries. The circumstance relating to somatropin is outlined overleaf. Thus, for the comparable, available and legally approved molecules (i.e. 8 in total) there is at least one biosimilar available in Ireland and it would appear that no market distortions exist.

Table 1: Biosimilar availability in Ireland, September 2017

Molecule	EMA Approved Biosimilars[4]	Biosimilars Available in Ireland[5]	Comment
adalimumab	3	0	The reference biologic is patent protected in Ireland and therefore a biosimilar launch is not possible at this time
enoxaparin sodium	2	0	A recent market research query indicates that there have been no sales of these biosimilars in other relevant EU markets*
epoetin alfa	3	1	
epoetin zeta	2	1	
etanercept	2	1	
filgrastim	7	4	
follitropin alfa	2	1	
infliximab	3	3	
insulin glargine	2	1	
rituximab	6	1	
somatropin	1	0	This product applied for reimbursement but was never launched
teriparatide	2	0	A recent market research query indicates that there have been no sales of these biosimilars in other relevant EU markets*

[4]http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit

[5] Sources: PCRS, Updates to the List of Reimbursable Items and High Tech Scheme List, https://www.sspcrs.ie/libr/html/monthlyproductupdate.pdf; QuintilesIMS Midas Dataview August 2017

*IPHA research request to QuintilesIMS who reviewed availability across 23 European countries

CASE STUDIES ON THE COMMERCIAL REALITIES OF SOME BIOLOGIC PRODUCTS

1. ERYTHROPOETIN PRODUCTS – ATC B3C

The class of medicines known as erythropoeitins are used to treat a variety of anaemic disorders caused by kidney disease or cancer treatment for example. The initial formulations of these products were very short acting and so required daily administration by injection. More recent product formulation developments (e.g. pegylation) have resulted in products which can be administered once a week which improves the experience for the patient and also reduces healthcare system costs associated with administration. In Ireland, and in most Western European countries, clinical practice has been to use these improved formulations. In Eastern European countries they tend to continue to use the older versions of the products which have biosimilar competition.

Learnings:

(a) Low penetration of certain biosimilar products may be due to a change in clinical practice to a more effective product.

(b) All system costs should be considered in the evaluation of value for money in the choice of one treatment option over another.

(c) In the absence of biosimilar entry and expansion, cost reductions are achieved by price re-alignments agreed through the 2016 IPHA/State Agreement.

2. INFLIXIMAB

Biosimilar competitors of Infliximab were first approved by the EMA in late 2013 and were available in the Irish market soon afterwards. At the time there was no automatic pricing mechanism in place to manage the pricing of the various alternatives. However, as was custom and practice in the hospital market, hospital pharmacists used the new entrants as a mechanism to drive price competition amongst the providers and gain discounts from suppliers. There has been a mix of formal and informal tender processes over the past few years which have driven down the price of Infliximab, however, since most hospital medicines budgets are fully devolved to each Pharmacy Department and since discount arrangements are confidential in nature, the quantum of these savings is not apparent. In addition, since the commencement of the 2016 IPHA/State Agreement there has been a cost reduction on the originator product of 30% net, which applies to the treatment of all patients.

Learnings:

(a) The introduction of a single biosimilar competitor is adequate to drive price competition.

(b) The value of savings may not always be obvious as some discounts are confidential.

(c) Savings do not just accrue from the biosimilar, they also arise from the price reduction on the originator product.

(d) Savings on the originator product delivered via the Framework Agreement are immediate and easy to realise, whereas savings from biosimilars may initially be limited as the product is used on smaller numbers of treatment naïve patients.

3. SOMATROPIN – HUMAN GROWTH HORMONE

Although the EMA first approved a somatropin biosimilar in 2006, reimbursement in Ireland was not sought until early 2015. As it turns out the product has never launched in Ireland as there are already four established products on the market and only 100 new patients each year it is unlikely that a new product, biosimilar or otherwise, would enter the market.

Learnings:

(a) In a country as small as Ireland the market may be too small to warrant launch of a product or even a particular presentation of a product.

(b) The size of the country/market will also influence the timing of commercial launch of products as suppliers will target larger markets first.

Section B – Legislation, National Guidelines and Quotas

1. Do you see a role for national, statutory or clinical prescribing guidelines for biosimilar medicines in Ireland? Please explain your answer.

Yes, **IPHA supports the development of evidence based national clinical prescribing guidelines** for biosimilar medicines which would complement the existing 'Guide to Biosimilars for Healthcare Professionals and Patients' published by the HPRA in 2015. IPHA believes that if clinical prescribing guidelines were to be developed it should be by an **expert multidisciplinary team** i.e. physicians, patients, industry, State, regulatory body etc.

The World Health Organisation (WHO) describes clinical guidelines as consisting of "*systematically developed statements to help prescribers make decisions about appropriate treatments for specific clinical conditions"*[6]. The WHO highlights that *"evidence-based clinical guidelines are critical to promoting rational use of medicines*"[4]. Along with the National Biosimilar Medicines Policy, clinical prescribing guidelines could "*promote the rational use of biosimilar medicines and create a sustainable environment for biological medicines in Ireland*"[7].

A 2016 study conducted by O'Callaghan et al, which surveyed a total of 480 physicians and pharmacists in Ireland to assess their awareness and attitudes to the use of biosimilar medicines, found that guidelines from professional societies were the most frequently used learning resource (72% of respondents reported frequent use of these guidelines) thus affirming the value for national clinical prescribing guidelines in Ireland[8].

2. Do you think that prescriber-led switching of patients to biosimilars should be encouraged in Ireland? Please explain your answer.

For clarity, IPHA is following the definition of switching as set out in the 'Biosimilars Information Guide for Healthcare Professionals in the EU' prepared by the EMA and the European Commission:

Switching: Switching is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent[9].

IPHA believes that clinical decision factors are paramount and so fully supports the treating physician's decision on the most appropriate treatment in consultation with their patient. When considering switching a patient between an originator biologic medicine and a biosimilar (or vice versa), IPHA aligns with current HPRA and other guidelines and reaffirms its position that:

a. The **decision to switch a patient should be made by the prescribing physician**, taking account of scientific evidence, in consultation with the patient and not by any third party.

[6] World Health Organisation, Promoting rational use of medicines: core components, 2002
[7] National Biosimilar Medicines Policy, Consultation Paper, August 2017
[8] O'Callaghan, J., Bermingham, M., Leonard, M., Hallinan, F., Morris, J. M., Moore, U. & Griffin, B. T. (2017) 'Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland', *Regulatory Toxicology and Pharmacology,* 88, 252-61
[9] EMA and European Commission, Biosimilars in the EU Information guide for healthcare professionals, May 2017

b. In the interest of patient safety, any decision to switch a patient from one therapy to another **should not be made on financial considerations alone**. The decision should take account of all relevant criteria including clinical evidence, pharmacovigilance, nature of administration device, cost etc.
c. As the availability of data relating to the long-term us of biosimilars is limited at this time, patients should not be switched back and forth between a biosimilar and the originator biologic medicines (i.e. reference medicines)[10].
d. Having regard to the points above, physicians should balance the level of evidence against the level of risk and related uncertainties on a case by case basis considering product and patient related factors.
e. Results from switching studies should not be extended to other biosimilars of the same originator biologic medicine.
f. Results of switching studies should not be extrapolated to other indications.
g. The **nature of the device and route of administration** for individual treatments should be considered when making a decision to switch a patient from one treatment to another.

In addition, **effective pharmacovigilance (PV) systems are of particular importance for biologic medicines**, especially when there are multiple treatment options available. These systems should include mechanisms to support reliable track and trace of the dispensed biologic to ensure that adverse events can be attributed to the correct biologic and can inform clinical decision making.

As biosimilars are considered to be similar but not identical to the originator biologic medicine, IPHA, **in line with international best practice, recommends that all biologic medicines should be identifiable throughout the prescribing, dispensing and pharmacovigilance processes by a distinct naming convention**.

a. In accordance with the European Cross-border Healthcare Directive, Directive 2011/24/EU[11] of the European Parliament, the prescription for a biologic medicine should be written by brand name and international non-proprietary name (INN).
b. The immunogenicity, manufacturing variability and stability differences across biologic medicines should be recognised and their specific pharmacovigilance implications considered accordingly.
c. Significant traceability challenges exist and appropriate mechanisms from the point of prescription through to the reporting of an adverse drug reaction (ADR) should be established. We therefore support the EU Pharmacovigilance legislation, Regulation (EU) No 1235/2010 and Directive 2010/84/EU[12], which advocates for and recognises the importance of effective pharmacovigilance and imposes an obligation on healthcare professionals to record ADRs for biologic medicines by brand name and batch number.
d. We recommend the development of robust pharmacovigilance reporting systems to ensure accurate attribution of adverse events i.e. there is a requirement for long term observation of clinical outcomes e.g. clinical registries.
e. The advice provided by the NCCP in relation to the use of biosimilars in oncology should apply in all therapeutic areas.

> *"Any medicine for which a biosimilar is available will need to be prescribed using brand name in order to ensure a patient receives the intended product and to ensure correct reporting of any adverse events.[13]"*

[10] HPRA, Guide to Biosimilars for Healthcare Professionals and Patients, 2015 http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare-professionals-and-patients-v2.pdf
[11] https://ec.europa.eu/health/cross_border_care/policy_en
[12] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf
[13] NCCP Guidance on the use of Biosimilar Medicines in Cancer Treatment, August 2017

3. Do you think that pharmacy-led substitution of biosimilars should be implemented in Ireland? Please explain your answer

For clarity, the following definitions for substitution and interchangeability have been adopted by the IPHA.

Substitution: Substitution occurs when a medicine is substituted for another medicine without the prescribing physician's knowledge. It generally takes place at pharmacy level[14].

Interchangeability: Interchangeability is where one medicine can be safely used instead of another. Interchangeability generally takes place in consultation with the prescriber[14].

The Health Act 2013[15] prohibits the interchanging and therefore the substitution of biologic medicines in Ireland.

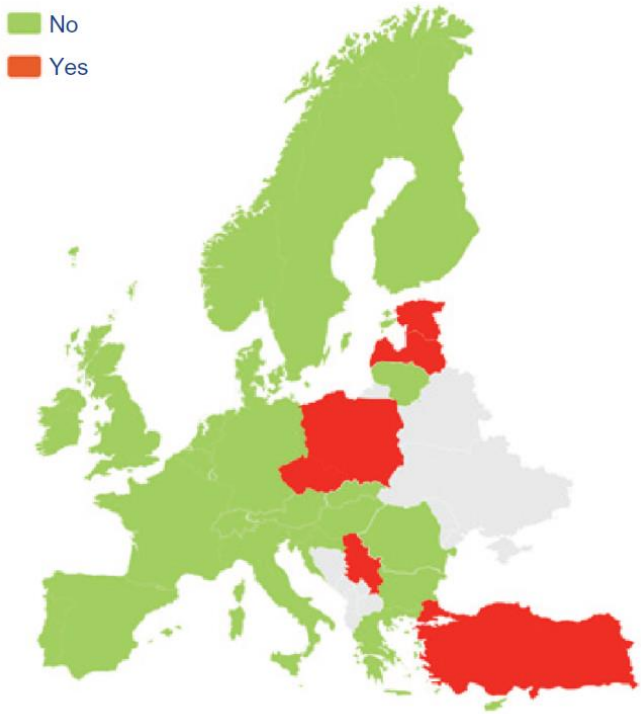
In line with both the current legal and regulatory positions on biosimilars in Ireland, IPHA does not believe that pharmacy-led substitution of biosimilars should be permitted. **In the interest of patient safety, IPHA advocates that no change be made to the current legislation to ensure that the decision to switch a patient from an originator biologic to a biosimilar continues to be made by the prescribing physician, taking account of scientific evidence, in consultation with the patient and not by a pharmacist.**

IPHA is of the understanding that a number of Irish physician groups have contacted the Minister of Health to state their position, considering available international data, that automatic substitution at pharmacy level is not suitable and not considered safe practice.

[14] HPRA, Guide to Biosimilars for Healthcare Professionals and Patients, 2015 http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare-professionals-and-patients-v2.pdf

[15] Health (Pricing and Supply of Medical Goods) Act 2013, http://www.irishstatutebook.ie/eli/2013/act/14/enacted/en/html

Figure 1: Biologics substitution across Europe in 2016[16]



Note: Pharmacy level substitution is only permitted in the Czech Republic, Estonia, Latvia, Poland, Serbia and Turkey, all of which have an opt-out provision for the physicians.

4. Do you see a role for prescription quotas in Ireland in order to increase biosimilar uptake?
i. What is an appropriate prescription quota to implement?
ii. Should quotas only be employed for a limited duration?
iii. Should quotas apply at a local or national level, and should they apply equally to new and existing patients?

IPHA endorses value optimisation by the HSE and the freedom of prescribers to make their prescribing decision primarily on the basis of clinical criteria relevant to each individual patient taking account of any clinical guidelines which may be in place.

IPHA does not believe that prescription quotas are an appropriate tool to measure value optimisation in the biologics market when considering all the factors and the desired outcomes for the following reasons:

a. Quotas are **difficult and resource intensive to administer** at any level – clinician, local, regional or national.
b. They could result in clinicians making a prescribing decision based on the need to achieve a target rather than the needs of an individual patient i.e. may affect a clinician's freedom to prescribe and a patient's safety.

[16] Roediger, Freischem & Reiland. What pricing and reimbursement policies to use for off-patent biologicals in Europe? – Results from the second EBE biological medicines policy survey. Gabi Journal, volume 6, 2017, issue 2

c. The introduction of a quota may represent a **disproportionate and highly distortionary market intervention** with potentially long-term harmful anticompetitive effects**.**

IPHA does believe however that there should be a dynamic and competitive market which provides savings that can be re-invested in improving access for Irish patients to new innovative or existing biologic medicines. We believe that this objective would be best achieved through two mechanisms:

a. **Education** of clinicians to build confidence in making appropriate clinical decisions taking account of scientific evidence.
b. The **introduction of relevant prescribing guidelines** which provide for the optimal use of suitable biologic medicines (originator and biosimilar) in each individual therapeutic area. Guidelines should take account of criteria such as the type of patient, severity of disease, the device and the patient support programmes. The relative importance of individual criteria will vary between therapy areas. Such a bespoke methodology by therapy area is more likely to be accepted by clinicians than a crude standard quota universally applied regardless of the patient's condition.

Section C – Education & Supports

1. Before reading this paper, were you aware of any educational programmes and/or national guidelines in place in Ireland aimed at increasing knowledge of biosimilars?

Yes, in advance of reading this paper, IPHA was aware of a number of educational programmes and national guidelines in place in Ireland aimed at increasing knowledge of biosimilars.

In Ireland the Health Products Regulatory Agency (HPRA) (2015) and the National Medicines Information Centre (2015) have both published information guides that cover several of the key concepts and definitions. Regulatory Science Ireland, a research network with representatives from academia, regulatory agencies and industry, has published guidance on pharmacovigilance requirements and a patient guide (Regulatory Science Ireland, 2017). More recent publications include those by the HSE Medicines Management Programme (2016) and the National Cancer Control Programme (2017).

2. Do you see a role for educational programmes and/or national guidelines in increasing biosimilar knowledge and awareness in Ireland? Please explain your answer.

i. If so, should these programmes and/or guidelines be tailored for specific groups i.e. patients, clinicians, pharmacists, nurses etc.? If so, which groups? Please explain your answer.

ii. Is there a need to provide education or guidance to biosimilar suppliers on entering the Irish pharmaceutical market? Please explain your answer.

Yes, IPHA does see a role for educational programmes and national guidelines in increasing biosimilar knowledge and awareness in Ireland.

The 2016 study conducted by O'Callaghan et al, which surveyed a total of 480 physicians and pharmacists in Ireland, revealed a lack of awareness and understanding regarding biosimilars with 21% of respondents considering a biosimilar to be the same as a generic, 16% had never heard of the term biosimilar before and a further 26% had heard of the term but couldn't define it[17]. A further study conducted by IPPOSI in 2016 which surveyed arthritis patients in Ireland found that patient awareness and understanding of biosimilars was very low, with the vast majority of patients unable to differentiate between a biosimilar medicine and a generic medicine[18]. It would appear that there has been very little patient education on biologic medicines conducted in Ireland to date.

The results of these studies would suggest that, while some education programmes and guidelines have been issued, there is **further work to be done to ensure all relevant stakeholders have the required level of knowledge regarding biologic medicines.**

The existence of biosimilars increases the range of available choices for any particular biologic molecule, thus enabling competition. However, this increased range of choices brings with it greater complexity to those responsible for making treatment and drug procurement decisions. The provision of **comprehensive education** and **information about the factors to consider when deciding** which

[17] O'Callaghan, J., Bermingham, M., Leonard, M., Hallinan, F., Morris, J. M., Moore, U. & Griffin, B. T. (2017) 'Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland', *Regulatory Toxicology and Pharmacology,* 88, 252-61

[18] Rogan, K. (2016) 'IPPOSI Outcome Report, Biologics & Biosimilars' http://www.ipposi.ie/images/Biologics__Biosimilars_Outcome_Report_May_2016.pdf.

version/s of a biologic to choose needs therefore to be a priority[19]. This education needs a **multi-stakeholder approach** and should be **tailored for each specific group** including prescribers, pharmacists, patients, nurses, procurement staff, hospital managers and national payors. **Different forms of education could be made available** such as instructor-led training, 'on the job' training, help-lines, online modules, booklets and frequently asked questions guides. It would be valuable for stakeholder groups to be educated about the multitude of factors that require evaluation when considering biologic choice. These factors include, but are not limited to, the following criteria[20]:

- Clinical data availability
- Indications and immunogenicity
- Regulatory factors
- Product criteria such as device and delivery factors
- Medical product support including nursing services
- Manufacturing experience of the supplier
- System criteria such as cost-effectiveness criteria, tracking and information systems

Education regarding decision factors and the implementation of a decision-making framework is highly important as too is education regarding the monitoring and tracking of patients and biologic medicine usage, both from a clinical and an economic perspective.

Healthcare professionals and patients **should be educated appropriately on the importance of safety monitoring and of the additional adverse event reporting requirements** due to a biosimilar's limited safety evidence at the time of marketing approval[21] [black triangle?]. Education and additional resources should be provided to support the closing of the knowledge gap regarding long-term outcomes and the long-term safety profile of biosimilars. **Registries, real world observational studies and enhanced information technology systems** in hospitals and pharmacies for tracking medicines would provide practice-based evidence.

[19] Boone, N., Kuy, H. V. D., Scott, M., Mairs, J., Krämer, I., Vulto, A. & Janknegt, R. (2013) 'How to select a biosimilar', *European Journal of Hospital Pharmacy: Science and Practice*.

[20] Ventola, C. L. (2015) 'Evaluation of Biosimilars for Formulary Inclusion: Factors for Consideration by P&T Committees', *Pharmacy and Therapeutics,* 40, 680-89.

[21] Reinisch, W. & Smolen, J. (2015) 'Biosimilar safety factors in clinical practice', *Seminars in Arthritis and Rheumatism,* 44, S9-S15.

Section D – Incentives & Disincentives

1.	**Considering what has been seen in other countries, should incentives and/or disincentives be used in Ireland to increase the uptake of biosimilars?**
i.	If so, should there be different incentives and/or disincentives for prescribing biosimilars to new patients and for switching existing patients?

Incentivisation of clinicians is a tool that could be used to effect a change in prescribing behaviour. However, as previously stated, **IPHA supports value optimisation and cost effective prescribing but believes that clinicians must be allowed to prioritise clinical parameters** when making individual patient prescribing decisions. These decisions should be based on the best treatment option for individual patients. In any given therapeutic area, relevant clinical guidelines should suggest the range of treatment options available to the clinician who can choose the most appropriate treatment at each prescribing event in consultation with the patient. In the event that a clinician is encouraged/deterred from taking a particular course of action because of an incentive their clinical decision is no longer independent.

We believe that comprehensive clinical guidelines would allow clinicians to make their prescribing decisions based on a comprehensive review of all the relevant factors, while still allowing them to **make individual decisions without the undue influence of non-clinically relevant instruments** such as incentives. IPHA wishes to reiterate that we believe **relevant clinical guidelines rather than incentives are the appropriate tool to influence prescriber behaviour** for clinical and cost effective prescribing of biologic medicines in all patients - new and existing.

2.	**Do you see a role for gain-sharing agreements in promoting the uptake of biosimilars in Ireland? How might this be structured in an Irish setting?**

Gain-sharing agreements which see some of the value gained through cost effective prescribing channelled back to the prescribing clinicians or departments are a particular form of incentive scheme which **can be effective when there is transparency in terms of financial flows and also where the organisational structure easily allows the re-allocation of value between the parties.**

The structure of the healthcare system in Ireland does not lend itself to the introduction of gain-share mechanisms for a number of reasons:

a. There is no single IT system across the health service which would facilitate simple and transparent tracking of prescribing activities and related financial flows.
b. Prescribers are often private practitioners and not wholly employed by the HSE, therefore, the allocation of any share of savings 'gained' would be challenging to administer.

There is another perspective on gain sharing – rather than assuming it is a retrospective distribution of savings, it **could be viewed as a prospective investment in service deli**very. For example, if a particular clinical group endeavoured to implement a medicines optimisation plan and they were provided with funding up front for a **patient registry or patient support** through a nurse or pharmacist led programme, it would increase the chance of a successful outcome without affecting the existing level of service.

3. Do you see a role for patient incentives, such as patient co-payment systems, in promoting the uptake of biosimilars in Ireland? How might this be structured in an Irish setting?

The Irish system is very egalitarian in relation to the supply of medicines and is designed to ensure that the patient is not incentivised to make negative cost-based decisions on the use of their medicines. IPHA supports this position and believes that the patient should get the right medicine at the right time in the right dose as decided by their clinician. Most patients do not have sufficient medical knowledge to make an informed decision on whether treatment is necessary or not, and indeed, as to the appropriateness of a given treatment. For this reason, the decision is devolved to a patient's clinician who has the requisite clinical expertise to make the most appropriate decision on their behalf.

IPHA firmly believes that the introduction of any mechanism which could result in **a patient making an alternative decision to that of their clinician is highly inappropriate**. We are **however supportive of patient engagement at the time of the prescribing decision**, so that the clinical decision is made in consultation with the patient which allows for their opinion to be considered by the prescriber.

Section E – Tendering

1. To what extent, if any, are you aware of tendering processes for pharmaceutical procurement in Ireland currently? Please explain your answer.

IPHA is aware of tendering for pharmaceutical procurement in Ireland. While IPHA does not participate in such tenders, IPHA members do.

IPHA strictly complies with applicable rules governing tender participation by its members, including competition rules. IPHA rules strictly prohibit discussion, information sharing or any other form of coordination between IPHA members on tenders.

Following representations from its members, carefully gathered in a manner to ensure compliance with applicable competition rules, IPHA understands that one aspect of current Irish tendering practices raises, at a general policy level, some concern.

Specifically, IPHA understands from members that current use of *pro rata* scoring to assess cost in tenders may have unintended and counterproductive consequences. Disproportionate weighting on lower unit cost, fails to consider all other criteria, and results in tenders awarded solely on an extremely narrow and ultimately misguided "cost" criterion. **The apparently cheapest or lowest cost bid is not always the most cost effective or medically effective option.**

EXAMPLE – EFFECT OF PRICE DIFFERENTIAL ON TENDER OUTCOME

There have been many tenders for biologic products – originator and biosimilars – in recent years, most of which have been conducted at a hospital level. In many cases the award criteria have been allocated in the following way – Price (40%), Quality (30%), and Product Suitability (30%).

On the face of it, it would appear that using that allocation would ensure that price is the main factor, but not the only factor in the final decision. However, we understand that it is the scoring methodology used for pricing element of the various products which is the main influencer of the outcome as demonstrated in the example below.

If a Product X was originally priced at €100 and a tender was issued in the format outlined above. If an alternative Product Y submitted a tender at a price of €40 and another Product Z submitted a tender at a price of €50, the current scoring methodology would mean that as the lowest cost item Product Y would be awarded the full 40 marks as the winner of that element. Product Z however at €50 is €10 more expensive which is 25% more than the winner, so they are penalised by 25% and so are only awarded 30 marks out of the original 40 marks available.

So while there is only 10% in the difference between the prices of products Y & Z with reference to the original price, this methodology amplifies the effect to a 25% differential. The ability to make up this difference across the other criteria is very difficult which means that despite appearances price is in fact the driver of the outcome.

IPHA calls for review and reform of this system of scoring to ensure tendering does not systematically exclude bids that are actually the most cost and medically effective solutions.

2. Do you see a role for tendering in biosimilar procurement in Ireland? Please explain your answer.

IPHA does see a role for tendering in biosimilar procurement in Ireland provided that the following are considered:

1. **Tendering of biologic medicines is only appropriate at the molecular level (within the same INN) and where a biosimilar is available on the market.**
2. **In the interest of best patient care it is important that the tender process reflects the specific nature of biologic medicines.**

    - Biologics are not interchangeable.
    - In line with HPRA guidance and section 5(7) (d) of the Health Act 2013, biologic medicines cannot be substituted at pharmacy level as they are not deemed interchangeable.
    - Switching a patient to another biologic should remain the decision of the treating physician, having regard to:

        i. Patient safety including pharmacovigilance and traceability
        ii. Patients whose condition has been stabilised with an existing medicine
        iii. Bio-naïve patients
        iv. The nature of the administering device

3. **Tenders should follow the 'Most Economically Advantageous Tender' (MEAT) criterion.**

    - In line with Directive 2014/24/EU on public procurement[22], tenders should not be judged on financial criteria alone and should follow the 'Most Economically Advantageous Tender' (MEAT) criterion i.e. objective consideration of price, quality, life-cycle, innovation, device and environmental/social factors. Accordingly, we recommend that the procurement of biologic medicines should consider the following criteria and apply an appropriate weighting to each element:

        i. Price
        ii. Continuity of supply – proven track record of supplier
        iii. Monitoring – the additional resources needed for additional monitoring by nursing staff or through patient registries
        iv. Education – the cost of training patients or staff in using new devices
        v. Support services – e.g. the cost of patient training or waste facilities
        vi. Quality
        vii. Innovation and life-cycle elements

    As stated previously, current tender processes in Ireland which adopt pro rata scoring to assess cost have the effect of assigning a disproportionate weight on the lowest cost submission. This distorts the outcome of the tender and can result in an adverse impact on patient outcomes and welfare. It is essential that an appropriate weighting is assigned to

[22] DIRECTIVE 2014/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL, of 26 February 2014, on public procurement and repealing Directive 2004/18/EC. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014L0024

each element considered within the tender document so that no one criterion can dominate the outcome.

4. **Individual tenders should be tailored according to therapy area.**

   - Due to the complex nature of biologic medicines a 'one size fits all' approach is not appropriate. Tenders must be tailored and developed on an individual basis taking account of the therapy area/indication and molecule in question.
   - There should be clinical input in the design of tender processes and documents.

5. **A pre-qualifying process should be established to ensure that all companies who participate in the tender process are in a position to follow through on all requirements if their submission is successful e.g. internal company procedures for traceability, continuity of supply, pharmacovigilance are essential and should be verified before suppliers can respond to the actual tender.**

6. **The following six principles of tender management set the basis of a fair tender process fostering innovation and therapeutic choice. These principles should be considered for each tender.**

   i. Transparency and scope – ensure the tender process is transparent across all stages and for all stakeholders and that the scope of the tender is specific as to product, presentation, usage, tender durations etc.
   ii. Competition - guaranteeing competition for tendering. Tenders should provide for sufficiently broad choice of products i.e. a single winner approach is not appropriate and a variety of biologic medicines should be made available to patients.
   iii. Therapeutic Choice - supporting freedom of choice for physicians while not encouraging usage outside the scope of the tender or indications.
   iv. Innovation - rewarding drug research innovation.
   v. Interchangeability & Switching – adherence to local regulatory agency guidance on interchangeability and upholding the prescribing physician as the decider on switching.
   vi. Price to value – the value of the broad product offering rather than price alone should be considered e.g. device, route of administration, ease of use, patient support programmes etc.

7. **The importance and value of Patient Support Programmes.**

   - Patient support programmes are provided to patients on certain medications where the treatment is complex e.g. injectables or where monitoring and/or other interventions are required. They add significant value to patients and research has shown that they enhance outcomes. As such, patient support programmes should be evaluated appropriately.
   - Patient support programmes play a key role in patient adherence to their medication which is a benefit to the patients' outcomes but also to the healthcare system through the reduction of waste.
   - The impact of patient support programmes should be included in any tender criterion i.e. offsetting costs to the state, enhancing patient outcomes etc.
   - Where appropriate, any preferred biologic medicine should have an efficient patient support programme in place.

8. The existence of national registries

- The monitoring of patients treated with biologic medicines is of considerable importance. It is therefore essential that appropriate systems and infrastructure are established to ensure appropriate 'track and trace' of all biologic medicines prescribed.
- Many jurisdictions have established national registries which enable them to capture this vital data e.g. DANBIO in Denmark, BSRBR & IBD in the UK, ARTIS in Sweden, BIOBADASER & ENEIDA in Spain and RABBIT in Germany. Such registries are not commonplace in Ireland and require significant investment in multiple resources i.e. finance, time, IT, HR.
- All new biologic medicines including biosimilars have a requirement for additional monitoring after launch and are highlighted as such through the Black Triangle process.

9. Single-Win Tenders

In line with HPRA, NCCP and EBE guidelines, biologic medicines should not be subject to automatic substitution and physicians should be provided with a sufficiently broad choice of treatments for their patients to ensure:

- Maintenance of clinical choice
- Patient safety
- Continuity of supply
- Patient choice
- Continuity of care
- Avoidance of multiple switches

For these reasons, single-win tenders are not appropriate for biologic medicines.

3. What role, if any, should healthcare providers play in a tendering process?

To ensure that all relevant components are included within the tender it is recommended that all stakeholders be engaged with in advance of publication. IPHA advocates that there should be input from all stakeholders, not just healthcare providers, throughout the tender process i.e. clinicians, pharmacists, nurses, patients.

- The prescribing physician is ultimately responsible for the healthcare of the patient and therefore should be at the core of all decisions surrounding the selection, administration and monitoring of medicines to patients.
- Hospital Chief Pharmacists play a lead role in procurement of medicines for the hospital to ensure access to medicines for physicians to prescribe.
- Decisions around the assessment surrounding suitability for prescribing, administration and monitoring should be done in close partnership between physicians, nurses and pharmacy as health care professionals.

4. If tendering is used in biosimilar procurement, what level should the tender be conducted at i.e. national tender, hospital group tender, hospital tender? Please explain your answer.

IPHA recommends that tenders be conducted at the hospital level.

- If tendering is to be used in biosimilar procurement, the tender should be conducted as close to where the decision making on patient care is conducted i.e. individual physician making

decisions surrounding individual patient care. Responsibility for individual patient care lies with the physician and therefor tenders should be conducted at the hospital level.

5. Should exclusive tenders (i.e. single winner tenders) be used for biosimilar procurement? Please explain your answer.

As stated previously, IPHA strongly recommends that exclusive tenders not be used for biosimilar procurement. Tender awards should offer sufficient product choice to physicians to ensure:

- Maintenance of clinical choice
- Patient safety
- Continuity of supply
- Patient choice
- Continuity of care

To ensure the best outcome for each patient, it is **important for physicians to have some degree of flexibility in treatment choice** at an individual patient level. This is of particular importance when managing patients with conditions that require treatment with complex medicines. Physicians should also have the option to ensure that stable patients with complicated disease history have the opportunity to remain on their current treatment.

In addition, the **continuous supply of products is of paramount importance** to patients so as not to interrupt their treatment. Single supplier models create a significant risk that in the event of a supply problem that there will not be an alternative source of product which could result in an interruption in a treatment programme.

Section F – Pricing Policies

1. To what extent, if any, do you see a role for internal and/or external referencing pricing in Ireland?

Both internal and external reference pricing are used in Ireland i.e. internal reference pricing is used in the pricing of generic medicines and external reference pricing is used for all patented medicines. Current practice suggests that internal reference pricing has been adopted by the HSE Corporate Pharmaceutical Unit (CPU) to assess the price of biosimilars launching in Ireland.

2. Should price linkage play a greater role in Ireland and what level of discounts off the reference drug should be sought?

The IPHA/State Agreement provides for a significant cost reduction and saving to the State of 30% on LoE when a biosimilar enters into the market. This mechanism ensures that benefits equivalent to those from any price linkage policy are already available to Irish patients and, as a result, reduces the need for further regulatory intervention to achieve the same goals (whether via adoption of a formal price linkage policy or otherwise).

3. Should the price of the reference treatment be reduced automatically on loss of exclusivity in the Irish market? Please explain your answer.

Yes, as provided for under the IPHA/State Agreement, the price of the reference treatment should continue to be reduced automatically on LoE in the Irish market. This automatic 30% reduction provides the State with **significant risk-free savings with minimal administrative burden**. In addition, further savings can be generated from the price point of the biosimilar and subsequent market competition leading to further price reductions in both the originator biologic medicine and biosimilars i.e. 30% is the **minimum price reduction and greater discounts may be applied** by the suppliers.

As stated within the consultation paper, the current automatic price reduction *'strikes a balance between reducing the price paid by the HSE and encouraging biosimilars into the market.'* This consideration has been confirmed by the launch of numerous biosimilar medicines on the Irish market post the introduction of the IPHA/State Agreement.

Section G - Inappropriate Business Practices

1**. Considering what has been highlighted by the OECD, are you aware of any inappropriate business practices operating in Ireland?**
i. If so, in your opinion, how might these affect biosimilar uptake in Ireland?

IPHA is not aware of any inappropriate practices carried out by IPHA members.

IPHA members must adhere to a strict Code of Practice that is based upon, and is more restrictive than, the medicine advertising legislation[23] which was introduced into national law by the Irish Government. For example, while the legislation permits the provision of gifts[24] to Healthcare Professionals, the IPHA Code does not, and has not done so for many years. The legislation also permits the provision of samples of medicines to those who are qualified to prescribe. The legislation permits up to six samples per year. However, IPHA members are not permitted to provide six samples per year. IPHA members are only permitted to provide up to four samples per year and only for the first two years after the first request from a prescriber. We have further strict requirements around hospitality, sponsorship, claims, comparisons, market research, non-interventional clinical research and much more.

IPHA is also committed to transparency. As would be expected, it is important that interactions between our industry and healthcare professionals and organisations **meet the high standards of integrity that patients, governments and other stakeholders expect.** While such interactions are already highly regulated, in June 2013, and to provide additional transparency, the European Federation of Pharmaceutical Industries and Associations' (EFPIA) adopted a **Disclosure Code regarding Transfers of Value to healthcare professionals and healthcare organisations** for implementation in 2016. IPHA, as a member of EFPIA, changed its Code of Practice to reflect this additional transparency. Under this revised IPHA Code, summary details of how IPHA member companies engage with, and support, healthcare professionals and healthcare organisations through direct or indirect financial support, or 'Transfers of Value', have been made public on www.transferofvalue.ie since 1st July 2016.

In brief, this means that each IPHA member company and also some non-IPHA companies that voluntarily wish to report, provide an annual report that includes:

- ToVs related to research and development;
- Contributions to costs related to events;
- Details of donations and grants;
- Fees for services & consultancy.

The amounts reported are the total per annum for specific categories rather than individual amounts for each transaction. Generally, these are per healthcare organisation or healthcare professional.

[23] Medicinal Products (Control of Advertising) Regulations, 2007
[24] Regulation 21(1) of the 2007 Control of Advertising legislation states the following: 'Inducements and hospitality: A person shall not, in the course of promoting medicinal products to persons qualified to prescribe or supply such products, supply, offer or promise to such persons any gift, pecuniary advantage or benefit in kind, ***unless it is*** inexpensive and relevant to the practice of medicine or pharmacy'.

However, to **adhere to data protection laws**, healthcare professionals **must give consent** to the pharmaceutical company for individual named disclosure. In the absence of this consent, annual data is published on www.transferofvalue.ie in aggregate form in respect of healthcare professionals who have not given consent to publish their names. In contrast, all annual ToVs to healthcare organisations are published on an individual organisation name basis, since agreements with organisations do not fall under the consent provisions of data protection legislation.

The first series of data, or central industry report, related to ToVs was made in 2015. Subsequent annual reports are published within six months of year end and are **publicly available for three years** from the date of initial publication on www.transferofvalue.ie. Between those periods healthcare professionals data may need to be republished by the companies as a result of healthcare professionals consent changes and therefore healthcare professionals data within the central report may change. However, changes to the other data is not expected.

IPHA believes that disclosing the financial aspect of industry support for healthcare professionals and healthcare organisations will **help assure the public that they can trust their healthcare professionals to recommend treatments or administer appropriate care based solely on clinical evidence**. We value our relationship with healthcare professionals and healthcare organisations and we recognise that healthcare professionals' experience and expertise play a vital part in informing the pharmaceutical industry's work on new treatments for best patient care and outcomes. The shared ambition of IPHA member companies is to make available innovative treatments for patients under the direction of healthcare professionals. Given that today's medical challenges are far more complex than before our member companies believe in connecting their own expertise and capabilities with those of healthcare professionals and healthcare organisations.

Connections between industry, healthcare professionals and healthcare organisations benefit all three and, most importantly, patients. **This collaborative work has a profound and positive influence on the quality of patient treatment and the value of future research**.

Additionally, we believe that we have a **duty to provide healthcare professionals and healthcare organisations with the latest information on our medicines** to help them make the best treatment recommendations to their patients. Healthcare professionals wish to stay informed about current and new medicines to provide patients with the best treatments and choice. In turn, they provide us with information on how to improve our medicines through ongoing feedback on how the medicines work in clinical settings.

2. Are there any other inappropriate business practices, not outlined by the OECD, operating in Ireland that might affect the uptake of biosimilars? Please explain your answer.

IPHA is not aware of any inappropriate practices carried out by IPHA members.

3. Should measures be put in place to manage the practices you have identified in your answers to section G, questions 1 & 2?

Not applicable.