

FINAL REPORT

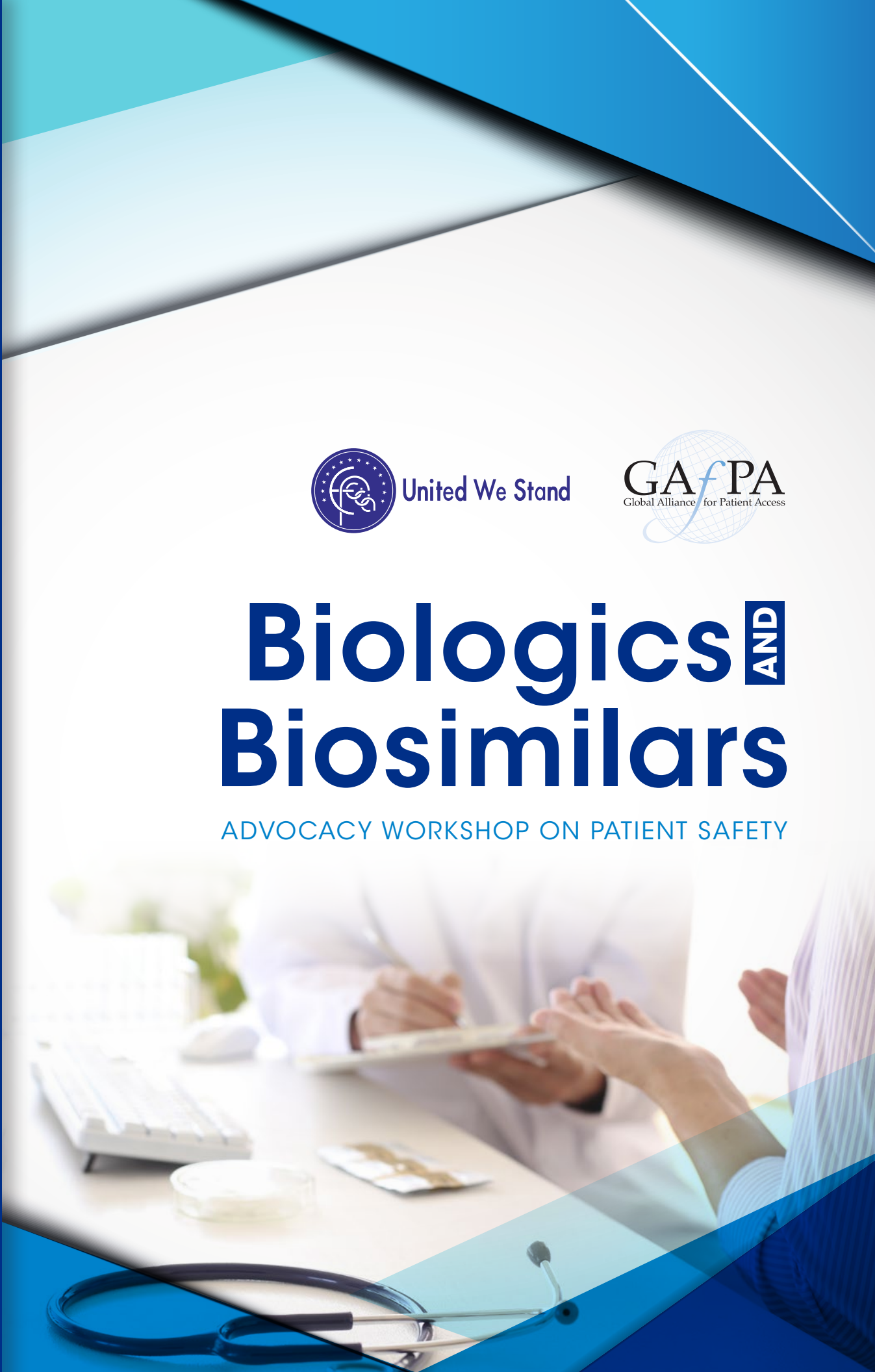


United We Stand



# Biologics **AND** Biosimilars

ADVOCACY WORKSHOP ON PATIENT SAFETY



# I N T R O D U C T I O N

Patient safety is a very important subject for the European Crohn's and Ulcerative Colitis Associations (EFCCA) and the Global Alliance for Patient Access (GAfPA), and lies at the core of our work. Within this framework EFCCA, together with GAfPA, organised an advocacy workshop on patient safety, which took place in Barcelona from 4-6 February 2016. The summit was attended by 60 advocates from 34 different organisations stemming from 27 different countries, representing patients with a variety of medical conditions including rheumatic disease, inflammatory bowel disease, psoriatic disease and hemophilia.



The main goals of the workshop were to create greater awareness amongst patient communities regarding the issues impacting access to biologic and biosimilar treatments and therefore to provide or improve basic understanding of the science and issues associated with biological medicines and biosimilars. Secondly, the workshop provided practical training on how to employ effective advocacy and communication strategies with the goal of raising awareness and understanding amongst key policy makers.



## BIOLOGICS AND BIOSIMILARS

It is the belief of GAfPA and EFCCA - and indeed the majority of patient group representatives at the Barcelona summit - that more education is needed around biosimilar medicines in order to ensure high levels of patient safety. **To put these concerns into context it is worth explaining the background of biologic and biosimilar medicines.**

Biological medicines are medicines that have been developed in living organisms. Unlike conventional (small molecule) medicines that are **made** by following a chemical formula, biologics are very large, complex molecules that are **grown** in living cells.<sup>i</sup> It's important to remember that biological medicines can **never** be exactly duplicated by two different manufacturers in the way that small molecules can because biosimilars are products that are 'highly similar' to - **but not exact copies of** - a biological medicine (which is often known as the 'reference' or 'originator' medicine).<sup>ii</sup> **As such, biosimilars cannot be automatically presumed to be an equivalent therapy.**<sup>iiiiv</sup> This matters because the differences that might exist between biosimilars and their reference products could range from the way they are built, the way they work, or the way they interact in our bodies. Because of these differences biosimilars must prove themselves to be clinically comparable in terms of quality, safety and efficiency data.<sup>v</sup>

## SWITCHING FROM ONE MEDICINE TO ANOTHER

The issue of 'switching' or 'substitution' of biologic and biosimilar medicines was raised at the Barcelona conference. There are three different types of 'switching' when it comes to biologics and biosimilars:

- Switching is a decision by the treating physician to change medication, usually because of efficacy or safety issue(s).
- Medical switching describes a physician's usual way to try to optimise treatment benefits when there is a clinical need.
- Non-medical switching is not driven by clinical need but by economic needs and procurement policies. The subsequent medicine is typically introduced in stable patients and patients who have been switched under those conditions may experience multiple switches, from and to other medicines.<sup>vi</sup>

The delegates at the Barcelona conference were concerned that in some countries, patients were being switched from one medicine to another (ie from a biologic to a biosimilar medicine) without being informed by healthcare professionals. The conference also heard that in some hospitals, biologic medicines were being 'substituted' for biosimilar medicines, without even the healthcare professionals being informed. When medicines are swapped without the prescribing physician's involvement, this is known as 'automatic' or 'involuntary' substitution.<sup>vii</sup> Many countries prohibit automatic substitution of biologic medicines due to concern for patient safety and physician freedom of prescription.<sup>viii, ix</sup> **Automatic substitution** could also make it harder to trace safety problems.

At present, limited evidence is available regarding the practice of switching between biologics, including biosimilars. Many professionals agree, however, that switching from an original biologic to a biosimilar, or vice versa, should always require both patient and physician consent.<sup>x, xi</sup> This is echoed by the European Medicines Agency (EMA) which states, **'for questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist.'**

### TRACEABILITY

Switching between biologic and biosimilar medicines raises another important safety concern – that of the traceability of a drug. Delegates at the Barcelona conference were in agreement that it is important to be able to trace back an administered drug in case there were adverse effects.

Traceability is the ability to **track and trace** medicines, including biosimilars, from the patient back to the manufacturer.<sup>xii</sup> This is important because adverse reactions may not be detected during clinical trials, therefore once the medicines are available to patients, drug regulatory authorities need to track and assess all unexpected reactions to ensure the long-term safety of a medicine. This monitoring process is known as **pharmacovigilance**.<sup>xiii</sup>



## EU POLICY AND REGULATORY ENVIRONMENT

### How many biosimilars are on the market?

The first biosimilars received their marketing authorisation from the European Commission in 2006. In 2015, 12 biosimilar molecules, marketed under 19 different brands, were being used by patients across Europe.<sup>xix</sup> In January 2016, the first etanercept biosimilar was approved for use in Europe, taking the total number of biosimilars being used in Europe to 20.<sup>xx</sup>

### How biosimilars are approved?

Biosimilars, like all biological medicines, must be approved centrally at European Union (EU) level. Marketing authorisations are granted by the European Medicines Agency (EMA), which carries out a robust comparison to make sure that the biosimilar medicine does not differ in terms of quality, safety and efficacy from the originator biologic medicine.<sup>xix</sup>

### How do European policies differ on biosimilars?

In Europe, the EMA does not have the remit to determine interchangeability of biologic and biosimilar medicines, leaving the decision to each country. At present, decisions taken as to the uptake and use of biosimilar medicines differs greatly among the 28 EU member state countries.



## PATIENT PERSPECTIVE: CASE STORY

During the two-day conference, a number of patient associations' representatives gave first-hand experiences of issues involving biologics and biosimilars in their respective countries.

### Alejandro Samhan Arias

One of these patient representatives was *Alejandro Samhan Arias* from the organisation Asociación de Enfermos de Crohn y Colitis Ulcerosa (ACCU). Alejandro highlighted that Spain is subject to great variability - in some regions 20% of patients are treated with biosimilars while in other regions it is 100%. However, some regions do not use them at all. Spanish law states that patients cannot be switched between biologic medicines without the physician's consent, but the workshop heard that this national regulation is regularly ignored. The workshop also heard that some hospital boards are creating steering committees that make the decisions on substitution. However, some pharmacists are doing automatic substitution of their own accord - not telling the patient, and in some cases, not even telling the physician. The summit heard anecdotally that in some cases patients have been switched without their consent. They were then denied access to the previous biologic they were being treated with before the biosimilar.



## EXTRAPOLATION AND THE PHYSICIAN PERSPECTIVE

Patient group representatives also raised concerns around the issue of extrapolation - this is when results from clinical trials for one disease group are applied to another disease group. **David Charles, MD**, of GAfPA gave a presentation to the conference in which he emphasised his view that there should be clinical trials in each of the disease groups in order to show the safety and efficacy of a medicine and also its potential side effects. He said that in his view, clinicians should have as many treatment options as possible and should be able to choose, along with their patient, the right option for them.

Another key speaker at the conference was **Professor Julian Panes**, Head of the Department of Gastroenterology at the Hospital Clinic in Barcelona. Professor Panes also made the point that once a biosimilar is proven to be highly similar in one indication, it may not be tested for efficacy in other indications. While he admitted that this extrapolation was controversial, Professor Panes said that the safety profiles were very similar in originator and biosimilar products. Professor Panes advocated the view that switching is safe - provided there is always informed consent from the patient, and provided that the decision always lies with the physician, not the pharmacist. However, Professor Panes was clear that health systems need to be vigilant going forward and should keep registries to record any problems with biosimilar medicines. In his view, worldwide pharmacovigilance is needed to detect any safety or loss of efficacy signal. Both Professor Panes and Dr Charles concurred on the point that it is incredibly important that pharmacists use the brand name of biosimilar medicines as well as the batch number to track adverse events and argued that traceability must start with the pharmacist.

## THE LEGAL SCENARIO

The scientific programme also included a presentation from the EFCCA chairman, Marco Greco, about his role as patient representative at the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC). PRAC is responsible for assessing and monitoring safety issues for human medicines and includes all aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audits. Patient representatives are an integral part of PRAC and key to achieving greater inclusiveness of European drug safety systems. Their role is to ensure that patient needs as a whole are taken into account in the deliberations of the committee. The patient representatives ensure also that communication on individual medicinal products consider specific patient requirements such as health literacy. They are bridging the gap between the statistical reality of the regulatory system and the personalised reality of clinical practice.



## BIOLOGICS AND BIOSIMILARS (BAB) SURVEY

1184  
RESPONSES

Carried out by EFCCA under the scientific coordination of Professor Laurent Peyrin-Biroulet (Department of Hepato-Gastroenterology CHU in Nancy, France). The survey aimed to assess patients' knowledge about biosimilar medicines and gathered 1184 responses.

**62%**  
HAD NEVER  
HEARD OF  
BIOSIMILARS

**62% of respondents had never heard of biosimilars – this was 'shocking' according to the author, Sanna Lönnfors. Of the 440 who had heard of biosimilars:**

**44%**

**44%** of respondents said they would want to know which medicine they were receiving (biologic vs biosimilar)

**47%**

The majority of respondents – **47%** – were concerned about their safety profile, **41%** their efficacy, **35%** about their molecular basis, **31%** worried about tolerability and **25%** had no concerns

**55%**

**55%** wanted extrapolation data and wanted to wait for IBD-specific data

**Interchangeability:** **28%** said this was acceptable if the treating physician approves it, **27%** said it was acceptable if evidence-based data is available and **22%** said it was acceptable if the patient is systematically informed

**56%**

**56%** said lower cost should not come before the efficacy or safety/tolerance of medicines

### KEY FINDING

Patients need more information so they can be better involved in decision-making about biosimilars.

## PATIENT GROUP PERSPECTIVE

A number of European patient groups have issued position statements on the use of biosimilar medicines.

These include:

### The European Crohn's and Colitis Organisation (ECCO)

ECCO's position statement on biosimilars defines the collective view of European specialists in inflammatory bowel disease (IBD). It states that the principal driver of decisions should, in all cases, be sound scientific evidence and a 'patient first' approach. ECCO continues by stating that direct evidence of safety and benefit from clinical trials in IBD, post-marketing pharmacovigilance, and unequivocal identification of the product as a biosimilar should be requirements before approval. Switching from an established biologic to a biosimilar to save costs is likely to be as inappropriate and ineffective as switching between current biologics that act on the same target, except when there is loss of response.

The position paper also outlines eight guiding principles which should guide decisions regarding therapeutic equivalence and interchangeability in the case of biosimilars in IBD. These include that post-marketing collection of data in both children and adults is necessary to confirm safety by recording less common but important potential adverse effects, as well as identifying any increase in frequency of predictable adverse events contingent on wider access to treatment. Most importantly, that any decision to substitute a product should only be made with the prescribing health care provider's specific approval and patient's knowledge.<sup>xx</sup>

### The European League Against Rheumatism Standing Committee of People with Arthritis and Rheumatism (EULAR: PARE)

EULAR: PARE argues that as for all medicines, patients need to be able to make fully informed decisions about whether to take a biologic or biosimilar. Codes of practice on the use of biosimilars are urgently needed and should be to be written in lay language, and drawn up with the involvement of patients.

A number of key areas for patients to consider when presented with biosimilars are identified and include variability, safety and availability. EULAR: PARE explains that pharmacovigilance is needed to enhance patient care and patient safety, and to provide reliable, balanced information for the effective assessment of the risk-benefit profile of medicines. Patients therefore need to know how to access this information and how, to whom, and by whom suspected adverse effects are reported.

EULAR: PARE warns that many patients consider that changing from a reference product to a biosimilar would introduce unacceptable uncertainties. Furthermore, it notes that the EMA makes no recommendations on whether a biosimilar should be used interchangeably with its reference medicine.<sup>xxi</sup> So there is no certainty that it will not take place.<sup>xxii</sup>

## ENSURING PHARMACOVIGILANCE

All biologics and biosimilars need to be carefully tracked and safety should be closely monitored through a process called 'pharmacovigilance'. Because of the complexity of the manufacturing process, EU legislation on pharmacovigilance has identified biologics and biosimilars as priorities for additional monitoring.<sup>xiv</sup> Medicines under additional monitoring have a black inverted triangle (▼) in their labelling. This triangle highlights it is a new product and encourages both prescribers and patients to report suspected adverse drug reactions (ADR).<sup>xv</sup> Under EU pharmacovigilance law, anyone reporting a suspected adverse drug reaction is asked to provide the brand name and specific batch number of the biologic medicine to ensure traceability.<sup>xvi</sup>



## COMMON AREAS OF CONCERN AMONG CONFERENCE ATTENDEES

- Switching
- Traceability
- Extrapolation
- Access To Innovative Medicines





## THE CONFERENCE CAME TO THESE CONCLUSIONS:

- There is a **need for strong collaboration amongst the patient community**: some delegates represented disease groups with very limited resource and low visibility. In order to maximise patient advocacy, it was essential that all disease groups gathered around common objectives in order to have a louder voice and high visibility in particular with policy and decision makers.
- There is a **clear need for the participation** of patients in decision-making. One group came up with this great message “no decision about me without me.”
- Referring to the issue of **switching**, it is **essential to communicate with all relevant stakeholders** (dispensing pharmacist, prescribing physician and patient) in order to optimize the outcome of the patient’s treatment.
- **Need for informing patients** to empower them to be involved in the decision making and management of their conditions.
- Finally, it is clear that patients **want to be informed about biosimilars and be aware of what they are being treated with.**

The workshop represented a further step towards a stronger coalition where the exchange of good practices and mutual learning are the concrete sign of the importance of international networking and commitment.

EFCCA and GAfPA continue to work together to raise awareness around the important issues of patient safety and accurate information, as well as educating and empowering patient groups. A number of future activities are currently in the pipeline and we look forward to sharing those with you in due course.

## REFERENCES

- i Sekhon BP, Saluja V. Biosimilars: an overview. *Biosimilars*. 2011;1:1-11
- ii Understanding biological & biosimilar medicines, Frequently Asked Questions, The Association of the British Pharmaceutical Industry. Available at: [http://www.abpi.org.uk/our-work/library/medical-disease/Documents/understanding\\_biological\\_biosimilar\\_medicines.pdf](http://www.abpi.org.uk/our-work/library/medical-disease/Documents/understanding_biological_biosimilar_medicines.pdf) Accessed January 13 2016
- iii Kumar R, Singh J. Biosimilar drugs: current status. *Int J App Basic Med Res*. 2014; 4:63-66.
- iv Choy E, Jacobs IA. Biosimilar safety considerations in clinical practice. *Semin Oncol*. 2014;41 (suppl1): S3-S14
- v Understanding biological & biosimilar medicines, Frequently Asked Questions, The Association of the British Pharmaceutical Industry. Available at: [http://www.abpi.org.uk/our-work/library/medical-disease/Documents/understanding\\_biological\\_biosimilar\\_medicines.pdf](http://www.abpi.org.uk/our-work/library/medical-disease/Documents/understanding_biological_biosimilar_medicines.pdf) Accessed January 13 2016
- vi AbbVie Understanding Biosimilars
- vii AbbVie Understanding Biosimilars
- viii Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol*. 2008;19:411-419.
- ix Cornes, P. The economic pressure for biosimilar drug use in cancer medicines. *Targ Oncol*. 2012;7 (suppl1):S57-S67
- x American Society of Clinical Oncology. Policy brief on biosimilars. 2007. Available at [http://www.asco.org/sites/www.asco.org/files/2013\\_biosimilars\\_0.pdf](http://www.asco.org/sites/www.asco.org/files/2013_biosimilars_0.pdf). Accessed January 13 2016
- xi American College of Rheumatology. Position statement on biosimilars. 2011. Available here <http://www.rheumatology.org/Portals/0/Files/Biosimilars.pdf>. Accessed January 13 2016.
- xii Casadevall N. Pharmacovigilance and biosimilars: considerations, needs and challenges. *Expert Opin Biol Ther*, July 2013. Available here: <http://www.ncbi.nlm.nih.gov/pubmed/23527621> Accessed 29.02.2016
- xiii The EU Pharmacovigilance system, EU Commission website. Available [http://ec.europa.eu/health/human-use/pharmacovigilance/index\\_en.htm](http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm). Accessed 29.02.2016
- xiv <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF>
- xv <https://www.england.nhs.uk/wp-content/uploads/2015/09/biosimilar-guide.pdf>
- xvi Guideline on similar biological medicinal products, European Medicines Agency. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/10/WC500176768.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf). Accessed January 13 2016.
- xvii What is a biosimilar medicine? NHS England, 2015. Available at: <https://www.england.nhs.uk/wp-content/uploads/2015/09/biosimilar-guide.pdf>. Accessed January 13 2016.
- xviii [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter%20keywords&searchType=name&alreadyLoaded=true&status=Authorised&jsenabled=false&searchGenericType=biosimilars&orderBy=name&pageNo=1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter%20keywords&searchType=name&alreadyLoaded=true&status=Authorised&jsenabled=false&searchGenericType=biosimilars&orderBy=name&pageNo=1)
- xix Understanding biological & biosimilar medicines, Frequently Asked Questions, The Association of the British Pharmaceutical Industry. Available at: [http://www.abpi.org.uk/our-work/library/medical-disease/Documents/understanding\\_biological\\_biosimilar\\_medicines.pdf](http://www.abpi.org.uk/our-work/library/medical-disease/Documents/understanding_biological_biosimilar_medicines.pdf). Accessed January 13 2016.
- xx <http://www.ncbi.nlm.nih.gov/pubmed/23623738>
- xxi [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/10/WC500176768.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf)
- xxii [http://www.eular.org/myUploadData/files/Biosimilars\\_2015.pdf](http://www.eular.org/myUploadData/files/Biosimilars_2015.pdf)



**United We Stand**

**The European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA)** is an umbrella organisation representing 29 national patients' associations from 28 European countries and 3 associate members from outside Europe. EFCCA aims to work to improve life for people with IBD and give them a louder voice and higher visibility across Europe and beyond.

[www.efcca.org](http://www.efcca.org)



**The Global Alliance for Patient Access (GAfPA)** is a network of physicians and patient advocates with the shared mission of promoting health policy that ensures patient access to appropriate clinical care and approved therapies. GAfPA accomplishes this mission through educating physicians and patients on health policy issues and developing education material and advocacy initiatives to promote informed policymaking.

[www.gafpa.org](http://www.gafpa.org)