Competitive Entry

A research paper on the role of drug delivery device design in supporting entry into competitive biosimilars markets

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Management Summary

The likely available market for biosimilar manufacturers seeking to compete with original reference biologics coming off patent between 2018 and 2023 is estimated to be \$3.12 billion per year in Europe and \$5.24 billion per year in the USA.

However, successful uptake of biosimilars depends on several factors: clinical confidence in the biosimilar; more competitive pricing of drugs through greater competition; and patient confidence in the drug delivery device.

This paper presents evidence for the importance of good device design in easing biosimilar adoption. It also illustrates the importance of patient/healthcare professional research to understand device preferences, as well as the key design process steps needed to create the optimal delivery device.



Biosimilars

As the pharmaceutical sector progresses into the third decade of the century, biological drugs are expected to offer world healthcare systems a step-change in therapeutic benefit and long-term financial cost. As one studyⁱ notes, "...biologics may increase drug costs. However, biologics offer demonstrated improvements in patient care that can reduce expensive interventions, thus lowering net healthcare costs."

Alongside the patient benefits, introducing biosimilars into the market after the original biological drug patent has expired has been seen to reduce prices through healthy competition, increasing patient access to treatments and proving to be an additional driver for adoption. In the longer-term, discounting needs to reach levels that help create a sustainable market - where competitive market cost savings are balanced by reasonable commercial incentive for pharmaceutical manufacturers to continue investing in new drug discovery, development and certification.

The EU already has far more approved biosimilars—59 products referencing 18 medicinesⁱⁱ —than the United States (17 products referencing 9 medicinesⁱⁱⁱ). Still, the number of European biosimilars available today represents just a fraction of what the market is expected to contain in the coming years.

In Europe, seventeen biologics will have come off patent over the five year period between 2018 and 2023. In the U.S., the equivalent number is fifteen. The entry of biosimilars to create a competitive market have been seen to generate price discounts that cluster around the 30% mark in the European Union^v (although in some countries these are much higher). A review of different local country biosimilar competition rules finds that mandatory discounts, where imposed, mainly focus in the 20-40% range versus the reference product pricing^{vi}. It is therefore encouraging that early signs from an emerging competitive market in the U.S. over one biologic^{vii} that came out of patent in 2015 reveals that 25% has already been discounted off the branded reference drug pricing, and that the market expects this discount to increase a little further before settling into sustainable competition^{viii}.

This paper's analysis of biologics coming off patent over the five year period 2018-2023^{ix} gives a picture of the market opportunities for competitive biosimilars. In Europe, the estimated market opportunity^x (factoring in competitive discounts and based on 50% market share) for biosimilar manufacturers is \$3.12 billion per year based on current revenues. The equivalent market opportunity in the USA comes to \$5.24 billion per year.





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Switching

A number of clinical and regulatory issues surround the process of switching patients between original biologics and biosimilars^{xi}. Although not the main subject of this paper, suffice to say that while regulators in global markets will continue to act with due caution in designating biosimilars as interchangeable, their level of confidence in making these decisions is fast growing as more real-world evidence becomes available (independent studies^{xii} are regularly adding to the body of real-life clinical evidence that switching patients to biosimilars is effective and well-tolerated).

At all events, healthcare regulators, managers and clinicians around the world are keen to encourage adoption of biosimilars where appropriate for the patient. In the UK, for instance, NHS England are now urging a more proactive and collaborative approach between commissioners, providers and patients to realise the potential savings from switching to biosimilar medicines^{xiii}. More broadly, with over 10 years clinical experience across the EU, confidence in the safety and efficacy of biosimilar medicines for their approved indications has grown, and this has alleviated some of the initial concerns about their use, particularly when initiating therapy in treatment-naive patients^{xiv}. Moreover, active regulatory moves have been, or are being, made to encourage interchangeability where the clinician considers it safe to do so^{xv}.

Device Design and Switching

Quite a volume of authoritative commentators now also emphasize that the design of the drug delivery device – typically an auto-injector or prefilled syringe device– plays a critical role in facilitating switching^{xvi} (post clinical judgement). This is an important issue for two reasons. First, larger molecule biological drugs tend to be more viscous and present challenges with volume of drug to be delivered as well as potential pain on administration. Weekly injections when treating rheumatoid arthritis are typical. In a parallel move, healthcare systems across the world are moving towards patient self-administration, in order to lighten the burden on hospitals and increase convenience for patients^{xvii}.

The influence of drug delivery ease is noted in a number of studies and the FDA has made it a requirement that human factor studies are run to both support the device design and demonstrate that user associated risks have been understood and mitigated. One - specifically looking at synthetic insulin - neatly summarises the situation thus^{xviii}:

"While regulatory guidelines cover aspects such as the structure, PK/PD, efficacy, safety, and immunogenicity of a biosimilar, one aspect that is equally important is the delivery device. Delivery devices are key factors in the patient experience with insulin administration, where regular use becomes part of the patient's life. While the precision of dosing is a key concern, ease of use, comfort, and convenience of the device are important factors that could potentially influence patient adherence and so have an impact on efficacy. Familiarity and comfort with a particular delivery device may encourage patients to remain loyal to a specific branded insulin, even if less expensive biosimilars are available. Conversely, if patients are required to change to a different manufacturer's product, a new or different device may discourage switching."

In fact, the drug delivery device is increasingly seen as integral to the overall therapy– the pairing of drug and device termed by the FDA as a 'combination product' and is regulated by its own regulatory pathway. As another study^{xix} puts it, "Products can be available in different presentations to their reference products, which, without proper guidance from a healthcare provider, could lead to inappropriate use by patients or caregivers. FDA guidance requires sponsors to provide data and information supporting the appropriate use and performance testing of the delivery device constituent part of the proposed interchangeable product." Further evidence is found in the fact that pharma companies are seeking exclusive arrangements with device manufacturers to gain competitive edge in the switching/retention process^{xx}.

In summary, commentators show clear consensus on the important impact of drug delivery device design, with one remarking, "It is [...] important to consider potential differences between delivery devices for biosimilars and reference products that may provide added benefit to patients and health care providers^{xxi}."Although, patient adherence and practice are also influenced by the delivery device, as another commentator summarises: "From the patient perspective, switching to a follow-on biologic may necessitate a change in delivery device, which may create issues for patient adherence and dosing^{xxii}."New designs that have been specifically developed for biosimilar drugs often offer improved features that favour patient usability. Greater ease of use is certainly an important driver to encourage new users to follow their treatment plan, while existing users are likely to increasingly favour usability over habit especially when suffering from degenerative diseases like osteoarthritis.

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A case in point

In the world of biologics and biosimilars, two factors dominate. First, clinicians want to bring the therapeutic benefits of biologics to as wide a patient audience as possible, encouraging therapy adherence and accurate selfadministration. In commercial terms, new biosimilar entrants want to remove obstacles to switching – this includes device design – while referce drug manufacturers want to keep patients, clinicians and nurses loyal to their product post patent period.

In every case, research is needed to determine the strength of preference for a particular design, both from healthcare professionals and from patients. Some details from a piece of research work done by Owen Mumford Pharmaceutical Services illustrates how revealing that research can be.

The research involved an original biologic and a biosimilar competitor.

In the case of the original biologic, a push-button delivery device made up the combination product. The biosimilar, on the other hand, used a pressure-activated auto-injector. Research aimed to understand where preferences lay between the two types of delivery device. For existing users of each drug, habit was shown to be hugely powerful, each cohort wishing to stay with the device type that they had become used to using. On the other hand, naïve patients just embarking on their therapeutic journey betrayed a strong preference (60%) for the pressure-activated device. Nurses – especially in the US – favoured the pressure activated device. Moreover, the strength of preference for push-button was significantly less marked than that for pressure-activated. The research also investigated envisaged ease-of-use, as distinct from preference. Both device types were considered easy to use.

All this data provided an evidential basis for pharmaceutical company and device manufacturer to establish a product design strategy, including short-term tactics to win customer preference, as well as longer-term migration strategies to wean patients from one device type to the other, backed up with communications and training materials to support clinicians and care staff and treasure patients.

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Key Design Issues

After researching user and healthcare professional preferences, the process of designing an optimum delivery device or device platform should go through a rigorous series of development steps. Consensus among expert commentators^{xxiii} may be summarised broadly as follows:-

- 1. Selection of the primary container; drug interaction; impact on drug stability; compatibility with manufacturing processes.
- Regulatory compliance; design reviews; human factor studies; device risk management considerations; test method development and qualification; risk and confidence parameters.
- Candidate device evaluation; robustness and usability based on target applications; assembly and manufacturing risks; supply chain reliability; environmental/disposal risks; post-shipping device performance.
- 4. Design control procedures; plans & fully documented histories; design review process; methods of operational transfer; post-market surveillance procedures.
- 5. Manufacturability and control strategy risk evaluation; application to both device and to combination product; device vendor site controls.
- 6. Packaging considerations; shipping risks; likely packaging complaints.
- 7. Biocompatibility; device handling patient/user safety; ISO10993

Footnotes

- i. Cancer Management Research, Can biosimilars help achieve the goal of U.S. health care reform? Jun 2017, Cancer Manag Res. 2017 Jun 1;9:197-205
- ii. Source: European Medicines Authority
- iii. Source: FDA
- iv. IQVIA, Advancing biosimilar sustainability in Europe, 2018
- v. See, for instance, The Oncologist, C.Nabhan, A.Valley, B.A.Feinberg, Barriers to Oncology Biosimilars Uptake in the United States, Jul 2018, The Oncologist vol.23 no.11 1261-1265
- vi. PLOSone, Moorkens, Vulto, Huys, et al, Policies for biosimilar uptake in Europe: an overview, 28 Dec 2017, https://doi.org/10.1371/ journal. pone.0190147
- vii. infliximab
- viii. Fierce Pharma, As competition heats up, U.S. prices for Remicade and biosims slip, 20 Dec 2018
- ix. Includes infliximab (U.S.), adalimumab, insulin detemir (Europe), teriparatide, eculizumab, trastuzumab (U.S.), trastuzumab emtansine (Europe), belimumab, ipilimumab, alemtuzumab, certolizumab (Europe), ranibizumab (U.S.), bevacizumab, denosumab, liraglutide, pertuzumab, ramucirumab, brentuximab. Rituximab (U.S.), secukinumab (U.S.), ustekinumab (U.S.), panitumumab (U.S.)
- x. Methodology: Latest patent-protected year revenues for original biologics coming off patent in the period 2018-2023 were researched. These were then reduced by typical discounting levels already experienced in the European and US markets
- xi. Such as: Current Medical Research and Opinion, L.McKinley (U.S. Regulatory Policy), J.M. Kelton (U.S. Medical Affairs), R.Popovian (U.S. Government Relations), Sowing confusion in the field: the interchangeable use of biosimilar terminology, 6 Sep 2018
- xii. Such as American College of Rheumatology, Biosimilar Infliximab (CT-P13) is Not Inferior to Originator Infliximab: Results from a 52-Week Randomized Switch Trial in Norway, 22 Oct 2016
- xiii. NHS England. Commissioning framework for biological medicines (including biosimilar medicines)v1.0; 12 Sep 2017 https://www.england.nhs.uk/ wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf; At the Mid Yorkshire Hospitals NHS Trust, pharmacy-led switching programmes for infliximab and etanercept resulted in around 85% of patients switching to a biosimilar. Patients were reported to have a good understanding of the benefits of saving money through biosimilars, notably to reinvest in wider services
- xiv. European Medicines Agency. Biosimilar medicines. http://www.ema.europa.eu/ema//index.jsp?curl=pages/medicines/general/general_ content_001832.jsp&mid=WC0b01ac0580bb8fda; European Medicines Agency. Biosimilars in the EU. Information guide for healthcare professionals. Updated 27 April 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf
- xv. APM Europe, Italy revises biosimilars regulation, opens way for interchangeability with originators, 29 Mar 2018
- xvi. European Medical Journal, Filipe C. Araújo,1,2 Joao Eurico Fonseca,3,4 Joao Goncalves,5Switching to Biosimilars in Inflammatory Rheumatic Conditions: Current Knowledge, EMJ Rheumatol. 2018;5[1]:66-74; GABI Online, Alternative delivery devices for biosimilars, 1 Jun 2012
- xvii. See, for instance: New England Journal of Medicine, Saving Medicare through Patient-Centered Changes The Case of Injectables, 25 Apr 2013; Deloitte, Global Healthcare Outlook, 2018
- xviii. Journal of Pharmacy Technology, J White, J Goldman, Biosimilar and Follow-on Insulin: The Ins, Outs, and Interchangeability, 28 Sep 2018
- xix. Drug Discovery Today, HC Ebbers, H Schullekens, Are we ready to close the discussion on the interchangeability of biosimilars? 26 Jun 2019
- xx. In-pharma Technologist, Pharma turning to injectable systems to protect biologics, 22 Jun 2015
- xxi. Pharmacy & Therapeutics, JS Smeeding, DC Malone, M Ramchandani, B Stolshek, L Green, P Schneider, Biosimilars: Considerations for Payers, Jan 2019; 44(2): 54–63.
- xxii. Endocrinology Practice, R Dolinar, F Lavernia, S Edelman, A guide to follow-on biologics and biosimilars with a focus on insulin, Endocr Pract. 2018 Feb;24(2):195-204
- xxiii. For instance: Pharmaceutical Online, M Song, 4 Important things to consider before designing a drug delivery device, 6 Aug 2019

