

Biologic Medicines Advocacy Handbook

Part 2 Practical Advocacy

How to shape your advocacy on biologic medicines

Section 1

Background

Patient advocates who have experience of advocating for a non-discriminatory access to a sufficient quantity of quality, safe, accessible, acceptable and affordable conventional chemically synthesised medicines must understand that they have to modify their advocacy when advocating for biologic and biosimilar medicines.

In our joint report with IFPMA *Biologic Medicines: Delivering on their potential for patients and the accompanying fact sheets*, we have highlighted that the biologic medicines have complex large molecules and the biotechnology and biopharmaceutical processes involved in manufacturing them are very intensive when compared with conventional chemically synthesised small molecule medicines.

Refreshing what has been covered in our previous toolkits, conventional chemically synthesised medicines are small molecules that are produced in large quantities using highly refined chemicals; their production requires fairly standard equipment and the manufacturing conditions generated are very predictable and controllable. The product produced is uniform batch after batch.

Upon the expiry of the patent of the conventional chemically synthesised medicines, a new company can replicate all the infrastructure and chemical processes faithfully and produce exact copies or generics of the reference patented drugs.

The most important issue for patient advocates to know is that the national medicines regulatory agencies do not require the generic producing company to undertake additional clinical trials. All they require to get market authorisation is a complete characterisation of the medicine and its ingredients. The manufacturer only needs to show how the generic's pharmacokinetics and pharmacodynamics will match those of the reference product.

Manufacturing biologic medicines, however, is very different to the standard approaches used in manufacturing conventional chemically synthesised medicines.

Biologic medicines production uses innovative and complex biotechnology and biopharmaceutical processes to 'craft' a living organism and harness its natural internal cell biology to synthesise the biotherapeutics we need.

The 'crafting' process first has to find the right organism. This is a complex biological and biochemistry hunt for the most suitable candidate. Once you have found the candidates, you then need to use genomic science to identify the gene sequences in humans that are needed to synthesise the target biotherapeutic. This requires a lot of skill and is also a nonstandard process.

The next step, the highly innovative step, requires you to place your identified human gene sequence into your living organism's DNA using gene editing technology (like CRISPR-Cas9 technology). Modifying an organism's DNA is a highly unpredictable process and requires a lot of skill and control.

Lastly having developed the ideal living organisms with your required human genes edited in, you then have to ensure that the organism can thrive and provide the optimum conditions needed. They need the right nutrients, temperatures and environmental conditions to 'ferment' and produce the best yields and product results. It is very challenging to control the internal cell biology of a living organism when compared with mechanical and electrical equipment used in the manufacturing of conventional chemically synthesised medicines.

Because you have used living cells and nutrients, unlike the highly refined chemical ingredients for conventional chemically synthesised medicines, you then have to 'harvest' the active biologic medicine from a 'soup' of very complex by-products comprising cell fragments and other protein debris that accumulates after the 'fermentation' is over.

Producing batch after batch of a consistent biologic product is not as simple as that of producing conventional chemically synthesised medicines. You require more highly trained biochemists and equipment on the production line to monitor and control the process. You require innovative non-standard equipment, that can sometimes have a process and mechanical design patent of its own, to allow you to produce high quality and consistent product in each batch all the time.

Your 'ordinary' pharmaceutical company that produces conventional chemically synthesised medicines may not have the knowledge, technology and experience that will be able to produce biologic medicines. Historically, small innovative biochemistry, biotechnology and genomic science start-ups based in some of the biotech innovation hubs (like San Francisco, Boston, Oxford etc.) have paired up with huge global pharmaceutical companies, who have the capital and resources, to engage in the making of biologic medicines.

Critical differences between producing generic and biosimilar medicines

As we have highlighted above, most competent pharmaceutical companies can make exact copies or generics of the chemically synthesised medicines of the originator medicines batch after batch. Also, the pharmaceutical companies and regulators can be assured from the product characterisation of the generics that the pharmacokinetics and pharmacodynamics of the generic in the body will be same as that of the reference medicine.

The challenge that we face in producing biosimilar medicines is that each new manufacturer will 'craft' their own organism and use a range of different nutrients, manufacturing and harvesting environments to that used in making the reference (originator) biologic.

This variation in approaches and the cell biology of the newly crafted organisms may introduce very small inherent differences to the large molecules of the biologic medicines. You cannot always control the internal cell biology of the organism and the way it has interacted with its environment. It may introduce some very small differences within the large molecules being produced.

You can never guarantee an exact faithful copy of a reference biologic; it will always be a highly similar copy thus it will be a biosimilar.

The immunogenicity or the interaction of large complex molecules with the immune system, compared to small molecules, is another difference between the biologic and conventional chemically synthesised medicines.

The regulators and the manufacturers have taken immunogenicity into account during the clinical trials and development of originator biologic medicines. The 'complete dossier' that the EMA requires before giving market authorisation will have this information. See Fact sheet 2: Regulation of Biologics Introduction to the regulation of originator biologic medicines <https://bit.ly/2Kil297>



The most important difference between the regulation of generics and biosimilar medicines is that of mapping biosimilar medicines and their immunogenicity, pharmacokinetics and pharmacodynamics when compared with the reference biologic medicine. The first challenge that a biosimilar manufacturer faces is that they have to show to the regulator what slight differences have been introduced by the living organisms into the biosimilar molecules. It is very difficult to provide a complete product characterisation of large complex molecules. Next they have to show what impact these differences may have on immunogenicity. See how this is dealt with in our: Fact sheet 3: Introduction to Biosimilars & Regulatory Requirements Introduction to the regulation of biosimilar medicines <https://bit.ly/2KjV9pd>

Lastly, the most significant difference between biologic medicines and conventional chemically synthesised medicines is in the frontline clinical and pharmacy practice. The practice of the physicians 'switching' one product for another, a generic for a branded originator, is permissible and even mandatory as a cost cutting measure when prescribing conventional chemically synthesised medicines. However, switching between biologic originator and its biosimilar medicine has created tensions between patient groups and payers in many health systems, especially the publically funded health systems. The debate is centred on immunogenicity and pharmacovigilance issues.

Even more challenging is the debate between patient groups and payers on the issue of the pharmacists' practice of 'substitution' of one product with another at the point-of-delivery. Should the pharmacist automatically without reference to the physician substitute a biologic reference with its biosimilar medicine, as they do for conventional chemically synthesised medicines?



The challenge for advocates is to try and understand how the legislation, regulation, and international treaty (within EU), handle switching and substitution. In the EU, the European Medicines Agency, as a regional regulator for 28 countries has left switching and substitution decisions to national medicines regulatory authorities and national parliaments (health is still a sovereign matter). This has resulted in a diverse national landscape in the EU with some countries allowing switching and substitution, and others not.

The FDA on the other hand has introduced an additional factor to the debate. The FDA has created a designation of 'interchangeability' within the market authorisation process.

FDA: An interchangeable product is a biosimilar product that meets additional requirements outlined by the Biologics Price Competition and Innovation Act. As part of fulfilling these additional requirements, information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated.

In this part of the toolkit we leave-out making any recommendations to national patient organisations as to what their policy and position should be on any matter of biologic and biosimilar medicines. It is the role of each patient organisation to work in collaboration with other national patient organisations and other stakeholders like the State and non-State actors and develop an evidence-based national policy and position. Section 2 attempts to sign post you and define the process pathway you can follow in this national consensus building on biologic and biosimilar medicines

Section 2

Planning your Advocacy on Biologic Medicines -Essential Building Blocks

Background

This part of the toolkit will be using some of the advocacy theories and concepts from our existing general capacity building toolkits and applying them to advocacy on biologic medicines. Our *Advocacy Fieldbook: Make Your Voice Heard* (2017) provides the necessary theory, guidelines and tools to help patient advocates to build capacity amongst their patient alliances to shape their own national advocacy on any healthcare issue.

[The Working with Partners and Stakeholders Toolkit \(2011\)](#) outlines how patients' organizations, both large and small, can work effectively with a range of partners and stakeholders. This can be applied to create a national alliance of patients on biologic and biosimilar medicines and a collaborative alliance with other partners and stakeholders.

Patient advocates are encouraged to read the above toolkits to understand the basic principles and approaches in advocacy and how they apply these principles to the specific issues of the availability of quality, safe, accessible, acceptable and affordable biologic medicines in UHC by 2030.

Setting the Scene

Part 1 of this toolkit stressed that in order to ensure that patients have a non-discriminatory access to a sufficient quantity of quality, safe, accessible, acceptable and affordable biologic medicines (originator and biosimilar) within our national universal health coverage by 2030, we need effective, efficient and timely global and national patient advocacy.

We introduced some of the evidence-based approaches to advocacy and the concepts of the Change Framework, Social Marketing, Policy Instruments Grid, Power Constellations and Policy Window in Part 1.

It was pointed out that health is a political choice, and politics is a continuous struggle for power among competing interests globally and in your countries. Patient advocates need to be savvy enough to know how to work with Power Constellations in their national landscapes to drive the biologic medicines agenda forward.

Lastly, we recounted the experience of the advocates behind the Framework Convention Alliance (FCA), one of the longest and most successful health advocacy campaigns. FCA advocates succeeded in getting 182 WHO Member States World's to ratify the world's first global public health treaty, WHO Framework Convention on Tobacco Control, in 2013.

The main lesson from the WHO FCTC global advocacy campaign was that we have to have work collaboratively and lead a whole of society, whole of government and whole of patient movement advocacy to move the three advocacy areas of the Problem Stream, Policy Stream and the Political Stream simultaneously and globally. Like the WHO FCTC and other successful global advocacy campaigns, we too need to:

- Define and refine the problem and position the issues affecting biologic medicines with great clarity first.
- Engage health economists, public finance experts and other partners who can help us cost-out and provide evidence-based policy instruments that we can propose to the decision-makers.

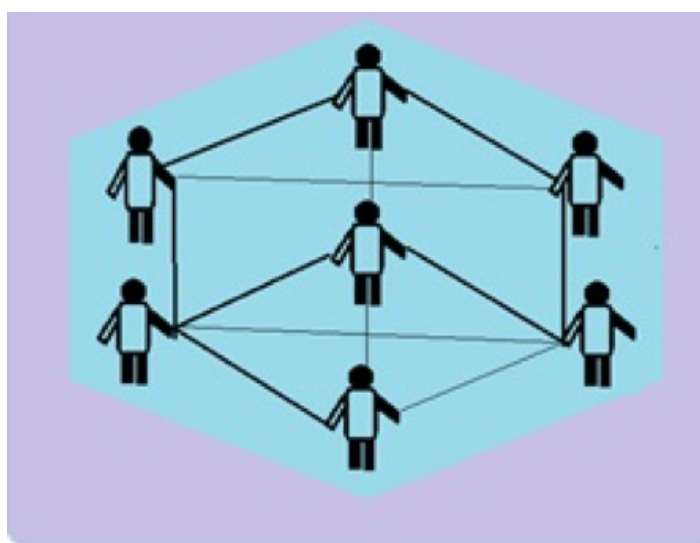
- Become savvy in social marketing and other campaigning approaches to move the political will and open the window of opportunity for us to have our desired changes in the institutes, laws, policies, practice and standards shaping our access to biologic medicines in our countries.

Laying the Foundations for good advocacy—the 12 Steps

Before you begin any campaign, you must lay a proper foundation within your alliances to ensure that you have the required knowledge, skills, attitudes and experience needed to advocate on biologic medicines. A good foundation for an advocacy campaign on biologic medicines has ten steps.

Step 1-Improve your alliances' health literacy on biologic medicines

Make sure your patients, partners, and publics (social marketing Ps) are health-literate, especially your health professional partners. Members of your alliance should know how to find, understand, analyse, appraise and, most importantly, apply biologic medicines related health information to your advocacy campaign.



You must have a balance of 'expert patients' (patient voice and patient perspectives) and other biotechnology and biopharmaceutical expertise on your alliance to be able to define and refine your problems issues for decision-makers, the media and your audiences.

Improving health-literacy needs you to create an enabling national environment to improve patient participation and engagement in health policy decision-making. The 2013 and 2018 biosimilar medicines tool kits have improved health-literacy on biologic medicines. Make sure your alliance accesses these.

Step 2 - Setting evidence-based SMART objectives

Before starting you advocacy campaign on biologic medicines, make sure that your alliance has set clear objectives that all members support. You need their commitment to support SMART objectives that are:

- Specific in detail. Defined and refined, and updated regularly
- Measurable over the inputs, outputs, outcomes and impact achieved
- Achievable and within your capacity, resources and timeframe. Ensure your alliance is able to handle the complexity of the issue and has the budgets to fund the programme adequately
- Relevant objectives that fit with the expectations of your patient community and to the evidence base on biologic medicines

- Timed in short, medium and long term deliveries

Most groups start with a general objective statement that we all want a non-discriminatory access to a sufficient quantity of quality, safe, accessible, acceptable and affordable biologic medicines by 2030.

However, you then need to drill down and develop a consensus as to what your advocacy campaign's SMART objectives are on the standards of availability, quality, safety, accessibility, acceptability and affordability by looking at the current issues faced by patients using biologic medicines.

In our 2018 Biologic Medicines Tool Kit, the Score Card has condensed some of the patient issues on the standards of availability, quality, safety, accessibility, acceptability and affordability of biologic medicines: In the same toolkit, the [FAQ Questions about Biosimilars: What Patients Should Ask Their Doctors](#) has brought to the front issues particularly affecting the practice of prescribing and dispensing biosimilar medicines.

The 2018 Toolkit has also highlighted some of the current global issues affecting specific areas of regulations and pharmacovigilance on biologic reference and biosimilar medicines.

2018 Tool Kit

Factsheet	Topic	Link
Biologic Medicines: Delivering on their potential for patients	An overview of current evidence base and best practice	https://bit.ly/2tqN-9MK
Fact sheet 2: Regulation of Biologics	Introduction to the regulation of originator biologic medicines	https://bit.ly/2Kil297
Fact sheet 3: Introduction to Biosimilars & Regulatory Requirements	Introduction to the regulation of biosimilar medicines	https://bit.ly/2K-jV9pd
Fact sheet 4: Biosimilars and the Importance of adherence to International Regulatory Standards	Regulating biosimilar medicines within cross border and global settings	https://bit.ly/2M-hmCsq
Fact sheet 5: Pharmacovigilance: Monitoring and Traceability across the System	The need for good pharmacovigilance systems and challenges faced	https://bit.ly/2Kh-BNBp

The WHO Expert Committee On Biological Standardization has produced the [Guidelines on evaluation of similar biotherapeutic products \(2009\)](#) and in its [annex 2](#) it has set out a systematic process for National Medicines Regulatory Authorities to use to authorise a biosimilar in their national market.

IAPO Fact Sheet 8 condenses this in: [Key Recommendations of the WHO Biosimilars Evaluation Guidelines](#)

Step 3 - Communicating your objectives

It is important that the patient advocates are thoroughly briefed about your advocacy objectives. You must develop a consensus and build support behind these objectives.

Before initiating any meetings with the Department of Health or Minister for Health, make sure you have accurately captured and agreed on all the issues and concerns affecting patients who are using biologic originators and the biosimilar medicines.

You must be able to speak with one voice. Discordant voices confuse policy makers and can reflect poorly on your alliance. The dissenting voices are an 'own goal' and may be used against you by the policy makers to deflect your arguments. The media is quick to pick this out. They like 'conflicting' views in their coverage. In judicial reviews, lawyers for the State always use the dissenting patients' voice as a counter position to neutralise the main patient voice.

Step 4 - Improve the quality of information available on biologic medicines

After improving health-literacy, the most common problems faced by patient advocates is a lack of access to quality health-related information that they can use to make informed-decisions.

Patient advocates must ensure that their alliances have access to accurate, relevant and timely information. We must ensure that we ALL have quality statistics on the availability, quality, safety, accessibility, acceptability and affordability of biologic medicines in our countries and regions.

A related problem to the access of quality information is the reliability of the information source. In countries with a 'democratic deficit', citizens and patients do not trust the government and authorities, even when they are being given quality information. In the Ebola crisis, this damaged the public health emergency efforts to control Ebola spread in West African countries.

Step 5 - Cultivating trusted sources of information

Your next task is that you must create a community of practice and build trust around the information and its sources on biologic medicines.

Poor media reporting and a lack of trust in information sources can overinflate the patients' perceptions on the health risks of innovative medicines and healthcare practice.

'Fake News' on healthcare is now a common phenomenon on the web and social media- it heightens our fear of the new. When patients do not trust the sources or the quality of the information, this then threatens early uptake and access to innovative treatment in many cases. Miscommunication by public authorities and the media must be challenged and set right.

Susanna Hertrich has produced colourful infographics using national data sets on various accidents and calamities to reveal that the public perceptions about the frequency and impact of an adverse event are far overinflated when compared to the actual real risk as revealed in the statistics.

You must work within a multi-stakeholder community of practice to test different sources of information and 'triangulate' their validity by cross checking with other partners. By cultivating good relationships with your information sources, you can get access quality data from academics and manufacturers leading on research and development of biologic medicines.

You must remember that the pharmaceutical company that has brought the originator biologic medicine to the market would have led a clinical trial for over ten years to test and develop the biologic medicine. They are the best source of information as they have undergone a rigorous regulatory approval process by providing all the necessary data to the regulators.

Most pharmaceutical companies will have a team responsible for putting together information on the biologic medicines not only for the regulators, but also for the patients. Establish a link with their patient affairs teams. The Working with Partners and Stakeholders Toolkit and the Advocacy Fieldbook share with you as to how you develop this trust and confidence in an alliance.

As an alliance, you must also lay the foundations to support patient participation within national health observatories and other data collection agencies to ensure transparency and accountability within national healthcare and medicines statistics. Link up with the World Health Organization in-country representatives. Their technical support is very useful when you don't have reliable national statistics and guidelines.

'Super Regulators' like the European Medicines Agency, US Food and Drugs Administration and Health Canada influence not only the European and North American countries, but also many other national medicines regulatory systems in Latin America and Asia. The EMA and FDA have a good track record in patient engagement and are excellent sources of accessible information on biologic medicines. Many Latin American countries are adopting Health Canada Regulations on biologic medicines. The African Medicines Agency is a new body looking after patients' interests in the 54 African Member Countries.

As a responsible alliance you must also have partners who can thoroughly vet new research findings. You have to be vigilant as even 'experts' can make mistakes. The Lancet, a reputable medical journal, published a 'peer-reviewed' paper that erroneously linked the innovative triple vaccine (measles, mumps and rubella) to autism in 1998; this paper caused panic in neo-natal care and a drop in the uptake of the MMR vaccine leading to serious and devastating measles outbreaks in unimmunised children later.

The European Patient Academy (EUPATI) developed a Patient Expert Training Course to improve 'research-literacy' amongst patient advocates to create that enabling environment for expert patients to engage with research and the medicines development process as co-creators and not just as subjects. EUPATI type of regional and national programmes are very useful in developing expert patient oversight and the quality of data in national healthcare statistics.

Step 6 - Dissemination: a 'one stop shop' on quality biologic medicines information

Having achieved access to quality information is half the battle. Dissemination of this information to your alliance is the full battle.

Having developed trusted sources and controlled the quality of information, you then need to control and improve the dissemination of this information to your patients, partners and publics. You must apply international information and health communication standards to ensure your information is accessible.

Your alliance needs to become a 'one stop shop' on everything related to biologic medicines and 'funnel' patient advocates to the relevant information in an effective and efficient manner using various formats and information architecture arrangement on the Web.

You can use the fast and easily accessible Social Media like Twitter and Facebook for urgent communication and Dropbox to share and collaborate on detailed information and content sharing. Your alliance must have partners who competent in the use of webinar portals like Google Hangouts, GoToAir, Skype and Webex to conduct capacity building training and face-to-face meetings.

Step 7 - Developing Effective Messages

Many patient advocates erroneously believe that in order to change something in the healthcare systems, you always need to produce lots of detail information on the clinical and therapeutically aspects of healthcare to move the Change Framework. You must remember that people with parents, siblings and children who are patients, or who may be patients themselves, head institutions and are the legislators, policy-makers, healthcare practice formulators and standards setters. They need simple messages and little convincing. Sometimes less is more in advocacy.

To the more savvy campaigners, health is still a political choice and it requires not only winning the battle of the minds, but also the war for the hearts of the decision-makers. To win the hearts you need brevity and creative messages that use slogans and straplines that match the message, medium and messenger to the target audience.

Your patient advocates' alliance must invite creative media and public relations communicators to help you translate the cold hard scientific facts into warm and heart touching messages that resonate with your different audiences.

Great advocacy campaigns have used humour, creative word play and striking images, infographics and drama to convey the main message of a campaign in the brief slogans, straplines and other communication.

'Clunk Click Every Time' was a very effective message in public health to reduce car crash injuries. 'Does exactly what it says on the tin' (Ronseal varnish) was another example from the commercial world, reassuring DIY home improvers.

Twitter has now encouraged new creativity as campaigners jostle for the best Hashtags # and try to compose effective Tweets in less than 280 characters. A good Hashtag and Tweet can do the job of large research report more effectively to move your Change Framework.

Many groups like the NCD Alliance use Branding as a tool. Branding sets you and your campaign apart from others. Your Brand radiates your 'unique selling position'. This requires you cleverly choosing logos and straplines, in addition to website domain names, twitter handles and Facebook pages that distil and condense your core Brand vision, values and mission.

Your audiences, partners and supporters should clearly know what they can expect from you and your Brand. A good Brand can be 'heard over the noise' created by other advocacy groups; policy makers take notice. Your policy issue can stand out amongst the general un-branded issues.

Many advocates have now started looking at Search Engine Optimisation to improve their messages. They develop messages with highly searched key words and terms to rank their issue high on the online searches. The powerful Google Search Engine and Google Scholar algorithms can connect your advocacy campaign to the right change makers in a timely and efficient manner.

Step 8 - The Reasonable Man and the intelligent 11 year old

Before any detailed advocacy campaign plan is drawn up, you must first decide who your audience (public) is. Many campaigns start by adopting the hypothetical 'reasonable man' (gender corrected to 'reasonable person') as first target.

The reasonable person is a fictional legal construction. This is the person on Clapham Omnibus (Joe Public) who will act in a reasonable and proportional manner based upon the information given to them. This person needs a reasonable level of detail in the information and facts presented to them. They will use their average cognitive skills to assess the information presented to them before making a rational decision.

Other campaigners use the 'Intelligent 11 year old' as their 'audience'. This adolescent requires simple but above average information to understand an issue. In your communications, your words and sentence construction should be simple. Use short sentences and small paragraphs. Use active voice and remember that: 'a sentence should contain no unnecessary words, a paragraph no unnecessary sentences' (William Strunk)

Step 9 - 20/80 Pareto and Rule of 10s

Good advocacy is efficient advocacy. It is a 'lean mean fighting machine'. The Pareto Principle emerged from an analysis of number of systems and arrangements. It states that 80% of the effects may be attributed to just 20% of the activities and interventions.

So within your Change Framework, only 20% of the institutions, laws, policies, practice guidelines and standards may bring about the 80% of the changes that you desire in biologic medicines affairs. Also, 20% of your Social Marketing mix may deliver 80% of the results. You need to map the high reach and impact interventions and partners within your advocacy environment and work with these first.

Rule of 10's states that sometimes there is stepped effect with each related intervention in multiple of 10s. For example if:

- A printed leaflet on biologic medicines impacts 1,000 patients
- A standard on a particular aspect of biologic medicines, eg substitution in a pharmacy, may impact 10,000 patients
- A policy guidance on switching sent to doctors may impact 100,000 patients
- Legislation on biologic medicines will impact 1,000,000 patients

Conversely, the amount of effort and resources needed is also commensurate with the Rule of 10s:

- A leaflet takes 1 week to research, discuss, write and print
- A standard would take 10 weeks-about 2 months
- A policy guidance 100 weeks- about 2 years
- Legislation 1000 weeks – about 20 years

Step 10 - Plan for the long-run and have a plan B ready

Pragmatic and effective patient advocate negotiators always come to the negotiation table with three positions.

You must open the negotiations with your first position and demand for the best standards on the availability, quality, safety, accessibility, acceptability and affordability of biologic medicines.

However, you must also have a back-stop position. These are the absolute minimum standards below which you will not go at all costs. This needs to be defended and fought over hard.

The third position is something that you craft and develop as you proceed with the negotiations.

The more savvy negotiators sometimes have a fourth position up their sleeve. They plan for the long run and are not deterred by set-backs. They try to get a 'holding' or an interim position agreed. They have a Plan B. This gives you the time and opportunity to come back to renegotiate. This allows you to make stepped progress towards the ideal standards.

Step 11 - Mapping the issues in your biologic originator and biosimilar medicines markets

One of the most challenging issues in patient advocacy is that of accurately mapping patient concerns and perspectives on what constitutes a non-discriminatory access to a sufficient quantity of quality, safe, accessible, acceptable and affordable biologic medicines within our national universal health coverage by 2030.

The Human Rights based approach to health has taken a step at defining the terms in right to health as:

- Availability: functioning public health and health care facilities, goods, services and programmes in sufficient quantity
- Accessibility: non-discrimination, physical accessibility, economic accessibility (affordability), information accessibility
- Acceptability: respectful of medical ethics and culturally appropriate, sensitive to age and gender
- Quality: scientifically and medically appropriate

We need to map patient concerns and perspectives in order define and refine the 'problem stream' accurately. We must use the best fit for purpose approach to help us map these concerns and perspectives and get them across to the decision-makers.

The legislators and policy-makers want high quality and accurate data. They need to be assured that your patient alliances have taken all steps have to remove any biases or distortions in the data collection. Many in healthcare will only accept the random probability sampling and face-to-face interviewing approaches in mapping patient concerns and perspectives. You need statisticians to advise you at the outset.

While you need to conduct your own national surveys to pinpoint your particular issues, there are some common patient questions and perspectives that have been shared in our 2018 Biologic Medicines Toolkit in the Score Card. This has condensed some of the patient issues on the standards of availability, quality, safety, accessibility, acceptability and affordability of biologic medicines.

In the same toolkit, the FAQ Questions about Biosimilars: What Patients Should Ask Their Doctors has brought to the front some other issues particularly affecting the practice of prescribing and dispensing biosimilar medicines.

Some patient advocates would like to raise concerns and put across patient perspectives to their NMRA as to why they have adopted or departed from the policy as recommended by the various biosimilar guidelines like:

- The WHO Expert Committee On Biological Standardization has produced the [Guidelines on evaluation of similar biotherapeutic products](#) (2009) and in the [annex 2](#) it has set out a systematic process for National Medicines Regulatory Authority to follow before they authorise a biosimilar in their national market

- [FDA Biosimilar guidance](#)
- [European Medicines Agency](#)

IAPO Fact sheet 8 condenses some of these in the: [Key Recommendations of the WHO Biosimilars Evaluation Guidelines](#)

You may look at things systematically in your national setting and frame them logically to aid a more robust and open discussion amongst your national patients and healthcare partners.

Framing Patient Concerns and Perspectives

Authorisation	Typical Patient Questions	
Reference Product Benchmark	<p>Against which biologic originator (the reference biologic) will the biosimilar entering the market be compared with to support authorisation?</p> <p>Has this been evaluated and authorised on the basis of a 'full dossier' in the EU or the USA Full Biologics Licence (Section 351 (a) Public Health Service Act)?</p>	<p>Quality and Safety</p> <p>Fact sheet 2: Regulation of Biologics</p> <p>Fact sheet 3: Introduction to Biosimilars & Regulatory Requirements</p> <p>Fact sheet 4: Biosimilars and the Importance of adherence to International Regulatory Standards</p>
Additional Clinical Trials	<p>What are the conditions and circumstances under which regulators need additional clinical trials data, and what should they show, to authorise a biosimilar?</p> <p>Will this is additional data requested be over and above the data already provided that compares the biosimilar to its reference biologic?</p> <p>What type of data is needed on pharmacokinetic, pharmacodynamics, efficacy, safety and immunogenicity?</p>	
Non-Clinical Trial Data	<p>What type of additional non-clinical data is needed? Is this is data over and above the existing requirements of non-clinical data comparing the biosimilar to its reference product?</p>	
Quality Assurance	<p>What data is needed on quality assurance and how will quality of the biosimilar be assessed and compared with the reference product?</p>	

Pharmacovigilance	Typical Patient Questions	
Naming	<p>What proprietary and non-proprietary names will be used to name the biosimilar?</p> <p>Is this naming distinct enough to ensure that the patient, physician and pharmacist can distinguish between the biosimilar and its reference biologic originator?</p> <p>Is this robust, sensitive and specific enough to be picked up by a national pharmacovigilance system?</p>	<p>Access, Acceptability, Quality and Safety</p> <p>Fact sheet 5: Pharmacovigilance: Monitoring and Traceability across the System</p>
Labelling (patient information and traceability)	<p>What patient information will appear on the label to indicate it is a biosimilar?</p> <p>What contraindications will be included to clarify usage when the reference biologic and/or other biosimilar products are being used together?</p> <p>What pharmacovigilance information will appear on the label?</p>	
Traceability, Post-marketing monitoring and safety-related systems	<p>How will the biosimilar and its reference biologic be monitored post-marketing of the biosimilar?</p> <p>In an adverse event, can the emergency and clinical care teams be able to respond correctly from the naming, labelling and other information provided with the products?</p> <p>Is the pharmacovigilance system robust, sensitive and specific enough to control adverse events?</p>	
Practice	Typical Patient Questions	
Switching, Substitution and the Interchangeability	<p>Which guidelines apply to switching and substitution (FDA interchangeability): European Medicines Agency, FDA, Health Canada and WHO?</p> <p>As health is still a sovereign matter and the EMA has left switching and substitution decisions with NMRAs, what policy conditions are set for biosimilar prescription and dispensing by the National Medicines Regulatory Authority?</p>	<p>Access, Acceptability, Quality and Safety</p>

<p>Off-Label Use and Extrapolation of indications</p> <p>Note: Increasingly biotherapeutics being used to treat cancers and autoimmune diseases show that they have an impact upon other inflammatory condition (eg CVD.) as with the case of bevacizumab on eye macular degeneration</p>	<p>Can NMRA's give a biosimilar authorisation for an additional indication already given to a reference biologic?</p> <p>What safety and efficacy data is needed to substantiate this? What happens if the biosimilar manufactures request authorisation for a new indication that has not been authorised for the reference biologic?</p> <p>What will the pharmacovigilance system then look like for off-label use?</p>	<p>Fact sheet 6: Talking to Patients About Biosimilars: Role of Health Professional</p> <p>FAQ Questions about Biosimilars: What Patients Should Ask Their Doctors</p>
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Step 12 - Universal health coverage

Achieving universal health coverage (UHC) by 2030 is one of targets of the Sustainable Development Goals 2030 that UN member States have adopted in 2015. UHC means that all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation, and palliative care.

Including biologic originator and biosimilar medicines into the essential medicines lists is very important for many patients with rare diseases and disorders who depend upon biotherapeutic treatments to remain healthy and get relief from the debilitating symptoms. For these patients further advances in genomic sciences promises final and effective cures.

These patients and their families also support UHC because they will receive the health services they need without suffering financial hardship. The treatments for rare diseases can be very expensive as the facilities, health professionals, equipment and medicines needed are highly specialised.

Concomitant with UHC is the human rights based approaches to healthcare that are being promoted by many State and non-State actors. [The Chilean Ricarte Soto Law](#) was one such advocacy approach that used human rights of patients with rare diseases to secure essential treatments.

Section 3

Getting going

Leveraging your Biologic Medicines' Change Framework

Most successful advocacy campaigns began with the advocates mapping their 'stakeholders'. This toolkit goes a little further and asks you to also map your Change Framework.

What impacts the current biologic medicines agenda and determining what is happening with regard to the availability, access, quality, safety and equity within the biologic medicines market?

Which institutions have the power to change the agenda, what legislation is being used to frame the rights patients and the obligations of the State and its public bodies and agencies? What is the official (and unofficial) policy at the Ministry of Health and its health agencies?

You then have to map the practice on the frontline in the clinics and hospital wards. What is the clinical, prescription writing and dispensing practice. This may be important with switching and substitution issues.

Which guidelines (issued by HTA and professional bodies) and codes of practice are in operation? Lastly, you map all the standards that are in place.

Mapping Institutions, Patients, Partnerships Patrons and Publics in Biologic Medicines Environment

Institutions	Patients and Partners	Patrons and Publics
<p>Executive Government President/Prime Minister and Cabinet of Ministers</p> <p>The Executive implements the laws, policies and standards set by the legislature (the parliament)</p> <p>It also regulates and controls other bodies through delegated legislation and regulations.</p> <p>Who is the health minister and who is in cabinet has a interest in health and pharmaceuticals?</p>	<p>Which patient groups and potential partners have an interest in biologic medicines and have access to the Executive?</p> <p>Which expert patients and partners have the experience and will add value to you alliance and advocacy campaign</p>	<p>Which patrons (personalities) and professional associations representing doctors, nurses and other health professionals are linked to biologic medicines and have access to the Executive</p>
<p>Parliament (The legislature)</p> <p>The legislature sets the laws, policies and standards in many healthcare issues. Which members of parliament are patients and/or are carers of patients.</p> <p>Who is in the All-Party health or biologic medicines group</p>	<p>Which patients and partners have parliamentary affairs experience and have worked with parliamentary committees and with All-Party Medicines and Health Groups and on Green and White papers. Who has seen through some health legislation from Bill to assent/enactment?</p>	<p>Ditto as above. Which patrons and publics have access to the parliamentary committees and All Party Groups</p> <p>Who was active in recent Green and White paper consultations, and seen through some health legislation enactment</p>
<p>Ministry of Health</p> <p>Who is the Minister, deputy minister and most senior civil servant (permanent secretary or director) at the Ministry?</p> <p>Under which department does the biologic medicines issue rest? Who are the technical officers and programme directors.</p> <p>Who are the staff and managers at the frontline?</p>	<p>You need members in your alliance who are professionals (biotherapeutic experts) or have very good health system insights. Expert patients and competent health professional partners are needed.</p> <p>The focus shifts to the Senior Civil Service. The target is not the Minister but the Permanent Secretary, Director-General and CEOs.</p> <p>Which patients and partners are competent enough and have experience in dealing with the senior policy and administration team at the Ministry of Health?</p>	<p>Ditto as above but now you need patrons and publics who are competent enough and have experience in dealing with the senior policy and administration team at the Ministry of Health?</p> <p>You need patrons and publics who understand public administration law and policy, they can undertake a judicial review</p>

Institutions	Patients and Partners	Patrons and Publics
<p>A National Health Authority</p> <p>Where universal health coverage has been created, the State may set-up a National Body to oversee it. The NHS Executive was an example in the UK.</p> <p>In some cases like Brazilian National Health System (SUS), it will be a Directorate in the Ministry of Health.</p> <p>These bodies are the operational part of the healthcare system and impact the implementation of all healthcare legislation and policy, in addition to managing clinical and therapeutically care</p>	<p>Ditto as above, but this time you need expert patients and partners who are well versed with healthcare systems and health economics.</p> <p>Patients and partners who have held management positions in the national health service are an asset.</p>	<p>Ditto as left, but high profile patrons and publics. In the UK Knighted ex-NHS executive and management staff are recruited by many large patient charities as patrons. Having an ex-NHS Sir or a Dame on your campaign adds weight.</p>
<p>National Medicines Regulatory Authorities (NMRA)</p> <p>They are set-up by law and have delegated powers to regulate all aspects of medicines from giving approval licences to the access local market and all post access issues.</p> <p>They impact quality, pharmacovigilance and access issues.</p> <p>Who is who in your NMRA?</p>	<p>Many NMRAs are now opening up and encouraging patient participation within national medicines regulation.</p> <p>But this is a very specialist and new area of development. The European Patients Academy (EUPATI) and EMA developed capacity building programme to upskill expert patients to engage in national medicines regulation.</p>	<p>Ditto as left. You will need patrons who are professionals like genomic scientists or biopharmaceutical experts. Your audience or publics will be the regulators and the communities like the physicians, pharmacists and even the pharmaceutical industry that interact with NMRAs.</p>
<p>Regional Medicines Regulatory Authority</p> <p>Ditto as above NMRA. However, the European Medicines Agency (EMA) and the African Medicines Agency (AMA) are regional regulators. EMA regulates for markets in 28 countries and AMA 54.</p> <p>Both EMA and AMA can impact national quality, pharmacovigilance and access issues.</p>	<p>The EMA and FDA have both extensive programmes to encourage patient and partner participation. The Patients' and Consumers Working Party (PCWP) at the EMA and the Patient Engagement Collaborative at the FDA are examples.</p> <p>But health is still a sovereign matter. While the FDA can approve interchangeable products, the EMA, however, has deferred the decision to allow the practice of switching and substitution between originator and biosimilars to the NMRA's</p>	<p>Ditto as above and left. You need patrons and publics who have access and credentials to address these bodies.</p> <p>Recruiting ex-NMRA chairs and staff to your alliance can be a very good strategy.</p> <p>The pharmaceutical industry can second some of their NMRA liaison teams to advise you.</p>
<p>Pharmaceutical Manufacturers Association.</p> <p>They represent the interest of the pharmaceutical manufacturers. The International Federation of Pharmaceutical Manufacturers (IFPMA) and Pharmaceutical Research and Manufacturers of America (PhRMA) impact global manufacturing standards and voluntary codes of practice.</p> <p>They can impact quality, pharmacovigilance and access issues.</p>	<p>You need expert patients and partners who have access to and experience of having worked international and national pharmaceutical manufacturers associations.</p> <p>IFPMA and PhRMA are now engaging patient organisations at various resolving global issues of access, quality, equity and pharmacovigilance.</p> <p>National PMAs are replicating this locally. They want expert patients and other partners to work with them to address common problems. Work closely with their teams to understand local biologic medicines manufacturing, regulation and distribution issues.</p>	<p>Ditto as above and left. You need patrons and publics who have access to and experience of having worked with the pharmaceutical manufacturers. Having ex-pharma management and staff</p>

Institutions	Patients and Partners	Patrons and Publics
<p>Medical Councils (Regulating Doctors and Nurses) and Professional Associations</p> <p>MCs are quasi-legal bodies. They are on one part concerned with improving medical practice, and on other, as medical regulators, they sit as court tribunal and hold hearings to strike-off doctors.</p> <p>Professional Associations have been set-up to grant degrees and qualifications, and advance training and representation of doctors, nurse tec.</p> <p>The impact clinical practice standards and ethics</p>	<p>This is a very specialist area and you need patients and partners who have access to and experience of having worked with MCs and Professional Associations-preferably you need patients who are doctors themselves.</p> <p>MCs also sit as malpractice tribunals and this function is often overseen by the judicial system in most countries; an appeal from an MC goes to the courts. MC decisions can impact the law and practice standards in healthcare.</p>	<p>Ditto as above and left. You need patrons and publics who are doctors and/or lawyers who have sat on MC tribunals.</p>
<p>Pharmacists' Authorities (PA)</p> <p>Ditto as Medical Councils, but regulating pharmacists.</p> <p>They impact pharmacy practice.</p> <p>NOTABLE: In biologic medicines the FDA's recommendation that an interchangeable product may be substituted for the reference product without the involvement of the prescriber will have guidelines to pharmacists from the Pharmacists' Authorities to support pharmacists.</p> <p>In the EU, there is no interchangeable category, but the switching and substitution issues is a NMRA issue and it too needs further guidelines to pharmacists from National Pharmacists' Authorities to support pharmacists.</p>	<p>Ditto as above. You need patient and partners who are pharmacists. The pharmacist authorities ensure pharmacists are fit to practice and follow national guidelines, policies and best practice.</p> <p>The PAs act as malpractice tribunal too.</p>	<p>Ditto as above and left. You need patrons and publics who are Pharmacists and/or lawyers who have sat on MC tribunals.</p>
<p>Health Technology Assessment Bodies</p> <p>In publically funded universal health coverages, the State has set-up HTA bodies like NICE (UK) and CONITEC (Brazil) to determine the cost effectiveness and availability of biologic medicines in the healthcare system. They are critical decision-makers on access to innovative medicines.</p>	<p>You need partners and expert patients like the EUPATI Fellows who are trained in the health economics to sit-in and make representations to the bodies during HTA public consultations and evaluation exercises.</p> <p>You need to articulate the patient voice and patient perspectives to ensure that patient outcomes that patients value most are incorporated.</p>	<p>Ditto as left. You need patrons and publics who are experts on HTA. Well-known health economists can add a lot of value to your alliance.</p>

Institutions	Patients and Partners	Patrons and Publics
<p>Health Ombudsman (HO) is a quasi-legal body set up by law in many In many publically funded healthcare systems.</p> <p>The HO is an independent body is set-up by law to manage patient complaints that have not been resolved by the Health Authorities, Ministry of Health and any other related government departments and public organisations.</p> <p>Ombudsmen use mediation to resolve individual patient issues. However, their greatest value is that they are empowered to identify systematic and systemic issues that result in poor healthcare and breaches of quality, patient safety and access.</p>	<p>Ditto as all above. You need expert patients and partners who can address the HO. You also need expert patients and partners who can act as amicus curiae (Friends to the Courts) and support the HO in undertaking specialist investigations.</p> <p>In many systems HO patients and healthcare providers are encouraged to use the HO and its mediation and alternative dispute resolution services to settle disputes to prevent expensive court litigation</p>	<p>Ditto as all above and left. You need patrons and publics who have access to and experience of working with HOs.</p>
<p>Consumer Protection Authorities</p> <p>In countries without a publically funded healthcare system and a large private healthcare providers sector, some countries have allowed healthcare issues be brought under consumer protection laws and regulations.</p>	<p>Ditto as above, but we now need consumer health experts. Some of these patients and partners will be commercial lawyers, others from consumer advisory agencies.</p> <p>We most definitely need experts who know how to undertake a claim in consumer courts. Many law firms offer Pro Bono support to patient groups. Having them as partners is vital.</p>	<p>Ditto as left, but we now need retired consumer court judges and consumer champions. Many TV stations and journalist now thrive as consumer champions.</p>
<p>The Judiciary</p> <p>The consumer courts, health tribunals, high courts and the Supreme Courts are the last resort for many patient advocates to seek redress.</p> <p>The courts can deal with civil matters, like clinical injury and adverse events, or with public law matters in a judicial review to decide if a State law, policy and practice is legal and constitutional, and implemented lawfully to the standards stipulated.</p>	<p>The ‘nuclear button’ in patient advocacy is a strategic litigation. A patient organisation that has a locus standi (the right to bring an action) and the patient can bring an action against the State. Very often the Supreme Courts in many countries have helped advance the law and healthcare policy for millions.</p> <p>You need patients and partners who have a legal background and know the judicial system well</p>	<p>Ditto as left and above. You need patrons and publics within the judiciary.</p> <p>Ex-Supreme Court judges who are patients make excellent patrons. The have the respect of their peers in the courts and the patient community. Their impartiality and sobriety is valued by all.</p>

Mapping Legislation, Policy Instruments, Practice Guidelines and Standards

In many countries, the State will use a framework of legislation, policy instruments, practice guidelines and standards to ensure patients can have a non-discriminatory access to a sufficient quantity of quality, safe, accessible, acceptable and affordable biologic medicines.

The Legislature (parliament, Congress etc) may provide a granular oversight through primary legislation first and then give powers to others to fill in the details in the secondary delegated legislation and regulations. Detail is normally provided by the Ministry of Health in consultation patient organisations, professional associations representing doctors, pharmacists and other health professionals. These specialist bodies will provide the policy, practice guidelines and standards.

Patient advocates must know how to use this framework and process. You must know the strengths and weakness of using legislation, policy, practice guidelines and standards to change the biologic medicines market and clinical practice.

Many believe that using legislation to change medical practice is not right. Doctors and lawyers do not make good 'bedfellows'. The lawyer should not interfere with medicine, and the doctor should not indulge in the law.

Clinical practice should always have the best interests of the patient at heart and should always reflect the current research evidence base and best practice. It is a tradition that most changes in clinical practice have been done using lower tier policy instruments like clinical guidelines and protocols.

But some advocates maintain that legislation is a very powerful change agent that can change national clinical practice quickly and system wide. Legislation impacts the whole country and all parts of its health system. All the health institutions and professionals must be compliant as it is the law.

It is important that any legislation enacted on biologic medicines should follow the evidence-base and best practice as developed by the various national clinical research institutions and regulators. If you do not have this, you can advocate using the evidence provided by the World Health Organization and its technical teams.

The WHO Expert Committee on Biological Standardization has produced the [Guidelines on evaluation of similar biotherapeutic products](#) (2009) and in the [annex 2](#) set out a systematic process for National Medicines Regulatory Authority to follow before authorising a biosimilar in their national market

	Legislation	Policy Instruments	Guidelines and Standards
State	<p>What is the constitutional provision on access to innovative medicines?</p> <p>Is there any International Treaty (eg EU or WTO TRIPPS) affecting access to biologic medicines?</p> <p>What is the national health-related primary legislation? Which primary legislation impacts biologic medicines?</p>	<p>Is there an official or unofficial policy in operation regarding access to biologic medicines?</p> <p>Is the country favouring national manufacturers in their national medicines procurement?</p> <p>In publicly funded health systems, is their medicines policy requiring the prescription of generics over branded medicines. Does this apply in biologic medicines also?</p> <p>Has the State joined a regional economic body- EU, African Union and UNSUR (Latin America)</p>	<p>What secondary legislation and regulations impact national guidelines</p>

	Legislation	Policy Instruments	Guidelines and Standards
Department of Health	What primary and secondary legislation defines the powers, obligations and role of the Department of Health in the access to biologic medicines?	Has the Dept. of Health issued any White Papers and policy guidelines? Has the Dept. of Health any policy on Health Technology Assessments (HTA) of biologic medicines? Has the Dept. of Health referred any biologic medicines issues for HTA?	What clinical guidelines and protocols has the Dept. of Health issued on biologic medicines? Has the HTA Body issued any guidance? Has it refused any application? What Standards apply? Who has issued them?
Healthcare Providers	What primary and secondary legislation defines the powers, obligations and role of healthcare providers in the access to biologic medicines?	What policy is being applied in the healthcare settings? Are there any recommendations and guidelines?	What clinical guidelines and protocols have the healthcare providers on biologic medicines? What standards apply?
Regulatory Agencies (Includes National Medicines Regulatory Agencies and other Healthcare regulators)	What primary and secondary legislation defines the powers, obligations and role of Regulators in the authorisation of biologic medicines?	Is there an official policy that they follow? How is this influenced by the policies of the larger regulators like EMA, FDA and Health Canada. Is WHO policy and guidance applied?	What guidelines and standards have the Regulatory Agencies issued on biologic medicines
Health Ombudsman	What primary and secondary legislation defines the powers, obligations and role of the Health Ombudsmen (HO)? Has the HO undertaken any hearings on biologic medicines?	Has the HO issued any policy recommendations on biologic medicines?	What guidelines and standards have the HO issued on biologic medicines
Physicians	What primary and secondary legislation defines the powers, obligations and role of the Physicians in prescribing medicines? What specific statutory instruments and other secondary legislation apply to the prescription of biologic medicines?	Keeping aside the issues of the 'best interest' of the patient and the 'doctor-patient relationship', what policy applies directly to the prescription of biologic medicines? Particularly focus on what policy applies to the prescribing of generics and biosimilar medicines? What is the policy on switching?	Has the Department of Health Medical Councils and various Professional Bodies issued guidelines on biologic medicines prescription? Are these guidelines consistent with WHO, EMA, FDA, Health Canada and other guidance? What is the guidance and standards on switching?
Pharmacists	What primary and secondary legislation defines the powers, obligations and role of the pharmacists in fulfilling prescriptions? What specific statutory instruments and other secondary legislation apply to the fulfilment of biologic medicines prescriptions?	What policy applies directly to the fulfilment of prescription on biologic medicines? Particularly focus on what policy applies to the fulfilment of prescriptions on generics and biosimilar medicines? What is the policy on substitution?	Has the Department of Health, Pharmacists Regulatory Councils and issued guidelines on biologic medicines prescription? Are these guidelines consistent with WHO, EMA, FDA, Health Canada and other guidance on prescription fulfilment practice on biologics?

Conclusion

Patient advocacy on biologic medicines needs not only to be evidence-based, but it also needs to be creative to affect the Change Framework.

You need to use the Social Marketing Approach to brand your advocacy and make it into an art form to reach the key decision-makers.

It is essential that you work across the three Kingdom areas of the Problem Stream, Policy Stream and the Political Stream simultaneously to open the Window of Opportunity.

Your advocacy alliances must have a range of partners with a mixture of knowledge, experience, skills and resources. You must be able to work on the whole Policy Instrument Grid. You should be able to handle patient registers and nomenclature as easily as dealing with legislation, policy, practice and standards affecting biologic medicines nationally.

Lastly do not forget the Power Constellations. Health is still a political choice, and politics is a continuous struggle for power among competing interests in your countries. Your alliance must be robust and resilient and be able to deal with this.

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