SafeBiologics
ALLIANCE for SAFE BIOLOGIC MEDICINES

BIOLOGICS ARE MAKING A NAME FOR THEMSELVES

Biologic drugs are revolutionizing the treatment of many chronic illnesses, but how they are identified differs throughout the world. Implementing a global policy of distinguishable names does not have to be difficult.

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Drug names are important. They identify medicine for prescribing and dispensing, as well as reporting problems to regulators. Manufacturers invest significant effort coming up with the brand name, while the World Health Organization (WHO) assigns the drug a technical name, referred to as an international nonproprietary name (INN)[1]. For example, Tylenol is a brand name and acetaminophen its INN.

When it is launched, a drug is under patent protection, so there is only one version on the market — with both a branded name and the INN. When patent protection runs out, however, competitors can sell their own versions of the drug, which are required to be structurally identical to the original medicine. These copies, generic versions, may carry a unique name, but have the same INN as the original product. It is the INN that is used globally when prescribing, dispensing, and identifying adverse events.

This system worked well, until recently. In the past 20 years, traditional drugs, which are made of chemical compounds and can be copied identically, have been complemented by a new wave of biological medicines. Biologics are made of large, complex molecules and are typically manufactured using living cells, which is the reason that no two versions of a biologic drug — produced by different manufacturers — will ever be identical. These subsequent products very closely resemble, rather than replicate, the original reference product. Hence, versions of biologics made by other manufacturers are called biosimilars, not generics.

This variation means that each manufacturer's version of the biologic must be uniquely identified so that it can be distinguished from other biosimilars. However, such a global naming protocol has been elusive. In the decade since the appearance of the first biosimilar, multiple products have been approved in the United States, Europe and Canada, among other regions. But the regulatory agencies have taken different approaches to the naming of biosimilars. Given that the development pipeline contains more than 240 biosimilars and the global market is expected to grow[2] to $61 billion by 2025, the issue of drug naming and identification could present significant safety issues.

On 11 April 2018, Scientific American and the Alliance for Safe Biologic Medicines (ASBM) hosted a forum in Washington DC to discuss international harmonization of

biologic naming as a crucial step for the incorporation of biosimilars into the global health-care arena. Participants included representatives of the US Food and Drug Administration (FDA) and Health Canada, as well as physicians, pharmacists, researchers, and members of patient advocacy organizations.

Panelists were clear in their position that global agreement on a distinguishable naming protocol for biologics is important to protect patients. If not reconciled soon, the divergent naming practices could impede access to and the safety of life-saving medicines. A unified approach to biologic naming could improve pharmacovigilance (monitoring the real-world effect of drugs after approval) and raise healthcare-provider confidence in biosimilars — and thus stimulate broader and faster biosimilar uptake. All of this would be a major advancement for the many patients who stand to benefit from cheaper alternatives to branded biologic drugs.

Why do biologics need **unique names?**

Biologics have revolutionized the treatment of many devastating and chronic illnesses, including rheumatoid arthritis, psoriasis, cancer and diabetes. As discussed above, biologics are different from chemical drugs in a number of important aspects that have consequences for how the products are used and regulated.

There are tight regulations surrounding the subtle differences between the original biologic and subsequent biosimilars. Nevertheless, biologics, made of large molecules, are detectable by a patient's immune system; so any tiny variation between products could trigger an unwanted immune response. And, unlike a typical reaction to a chemical drug, it can take years for an immune response to a biologic to develop or become apparent. Consequently, knowing the specific products prescribed

over time is crucial when it comes to identifying any problems that patients experience. Each version of the biologic must be distinguished from any other approved biologic, even if they are copies of the same medicine. This will facilitate effective pharmacovigilance and rapid traceability should there be a systemic problem with a product.

Furthermore, distinguishable naming could help increase physician confidence in biosimilar use and help drive uptake. A doctor can best treat a patient when he or she has all the information about a product administered over time. In some cases, a patient might find that one biosimilar works better for them than another version of the product — biosimilar or originator. Indeed, physician support for distinguishable naming is globally established[3]. Conversely, a lack of distinguishable naming creates risk. "A poorly regulated or manufactured biosimilar that cannot be easily identified could taint the entire industry," warns Madelaine Feldman, a rheumatologist and chair of the ASBM.

Why is biologic naming **a global issue?**

The importance of harmonized naming protocols is widely recognized. The WHO has managed the INN system since it was implemented in its current form in 1950 and explains the value of a unified system on its website[1]. "The existence of an international nomenclature for pharmaceutical substances, in the form of INN, is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide."

Global naming harmonization is also important for patients traveling or relocating abroad. If an individual needs a prescription filled while abroad and the drug names are different between countries, it may be very challenging for them to get their prescription filled and to track the specific medicine they received. Equally important, lack of clarity globally will make identification and association of adverse reactions across jurisdictions, and resolution of problems, more difficult. "A regulator's job is not confined to the corners of their geography," says Anthony Ridgway, acting director of the Centre for Evaluation of Radiopharmaceutical and Biotherapeutics at Health Canada.

> "Despite their strong recommendation in favor of the BQ, robustly supported by other stakeholders, the WHO has not advanced implementation of a distinguishable naming protocol for biologics."

Synchronization of distinguishable naming protocols is particularly important for low- to middle-income countries that may have less robust or comprehensive regulatory and pharmacovigilance systems. "In jurisdictions where the data standards to get drugs approved might be lower, many more biosimilars may come to market, not all of high quality," says Sadie Whittaker, a consultant for ASBM. "It can become a mess really quickly."

The need for improved pharmacovigilance in low and middle income countries has been recognized by The Bill & Melinda Gates Foundation. Alongside the WHO and the UK's Medicines and Healthcare products Regulatory Agency, the Gates Foundation launched Project 3-S (Smart Safety Surveillance), which builds upon pharmacovigilance initiatives for new drugs and vaccines. The foundation has invested about $7.5 million in Project 3-S since September 2017. "Pharmacovigilance provides a safety net if a new product, which has been rigorously tested in clinical trials, behaves unexpectedly once it's introduced on a large scale," says Raj Long, senior regulatory officer at the Bill & Melinda Gates Foundation.

Finally, in this era of big data, we should not squander the opportunity to advance science and record as many details as possible. Biologics are complex medicines — and the collective scientific understanding continues to evolve. Unexpected things do occur. When a patient's condition changes, the doctor can watch for a pattern. If a new medicine triggers the change, it may be worth examining the product differences. What seemed like an inconsequential difference between biosimilars could be the key to an improved medicine or the next cure. It is only by capturing these details that we can learn from them.

Many possible **solutions**

The need for specific product identification is widely recognized but, in the absence of a global leadership, jurisdictions have come up with their own naming systems. The FDA appends a unique, 4-letter suffix to the INN for each biologic and biosimilar. "Employing suffixes more broadly provides a consistent, readily available, and recognizable mechanism for healthcare professionals and patients to correctly identify these products, particularly as more biosimilars or other biological products containing related drug substances enter the market," an FDA spokesperson explained.

Similarly, the Japanese Pharmaceuticals and Medical Devices Agency implemented a naming scheme with the INN and additional descriptors, such as a suffix — albeit a different suffix than the FDA's. Health Canada is currently undergoing consultation and has expressed an interest in both distinct naming and the implementation of an international solution.

The EMA has taken a different approach to specific product identification, relying on the recording of each drug's proprietary name (a requirement in Europe but not other jurisdictions), INN, lot number and bar code. Australia's Therapeutic Goods Administration chose not to use specific identifiers, but relies on mandatory use of the brand name, and is considering adopting a bar-code system.

There is momentum building towards a more comprehensive global approach. In 2014, the International Nonproprietary Name Expert Group of the WHO recommended the implementation of a four-letter suffix called the Biological Qualifier, or BQ. Despite their strong recommendation in favor of the BQ, robustly supported by other stakeholders, the WHO has not advanced implementation of a distinguishable naming protocol for biologics. This lack of progress has led to the current patchwork of country-specific naming standards in urgent need of a better solution.

A promising path **forward**

Regulators like Health Canada's Ridgway believe that the WHO should provide the international framework for distinguishable biologic naming harmonization so that every country, regardless of population size or income level, can benefit from safe biosimilars. The WHO is the organization best positioned to provide a coordinated approach to biologics naming protocols — and to lead uniform adoption by the various national regulators. "The WHO is indispensable in building a global system of pharmacovigilance," says Michael Reilly, ASBM's executive director.

To move any policy forward, the WHO needs support from its member states. The good news is that key stakeholders around the globe widely support distinguishable naming, making the environment conducive for a unified solution. According to a recent ASBM survey[3], two-thirds of biologic prescribers in the United States and Canada believe distinct names are needed; 94% of physicians in Latin America are supportive; as are 79% of physicians in Australia. Additionally, the FDA, which has the most experience implementing distinguishable naming for biologics, is in discussion with the WHO. According to an FDA spokesperson, "The FDA regularly engages with the World Health Organization INN Programme; we have been working closely with the WHO to understand the technical aspects of its proposed naming policy." Experts on the issue from ASBM, the FDA, Health Canada, and WHO met in Washington DC in July to discuss the issue further.

According to surveys conducted by ASBM[3], there is reluctance among healthcare professionals and patients to use biosimilars, because of questions about their effectiveness and safety, says Reilly. Improved pharmacovigilance will help instill confidence so that the healthcare industry can reap the benefits of this emerging market. "A unified naming system could ultimately advance this new era of promising treatments," says Reilly. ●

References

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