Layperson materials in the sphere of biosimilars and generic medicines

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Abstract
Generics and biosimilars offer effective treatment alternatives to branded reference drugs at a lower cost. Despite their widespread use, patients have misconceptions regarding their efficacy and safety. Layperson materials offer an important means by which patients can be educated in this regard. Here, we provide an overview of generics and biosimilars, describe how layperson materials fit into this landscape from a patient-centricity and regulatory perspective, and provide example language that can be used when developing layperson-orientated materials for generics and biosimilars.

In recent years, the pharmaceutical industry has seen an increased recognition of the importance of patient- and layperson-orientated materials.[1,2] This has likely stemmed from an acknowledgement of the key role that patients play as active contributors to the drug development process as study participants, as well as being the end-users of medicines. Additionally, patients and patient-advocacy groups are becoming increasingly mobilised and vocal in relation to taking control of their health decisions, and have a growing appetite for tailored information about the drug development process and available treatments.[3] This increased appreciation for the central role of patients within health systems has manifested itself in two tangible ways:

1. an increase in patient-centred initiatives on the part of pharmaceutical companies and
2. new patient-focussed requirements set out by pharmaceutical regulators.

Patient centricity has been defined as "Putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family". In practice, this involves ensuring that people who need medicines have access to them; providing transparent and unbiased information on diseases, treatment options, and other available resources; equipping patients to make informed healthcare decisions; companies listening and responding to patient feedback with respect and humility; and providing easy-to-understand and convenient information in plain language.[4]

With regards to regulatory initiatives that have the patient in mind, European Union regulation 536/2014 stipulates that, in addition to providing a technical trial report, sponsors of clinical trials with at least one site in the European Union will be required to provide a trial summary "that is understandable to laypersons". This requirement will become live following the launch of the online EU Clinical Trial Portal and Database, which is expected to happen during 2019. Having this online repository of plain language trial summaries will provide

patients with a valuable resource, empowering them to make informed healthcare decisions. Currently, these plain language trial summaries are only required for trials with a site in the European Union, though it is expected that other regulatory bodies will implement similar requirements in the future.

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Key principles in the preparation of lay summaries

There are some key guiding principles that can be used when developing layperson materials, most of which can be grouped under three headings:

- **Format:** Documents should be as short as possible to improve accessibility and increase the likelihood that readers will read the whole document. Content should not be squeezed onto pages; rather there should be sufficient white space. Graphics can be used to break up text and to improve the aesthetic appeal of the document.
- **Word choice:** The choice of words used in these documents should facilitate readability and be understandable to people from the age of 12 years. Tools like the Flesch-Kincaid test can be used to assess readability. Short sentences can also aid comprehension.
- **Numeracy principles**: For example, presenting percentages rather than risk ratios or odds ratios, using whole numbers rather than decimals, and stating the numerator and denominator when reporting percentages.

Although following these guidelines will help develop quality layperson materials, there are still challenges.[5] Perhaps the biggest challenge is the tension between the need to develop short documents with the fact that a large number of words is often required to explain a single medical term in lay language. For example, to someone with a basic knowledge of oncology, the single word 'metastatic' will be well-recognised. To someone with no medical knowledge, however, it may take several words to explain what this means: e.g., "a cancer tumour that has spread to other parts of the body". It's therefore easy to see how the length of a document can increase substantially. Other challenges include avoiding generalisations that may be perceived as promotional, communicating necessarily complex terms such as lists of adverse events, and selecting appropriate graph or chart types that can be understood by non-specialists.[6]

Recommendations have been provided by the European Commission on the development of layperson summaries in the EU regulatory context.[7] However, these recommendations appear to be open to a degree of interpretation that may lead to variability between documents in terms of content and appearance. Furthermore, those who have traditionally been responsible for developing technical study reports may not be best suited to developing clinical trial lay summaries, given that their frame of reference has almost exclusively been related to high-level scientific language. Writing for a lay audience requires not only an understanding of the science, but also the skillset to communicate this information to a non-scientific audience.

Background to generics and biosimilars

Before it can be approved for its use in humans, a new drug undergoes a protracted and complex stage of development and testing. This involves the systematic completion of laboratory-based studies, studies in animals, safety testing in humans, and large-scale clinical trials. Once complete, data from these studies are assessed by regulatory bodies such as the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), who decide whether or not the drug may be made available for use. This process is both lengthy and costly, and once approved, the drug makers may have limited time to make and sell the drug exclusively before the patent expires. Once this exclusivity period comes to an end other companies may seek to develop and market the same (or very similar) drug under a different name. Such drugs are known as generics and biosimilars; the key characteristics of generics and biosimilars are outlined in Table 1.

One of the key differences between a newly developed drug (i.e., a reference or originator drug) and a generic or biosimilar is the regulatory approval process applied. The reference drug will have gone through a lengthy rigorous development process, as described above. However, the manufacturer of a generic must simply provide evidence that the generic drug is equivalent to the reference. Equivalence must be shown with respect to identity, strength, purity, and quality, and it must be demonstrated that the generic medicine produces the same levels of the active substance in the human body as the reference medicine. This is usually achieved by conducting "bioequivalence" studies, demonstrating that the generic drug reaches the bloodstream in the same time and at the same concentration as the reference drug. Once the generic drug has been shown to have an identical structure *in vitro* and identical pharmacokinetics *in vivo* to the reference, it can be approved.[8]

In the case of biosimilars, the regulatory bodies compare molecules from the biosimilar to

Table 1. Key characteristics of generics and biosimilars

	Generics	Biosimilars
Composition	Simple molecules	Complex molecules
Storage	Stable and easy to store	Sensitive to storage and handling conditions
Mechanism of action	Do not induce an immune response	Induce an immune response
Manufacture	Straightforward to manufacture	Require intensive complex processes

Table 2. Example lay language for commonly used technical terminology in the sphere of generics and biosimilars

Technical term/concept	Lay language explanation
Generic medicine	• A generic medicine is a medicine that contains the same ingredients and has been made in the same way as another medicine already available for use by patients. • The medicine that is already available for use by patients is known as the reference medicine. • Generic medicines have a simple chemical design (or structure) and the manufacturing process for generic medicines is quite straightforward. • It is therefore possible to make generic medicines that are almost identical to the reference medicine.
Generic medicine approval process	• Reference medicines go through a very long and complex development process before they can be used by patients, to make sure they are effective and safe to use in humans. • This involves doing tests in laboratories and running several studies in humans known as clinical trials. • Generic medicines do not need to go through as much testing before they can be used by patients. • Instead, the makers of a generic medicine only need to show that their medicine works in the body in the same way as the reference medicine.
Biosimilar	• A biosimilar is a very complex type of medicine that has been designed to work in the body the same way as a medicine already available for use by patients. • The medicine already available for use by patients is known as the reference (or bio-originator). • Bio-originators have very complex chemical designs and require precise manufacturing processes. • This makes it very difficult to make a biosimilar that is exactly the same as the bio-originator.
Biosimilar approval process	• Bio-originators go through a very long and complex development process before they can be used by patients, to make sure they are effective and safe to use in humans. • This involves doing tests in laboratories and running several studies in humans known as clinical trials. • Biosimilars do not need to go through as much testing before they can be used by patients. • Instead, the makers of a biosimilar need to show that there are no major differences between their medicine and the bio-originator. This involves doing tests in laboratories and doing one clinical trial in patients to show that the biosimilar has a similar level of effectiveness and safety compared with the bio-originator.
Regulatory body/agency	• A committee of experts that reviews laboratory and clinical trial data for a medicine and decides whether the medicine can be used safely in patients.
Bioequivalence	• Two drugs are said to be bioequivalent if, when taken at the same dose, they reach the same concentration levels in the body and reach these concentrations after a similar period of time.
Immunogenicity	• Immunogenicity is the term used to describe the process of the body's immune system being activated against a perceived external threat. This can sometimes happen when patients take biosimilars.
Pharmacokinetics	• Pharmacokinetics describes the study of how a drug moves in the body. This relates to the maximum concentration a drug will reach in the body, how long it will take for a drug to reach the maximum concentration, and how long it will take for a drug to leave the body.
Pharmacodynamics	• Pharmacodynamics describes the study of how a drug affects the body. For example, establishing whether a drug speeds up or slows down certain normal biological processes in the way it was designed to do.
In vitro	• *In vitro* relates to study techniques that are done on cells or molecules outside of their normal living environment. For example, studies done using test tubes in the laboratory.
In vivo	• *In vivo* relates to study techniques carried out using whole living things such as animals or humans.

those of the reference drug to make sure that there are no meaningful differences that would affect how the drug works in the body. In practice, this involves establishing that the new medicine is similar to the reference in its physicochemical characteristics, composition, and *in vitro* biological function (based on a wide range of relevant assays). Additionally, a single pharmacokinetic study must be conducted to establish equivalence, and a single suitably-sized randomised trial conducted to demonstrate clinical and safety equivalence (including immunogenicity).[8] Biosimilars may be approved via "extrapolation", a process that allows approval of a biosimilar in a non-studied indication, based on studies in other indications. Extrapolation is permitted by regulatory authorities providing biosimilarity has been established and there is a scientific justification.

Lay summaries in the sphere of generics and biosimilars

What then is the role of lay summaries in the sphere of generics and biosimilars? Generics and biosimilars are often copies of well-established well-known drugs for common diseases. Add to this the fact that they are far less expensive than reference drugs; therefore, generics and biosimilars are widely used by the general population. Despite their widespread availability and use, patients still have misconceptions about these types of medicines, including that generic drugs are less effective and take longer to work, are not safe, and are manufactured in substandard facilities.[9,10] Here then lies one of the key reasons why lay person materials are important in this context: to ensure that patients understand that generics and biosimilars are of the same standard as the original 'branded' reference drug, and are

not in any way "substandard" because of their lower price.

While clinical trials are not necessary for the approval of generics, and therefore not subject to the requirement of EU regulation 536/2014 to have an associated lay person summary, sometimes the manufacturers of a generic drug will run a trial comparing the generic to its reference. In such cases, the trial sponsor will be required to develop a lay person summary in addition to the technical trial report. With regards to biosimilars, because a single clinical trial is required to establish clinical and safety equivalence, then a corresponding lay person summary will be required. As such, from a regulatory perspective, lay summaries of clinical trials may be more prevalent for biosimilars than generics.

Aside from the regulatory imperative for clinical trial lay summaries, given the increasing move towards patient centricity, it may be prudent for the makers of generics and biosimilars to develop layperson materials as standard practice. In so doing, they will help to educate patients, empowering them in their treatment decisions.

Describing the clinical trial process in layperson language can be challenging at the best of times, and this arguably becomes more complex by adding generics and biosimilars into the equation, because of the need to explain complex processes and procedures like pharmacokinetics, pharmacodynamics, and bioequivalence. As such, we have provided some suggested wording that writers may find helpful to use when developing layperson materials related to generics or biosimilars (Table 2).

Conclusions

Generic medicines and biosimilars are widely used, yet there is large scale misconception among patients regarding their safety and effectiveness. Layperson materials therefore represent an important way to educate patients in this regard, helping them to make better-informed treatment decisions. Fewer clinical trials are required in the development of generics and biosimilars compared with reference or originator drugs. However, there are still circumstances where trials are carried out in this setting, and where there will therefore be the requirement for a trial lay summary, in line with EU regulation. Outside of the regulatory sphere, while not mandatory, it may be prudent for the manufacturers of generics and biosimilars to develop layperson materials as standard practice, given the increasing appetite for, and importance of, patient-orientated materials.

Conflicts of interest

The authors have ownership interest in Lay Summaries Ltd.

References

1. Goel N, O'Sullivan D, Steinkoenig I, James J, Lindsay CA, Coates LC, et al., Tackling patient centricity: A report from the GRAPPA 2016 annual meeting. J Rheumatol. 2017;44:703–705; DOI: https://doi.org/10.3899/jrheum.170152.
2. Stegemann S, Ternik RL, Onder G, Khan MA, van Riet-Nales DA. Defining patient centric pharmaceutical drug product design. Amer Assoc Pharmac Sci J 2016;18:1047–55. https://doi.org/10.1208/s12248–016–9938–6.
3. Sacristan JA, Aguarón A, Avendaño-Solá C, Garrido P, Carrión J, Gutiérrez A, et al., Patient involvement in clinical research: why, when, and how. Pat Pref Adher. 2016;10:631–640.
4. Yeoman G, Furlong P, Seres M, Binder H, Chung H, Garzya V, et al., Defining patient centricity with patients for patients and caregivers: a collaborative endeavour. BMJ Innovations 2017;3:76–83.
5. Schindler T. The joys of the impossible: The writing of lay summaries of clinical study results. ClinicalTrialsArena [Internet]. 2016 December 20 [cited 2019 April 24]. Available at https://www.clinicaltrialsarena.com/news/the-joys-of-the-impossible-the-writing-of-lay-summaries-of-clinical-study-results-5697962–2/.
6. Gillow CL. Layperson summaries of clinical trial results: Useful resources in the vacuum of regulatory guidance. Med Writ. 2015;24:205–209.
7. European Commission. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. February 2018. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf.
8. Isaacs J, Gonçalves J, Strohal R, Castañeda-Hernández G, Azevedo V, Dörner T, et al., The biosimilar approval process: how different is it? Consider Med. 2017;1:doi: 10.1136/conmed-2017–100003.
9. Alrasheedy A, Hassali MA, Stewart K, Kong D, Aljadhey H, Ibrahim MIM, et al., Patient knowledge, perceptions, and acceptance of generic medicines: a comprehensive review of the current literature. Pat Intell. 2014;6:1–29.
10. Sanchez CK & Zurek AM. Patient perceptions of generic drugs: dispelling misconceptions. US Pharm. 2016;41 (Generic Drug Review suppl):36–41.

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