Lifescience Dynamics
Decision support

P30: Potential Impacts of the New MHRA Policy for Biosimilar Approval for the Industry and Patients

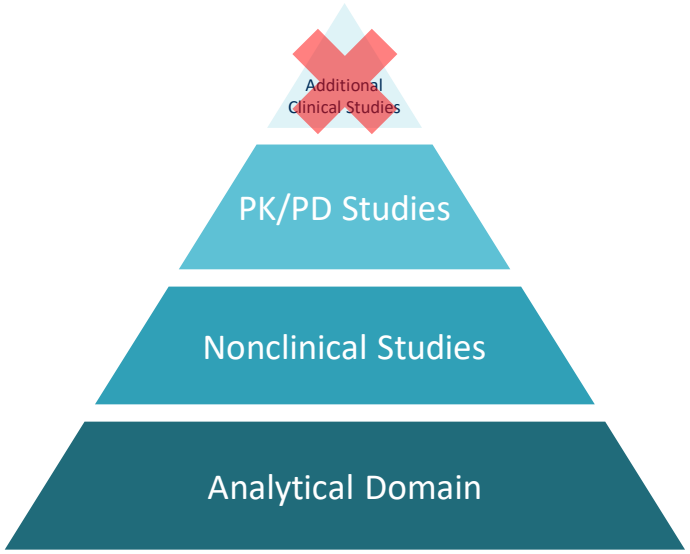
ISPOR
Improving healthcare decisions

Andreia Ribeiro, PhD; **Ndrit Mulaku**, MSc;
Ken Walsh, MSC

Date: **22 November 2021**

The views, thoughts, and opinions expressed in this presentation are the personal views of the presenters and may not be understood or quoted as being made on behalf of or reflecting the position of the presenter's employer, organization, committee or other group with which the authors are affiliated.

In May 2021, the MHRA has discontinued the requirement for biosimilars to undergo confirmatory efficacy trials as a licensing condition



- Faster and cheaper development process
- Earlier access to biosimilars
- Increased savings to UK's healthcare system

Policy change received with praise by the biosimilars industry

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Positive milestone

Home | About us + | Members + | Committees + | Annual Conferenc

IGBA Applauds UK MHRA Biosimilar Guidance Revision: Science-driven Evolution for Sustainable Access to Biologics (May 2021)

EPR EUROPEAN PHARMACEUTICAL REVIEW

Innovative

ARTICLE

New regulatory guidance could lead to UK biosimilar boom

New guidance on the licensing of biosimilar products that reduces unnecessary clinical trials is expected to put the UK ahead of Europe and facilitate a boom in these essential life-saving medicines, creating greater patient access and saving the National Health Service (NHS) hundreds of millions of pounds. It could also make biosimilars available for a broader range of less

https://www.europeanpharmaceuticalreview.com/article/157326/new-regulatory-guidance-could-lead-to-uk-biosimilar-boom/2/
https://www.igbamedicines.org/news/139-igba-applauds-uk-mhra-biosimilar-guidance-revision-science-driven-evolution-for-sustainable-access-to-biologics-may-2021

The EMA and FDA have approved biosimilars of (peg)filgrastim without comparative Phase 3 trials, paving the way for a potential paradigm change

The EMA and FDA do not explicitly state a Phase 3 trial is required for biosimilar approval, and have approved 2-3 biosimilars of (peg)filgrastim based on their strong chemical characterization demonstrating comparable PK, PD and immunogenicity profiles to the reference product

*"As a scientific matter, FDA expects a sponsor to conduct **comparative human PK and PD studies (if there is a relevant PD measure(s)) and a clinical immunogenicity assessment**. In certain cases, the results of these studies may **provide adequate clinical data to support a conclusion that there are no clinically meaningful differences** between the proposed biosimilar product and the reference product. However, **if residual uncertainty about biosimilarity remains after conducting these studies, an additional comparative clinical study or studies would be needed** to further evaluate whether there are clinically meaningful differences between the two products."*

-FDA biosimilar guidance

*"In **specific circumstances, a confirmatory clinical trial may not be necessary**. This requires that **similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD** profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern. It is recommended to **discuss such simplified approaches with Regulatory Authorities**."*

-EMA biosimilar guidance

UDENYCA® pegfilgrastim-cbqv

INJECTION Nyvepria™ pegfilgrastim-apgf

INJECTION Nivestym® filgrastim-aafi Pfizer

The industry has been debating the value and need of the confirmatory Phase 3 trials in biosimilar development, with an emerging view of demonstrating comparable PK as the critical step in successful biosimilar development. However, will a simplified approach be accepted for all biosimilars alike?

Current Opinion | Published: 26 June 2018

The End of Phase 3 Clinical Trials in Biosimilars Development?

Pharmaceutics. 2021 Jan; 13(1): 48. PMCID: PMC7824407
Published online 2020 Dec 31. doi: 10.3390/pharmaceutics13010048 PMID: 33396369

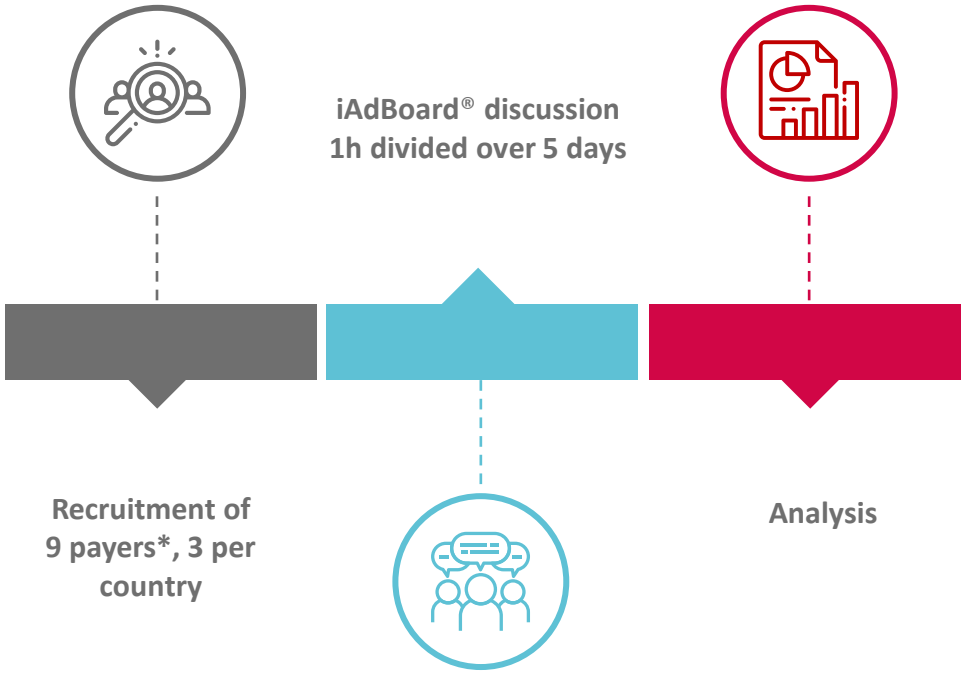
The Biosimilar Landscape: An Overview of Regulatory Approvals by the EMA and FDA

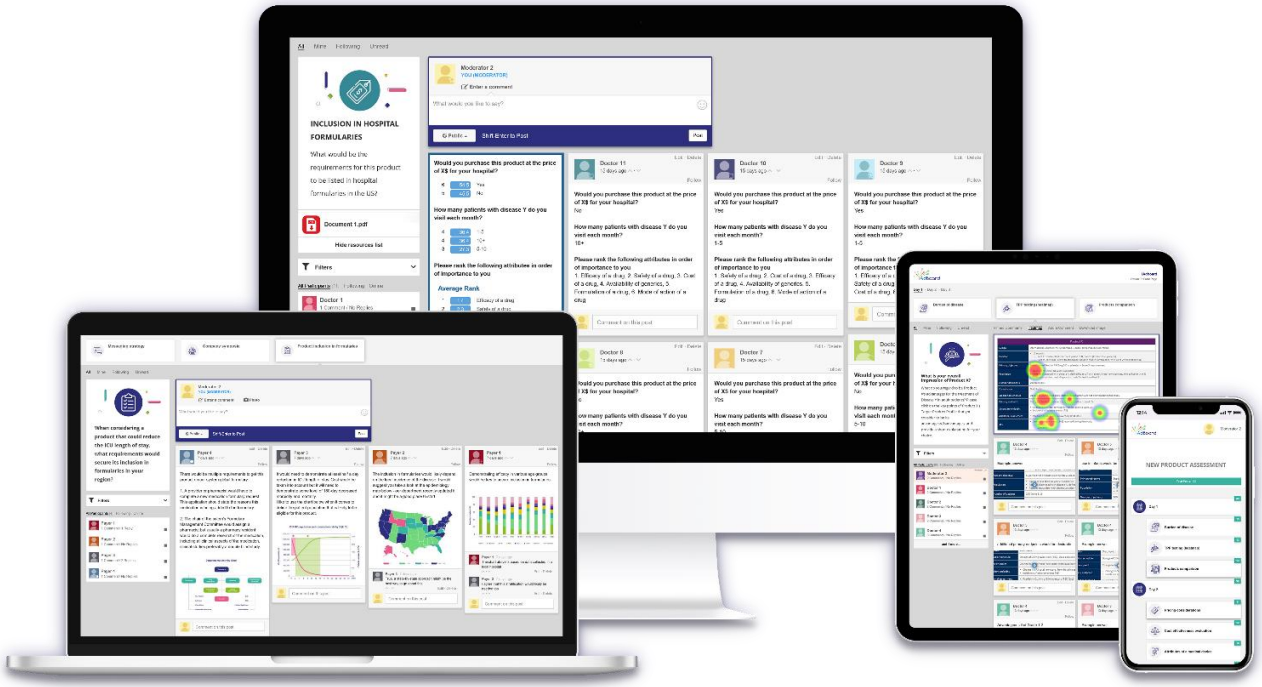
https://link.springer.com/article/10.1007/s40259-018-0287-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7824407/#B14-pharmaceutics-13-00048

We organized 3 virtual advisory boards with payers/KOLs from France, the UK and US to capture different perceptions on the new MHRA policy and downstream impacts on biosimilar access

Timing of research:
Sep/Oct 2021

Geographic scope:





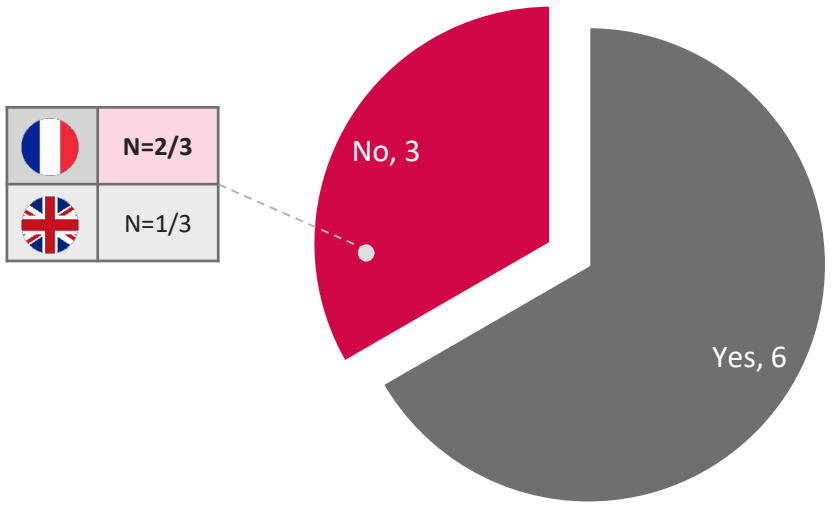
*All payers/KOLs involved in biosimilar policy, recommendation, coverage or utilization

www.iadboard.com

Despite group awareness of FDA/EMA regulatory requirements for biosimilars, 1/3 were unaware of approvals without Phase 3 trial data

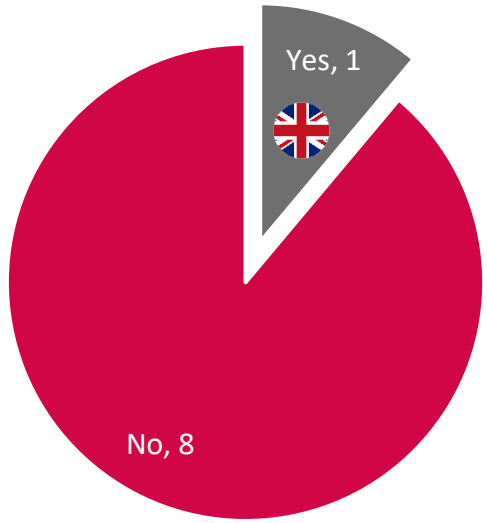
All payers (n=9) were aware of both FDA and EMA regulatory guidelines which do not mandate comparative Phase 3 trials for biosimilar approval

Awareness of pegfilgrastim approvals without a Phase 3 confirmatory trial in the US/EU (n=9)



All US payers and the majority in the UK were aware of non-Phase 3 pegfilgrastim approvals, while the majority of French payers did not

Awareness of MHRA guidance publication removing the requirement of a Phase 3 confirmatory trial for biosimilar approval (n=9)

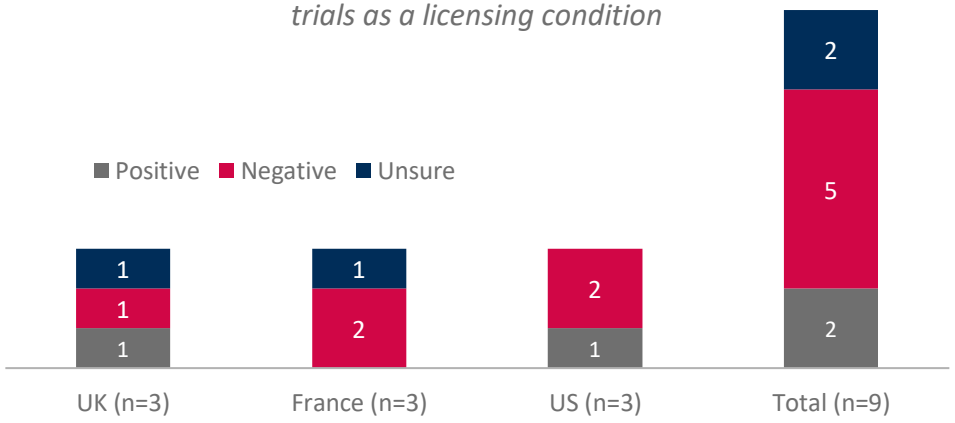


Large majority of payers were unaware of the MHRA policy, even those within the UK

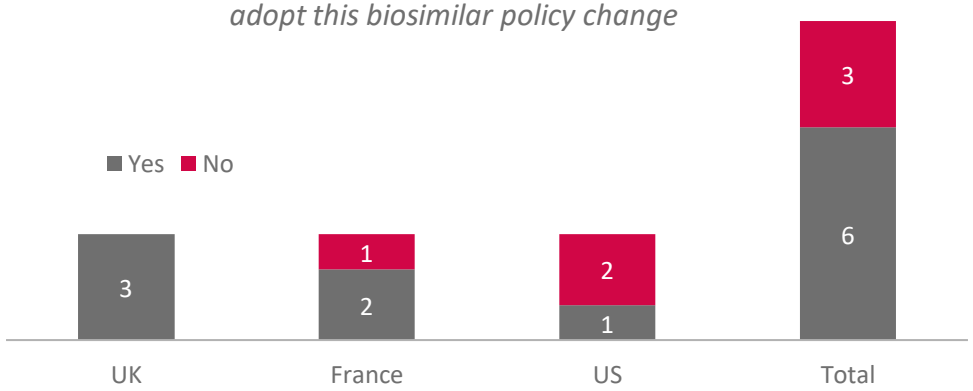
Despite an initial reaction of concern to the MHRA policy change, most payers would support a similar position from the FDA or EMA

All UK payers and the majority in France would support the FDA and/or EMA's position to adopt the MHRA's biosimilar policy change, whereas most US payers would not endorse such change

Payers view on the recent MHRA policy change to discontinue the requirement for biosimilars to undergo confirmatory clinical efficacy trials as a licensing condition



Payer support of the FDA's and/or EMA's position should they also adopt this biosimilar policy change



*"As biosimilars are **based on the reference product and its PK studies, there is no need to test Phase 3**/4. We already have the safety profile and efficacy data for the originator and therefore the biosimilar, in theory, follows the same. "*

– Payer 2, UK

*"**Currently, I am quite worried about this policy**. […] **phase 3 studies were reassuring** confirming comparable rates of retention and anti-drug-antibodies production between biosimilars and originators. I can understand that, **based on these reassuring data, it may be tempting to bypass phase 3 studies**. In that case, I think that one must **distinguish between biosimilars of molecules that have already been "biosimilarized" (e.g. adalimumab) and totally new biosimilars**. In the latter, I think that phase 3 trials will always be needed. (…)*
***I trust the decisions of EMA** and I think that if this policy is retained this will be done based on sound and solid data."* **– Payer 1, FR**

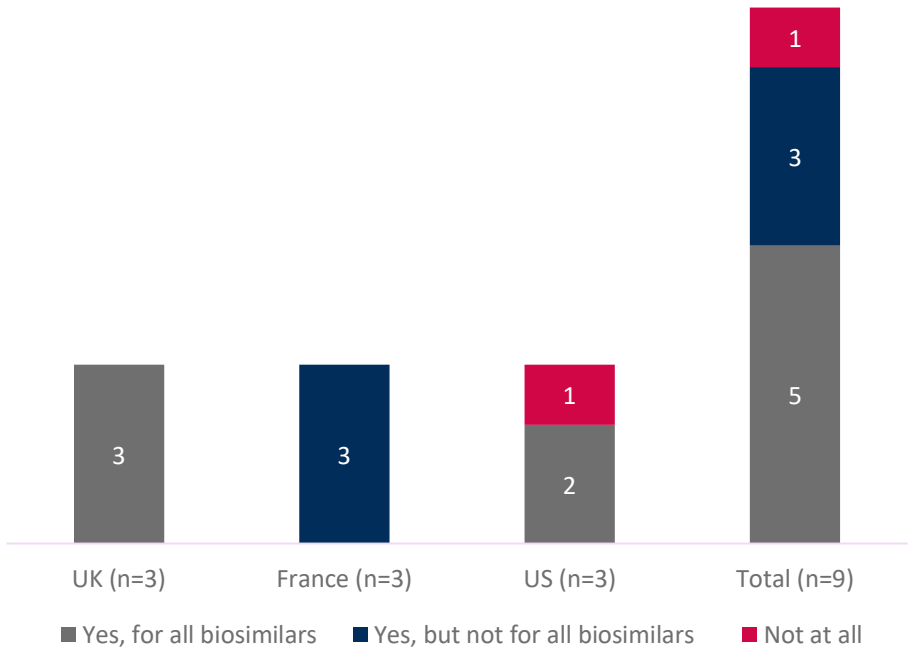
*"Unless there is sufficient cause to make the requirement. **The uptake of these products may not happen as readily** as they have been [otherwise with Ph3 data]."*

– Payer 2, US

UK payers were much more willing than their French and US counterparts to waive the comparative Phase 3 trials for the approval of all biosimilars

French payers reservations revolved primarily around larger molecules (e.g. mAbs), first biosimilars of a given biologic or biosimilars used in oncology or other immunocompromised patients

Do you believe the ''totality of the evidence'' standard set by the FDA and EMA can be met without confirmatory efficacy trials (…)?



*"**The PK data and PD data are the only way of ensuring quality and consistency within a range**. Patients differ in their response to drugs in terms of PK and PD. We need to remember that not all patients will respond to drugs in the same way. **We know the original molecule had efficacy so no need to keep testing** - especially large molecules such as mAbs. (…)*
***Originator molecules are biosimilars of themselves anyway!** For example Remicade produced 5 years ago is not the exact copy of Remicade produced today."*
– Payer 2, UK

*"Maybe for gcsf and epo but **not for monoclonal antibodies**."* **– Payer 2, FR**

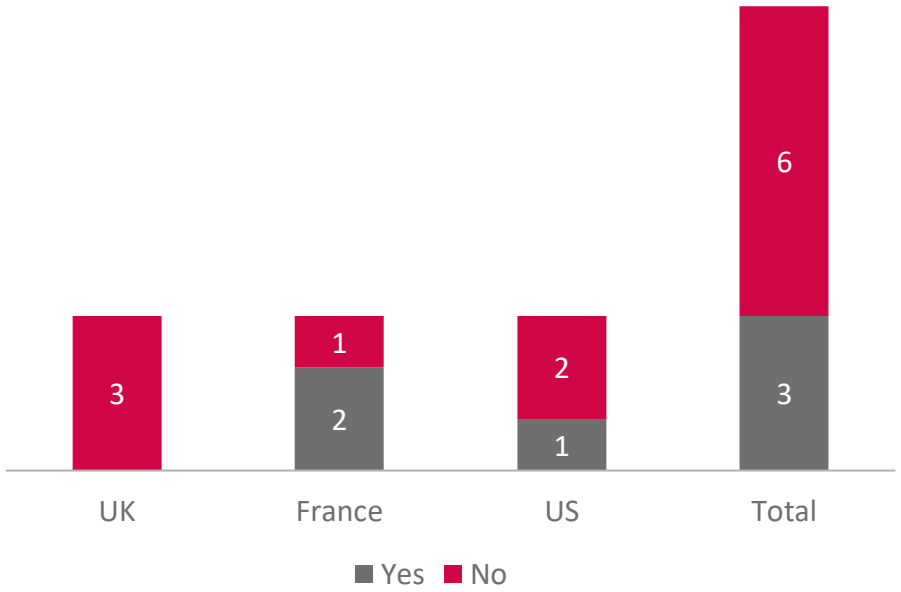
*"Some drugs and **disease (oncology**, relapse) may need direct comparison in order to reach non-inferiority level".* **– Payer-advising KOL, FR**

*"I could have chosen Yes, but not for all Biosimilars. For years, if you attempted to change drug products the push back would be "**where are your studies that demonstrate outcomes**" was the mantra that the Pharmacist was presented. This still holds true in almost all areas of Pharmacy. If you look at the Orange book with the ratings of the generics, AB rating is interchangeable in 80% - what about the 20% where the interchange may fail? I think that if clinical outcomes are extrapolated to the biosimilar which were originally attributed to the branded biologic, **the first representatives of this process must be clinically effective**."*
– Payer 1, US

In line with their positive views, UK payers were fully supportive of recommendation and use of biosimilars approved with a simplified package

UK payers agree the overall positive experience with biosimilars to date will drive similar recommendations and behaviors towards biosimilars approved without Phase 3 data. In contrast, French payers believe that if given a choice, physicians would prefer to use a biosimilar with a stronger data set for their patients. US payers would endorse these biosimilars primarily due to the perceived additional cost-savings they could offer given the elimination of the costly and time-consuming Phase 3 trial

Would you recommend or use biosimilars that have been approved without Phase 3 confirmatory safety and efficacy data any different from those that have undergone a Phase 3 confirmatory trial?



"I'd rather say "maybe" (…). If I had the choice between two biosimilars of the same biologic I would chose the one that has undergone a Phase 3 trial. (…) if health authorities impose the use of fast-track approved biosimilars over the others I would of course use them. ***If the choice is left to physicians, I think they would always choose the biosimilar with the strongest experimental background. For biosimilars approved without Phase 3 trials, real-life, phase 4 and registry data will be of paramount importance to reassure the medical community.****"*

– Payer 1, FR

"I think if these [Phase 3] trials were [always] required ***the cost-savings from biosimilars would be eroded*** *and I would not expect and different outcomes from the trial (…)"*

– Payer 2, US

Receptivity towards biosimilars approved without a Phase 3 confirmatory trial is expected to vary by stakeholder

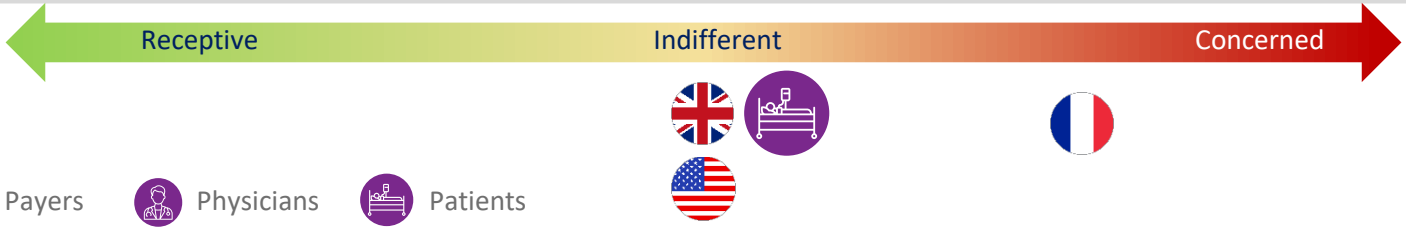
*Do you believe **PAYERS** will be generally receptive, indifferent to or concerned with **recommending** a biosimilar with no Phase 3 confirmatory data?*

Overall PAYER receptivity driven by perceived increase in cost-savings offered by these biosimilars

*Do you believe **PHYSICIANS** will be generally receptive, indifferent to or concerned with **prescribing** a biosimilar with no Phase 3 confirmatory data?*

PHYSICIAN concern is linked to less evidence demonstrating biosimilarity (if aware of the fact). However, general consensus is that initial concerns will decline over time, as was the case with current biosimilars

*Do you believe **PATIENTS** will be generally receptive, indifferent to or concerned with **being prescribed** a biosimilar with no Phase 3 confirmatory data?*



General agreement (except in France) that PATIENTS will be indifferent to the change unless their physicians express visible concern. In the US, the expectation for additional cost-savings to the patient can help drive potential receptivity

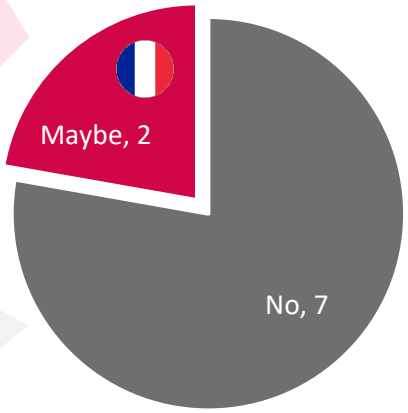
Payers Physicians Patients

In practice, the majority of respondents agree the removal of the Phase 3 requirement for approval will have no impact in biosimilar policy or uptake

Do you believe the removal of the phase 3 requirement will have an impact on biosimilar policy moving forward (e.g. switching, interchangeability)?

"While mandatory prescription of biosimilars to biologic naive patients may be a natural evolution of current policies, I feel that ***automatic switching at the pharmacy level may be facilitated by the removal of Phase 3 trials, as biosimilars would be considered more and more like "generics"*** *and clinicians might lose control over the decision on which biosimilar to use."* **– Payer 1, FR**

"I think these biosimilars will be viewed as ***alternatives*** *(already are)* ***so switching is not a major concern even if [automatic] substitution was not allowed****."* **– Payer 2, US**

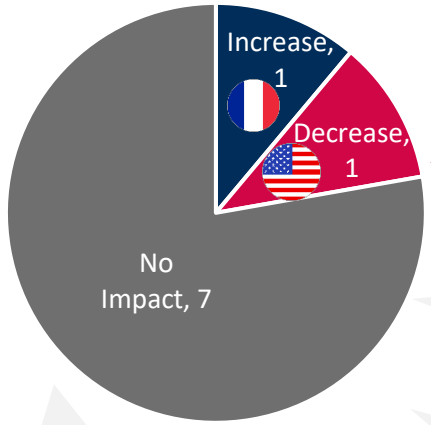


Biosimilar policy change	N
Mandatory requirement to prescribe biosimilars to biologic-naïve patients	2
Automatic switching at the pharmacy level	1
Interchangeability policies	1

Do you believe the removal of the Phase 3 requirement will increase or decrease biosimilar prescribing and therefore patient access to biosimilars?

Increase in biosimilar prescribing in patients naïve to biologics, overall biosimilar availability in pharmacies (more options) and in biosimilar market share

Decreased biosimilar prescribing in patients both naïve and experienced to biologics, due to potential concerns over safety



"I believe adoption may be slower at first, but ***overtime, no impact****."* **– Payer 2, US**

"We are already using biosimilar when it's possible. ***The only impact will be on price****."* **– Payer 1 and KOL, FR**

"I expect ***newer patients to be started on the most cost-effective biosimilar, regardless of clinical trial*** *phase (…). I can't see this changing the availability, if anything it may improve, or more or less patients receiving a biosimilar."* **– Payer 3, UK**

"The evidence, logic and real-world experience suggest there should be ***no reduction in outcomes*** *whether the innovator drug or the biosimilar is used. Informed stakeholders are already making* ***cost-effective decisions****. Payers and providers with concerns will remain unconvinced."* **– Payer 3, US**

Conclusions

Given the growing body of evidence supporting safe biosimilar use, most payers would be supportive of the elimination of the confirmatory efficacy trials as a licensing condition for biosimilars

There is hesitation towards eliminating this step for more complex biologics and/or those used for the treatment of immunocompromised patients (e.g. oncology)

All payers agree/expect:

- Increased speed of biosimilar development (though biosimilars approved to date without Phase 3 trials did not save in development time)
- Increase investment in biosimilars of non-blockbuster biologics

Most payers agree/expect:

- Additional cost-savings from biosimilars approved without undergoing Phase 3 clinical trials
- Increase in biosimilar availability
- Initial hesitation by some physicians given the reduced data package, without significant impact in the long-term

Overall, expecting limited to no impact in policy, prescribing and patient access to biosimilars

Final considerations for biosimilar market dynamics

Opportunity for increased cost-savings with more and different biosimilars coming earlier to market and potentially cheaper options. Reassurance across molecules needed in addition to education around strength of the totality of evidence without Phase 3 trials, supplemented with Phase 4/ long-term follow-up studies and registry data capture, in addition to experience and RWE from currently approved biosimilars with Phase 1 data only.

Lifescience Dynamics
Decision support

Thank you

Andreia Ribeiro, PhD
ARibeiro@lifesciencedynamics.com

Ken Walsh, MSC
KWalsh@lifesciencedynamics.com

vault career intelligence

OVER 15 YEARS ESTABLISHED IN 2004 OF EXCELLENCE

THE QUEEN'S AWARDS FOR ENTERPRISE: INTERNATIONAL TRADE 2016

Copyright Lifescience Dynamics Ltd. 2021 Confidential