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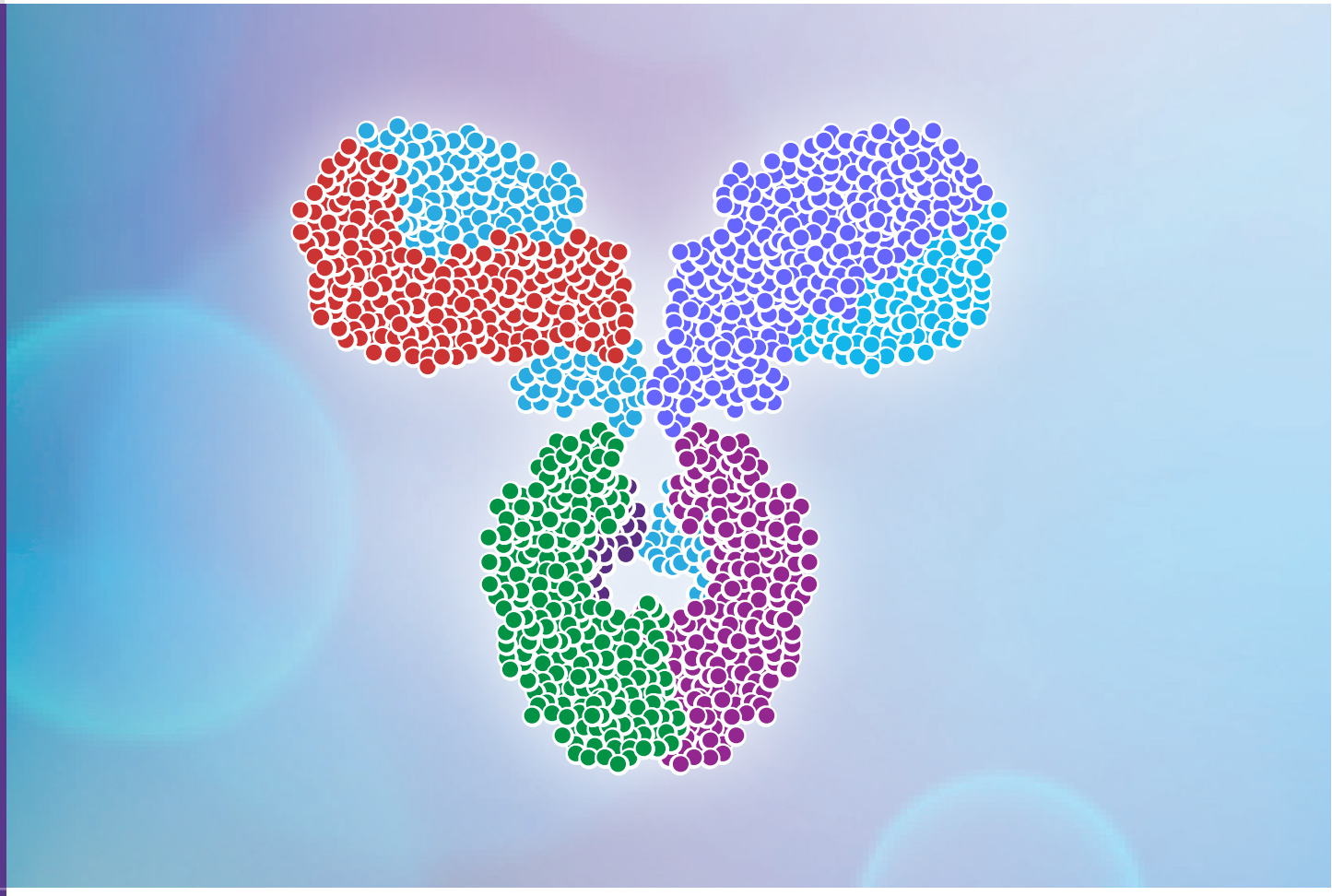
POLICY PAPER



WHAT'S IN A NAME?

The Importance of Biosimilar Nonproprietary Names for Healthcare Innovation

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EXECUTIVE SUMMARY

In my 20-plus years practicing medicine and developing therapies, I have had the great fortune to see patients in Europe and Australia begin to benefit from more affordable, accessible, just as safe and just as effective biologic medications known as biosimilars. I eagerly await approval of these biosimilar therapies in the United States. But I'm concerned that even when biosimilars become available in the U.S., patient accessibility to these life-saving products could be limited by something as seemingly innocuous as the way the drugs are named.

Even though regulatory bodies in many countries and regions have approved biosimilars, important pieces of the puzzle—including ones that could make or break the success of these products—remain on the table, with decisions still to come from regulatory bodies like the U.S. Food and Drug Administration (FDA). One major missing piece of this puzzle? How biosimilars are named in the global healthcare community and whether the naming process remains consistent with historic practice.

So what is in a name? And why am I stressing its importance for biosimilar drugs? Shakespeare declared that a rose by any other name would smell as sweet, but the pharmaceutical world is different. A name means a great deal when it comes to medications, affecting everything from how clinicians perceive the drug to how pharmacists dispense it. In the specific case of biosimilars, a drug's name can clearly signify whether or not it has met certain regulatory criteria and is officially considered "biosimilar." If the name doesn't communicate that to clinicians, biosimilars are less likely to be prescribed, limiting access to these lower-cost, safe and effective drugs. Or worse, confusion about biosimilar names could lead to prescribing errors.

We at Hospira, the first U.S. company selling biosimilars in Europe, believe patient safety and accessibility are best ensured when a biosimilar shares the same "nonproprietary" name, often known as the international nonproprietary name, or INN, with the original biologic. Hospira is uniquely positioned to make this case, having provided more than 5 million doses of biosimilar medicines, at a savings of 25 to 30 percent, to patients in Europe and Australia over the past five years.[1] Through this experience, we

BIOTECHNOLOGY 101: From Original Biologics to Biosimilars

Original biologic medicines revolutionized the pharmaceutical industry, producing significant advances in treatment options for cancer and autoimmune diseases, like rheumatoid arthritis and multiple sclerosis, and other difficult-to-treat and sometimes rare illnesses.

But what exactly are biologics, and how do they differ from traditional drugs, like the Advil™ you might buy at the pharmacy? The most basic explanation is that biologics are made out of biological systems such as living entities like cells and tissues. Small molecule drugs like Advil, in contrast, are traditionally built out of synthesized chemicals.

Although the biologics revolution in drug manufacturing has taken off in the past two decades, biologics have actually been around for hundreds of years. Vaccines and even blood transfusions are considered "biologic" products because they are medical therapies made or extracted from living organisms.

In their simplest form, biologics are proteins that are engineered by scientists and built using a living cell. Or put another way, scientists are able to manipulate a cell

have shown the ability to successfully track use of biosimilar products and monitor their safety in the marketplace.

It is imperative that the World Health Organization (WHO), U.S. Pharmacopeia (USP), the FDA and other international regulatory bodies support the use of the same nonproprietary names for original biologics and biosimilars, mimicking the same practice followed for more than 40 years with the "small molecule" generic drugs that millions around the world have come to rely on.

Why is this issue so important? In the coming pages, this paper will show how using a different nonproprietary name for a biologic and the biosimilar product modeled from it will create confusion among the clinicians who rely on international and local standards to fill prescriptions for patients. Moreover, it may impede access to the annual $20 billion savings—in just the U.S. alone—that biosimilars have been estimated to deliver.[2]

This paper first explains exactly what biologics and biosimilar products are, in plain terms, for any readers unfamiliar with this science. We then review, for the first time, Hospira data that unequivocally show biosimilars can be safely tracked when on the market. In fact, between 2008 and the present, in more than 99 percent of post-marketing reports received by Hospira and reported in the European Union concerning Retacrit™—Hospira's biosimilar erythropoietin—the product was identified by its brand name. For Hospira's Nivestim™ (filgrastim) biosimilar, more than 95 percent of post-marketing event reports were reported by its brand name between market introduction in 2010 and present.

We then examine how no two biologic products, including those made by the original manufacturer, are identical from one manufacturing batch to the next, and recount the 40-plus-year history that will be ignored if different nonproprietary names are used for biosimilars that have comparable clinical effects to the original biologic.

Finally, we will review how having different standards for naming a biosimilar in each country will undermine the point of having nonproprietary names in the first place, creating further confusion for clinicians and patients across the globe, especially in the evolving globalization of medical practices.

into being a protein factory that produces the biologic drug.

However, many of these therapies are very expensive and can range up to $100,000 or more for a year of treatment.[3] Many of these drugs are also losing their patent protection from market competition, meaning there is a significant opportunity for cost savings by introducing more affordable alternatives. Those savings will be achieved by the regulatory approval and market availability of biosimilars, the "generic" version of a biologic product. Biosimilars are biologics that are developed to be similar or comparable products to the original biologics they are modeled after. Biosimilars have been approved numerous times in Europe, Australia and other markets, providing patients affordable alternatives and improved access and already delivering significant savings to healthcare systems.

Unlike a small molecule drug such as Advil, it is impossible to get an exact copy of an original biologic drug every single time because the biologic is made in a living system that is sensitive to its environment. The biologic product made by the living system can change, ever so slightly, based on the very specific conditions in which these cells

WHAT'S IN A NAME?

When the WHO established the INN system in 1950, it did so with a purpose: to facilitate clear, safe and accurate identification, prescribing and dispensing of individual pharmaceutical substances within the international medical and scientific community.[4]

Under that goal, the WHO established a system where a drug's nonproprietary name signals what makes up the active ingredient of a given drug.[5]

If the WHO, USP or FDA adopt a practice of giving a different INN to biosimilars, it will set a precedent that will have grave ramifications in clinical practice and in the current naming conventions that have become the global gold standard.

This system—where different elements of a drug's name indicate, for example, whether it's going to impact a particular mechanism of a cell or describe which molecular class the drug fits in—has worked for thousands of brand name and generic drugs for decades.[6] If the WHO, USP or FDA adopt a practice of giving a different INN to biosimilars, it will set a precedent that will have grave ramifications in clinical practice and in the current naming conventions that have become the global gold standard.

First and foremost, the clinicians who prescribe drugs and the patients who receive these drugs will see an INN with an added prefix or suffix and think: if it is named differently, then it must be a different drug with a different way of acting. It is even worse if the biosimilar has a prefix, because clinicians may not recognize the INN name at first, leading to confusion and potentially harming patient safety. The worst option, of course, is if a biosimilar has a completely different INN altogether.

are grown and fed to produce the biologic. So a biologic and its biosimilar will always be slightly different, while still producing the comparable clinical results for safety and efficacy. Importantly, the same is also true for the original biologic drug. Even if a manufacturer uses the exact same process to produce an original biologic, slight differences occur during the production process due to the vulnerability of living things. Unlike synthetic products and based on today's technologies, an exact copy of a biologic cannot be made every time.

The most important takeaway is that original biologics and biosimilars are required to deliver comparable clinical results for the patients who are getting treated. But they may nonetheless vary in the shapes the molecules of the drug ultimately take.

Say, for example, Biosimilar Company ABC wants to create a biosimilar of Biologic Drug 123. The scientists at Biosimilar Company ABC know which amino acids make up the protein used in Biologic Drug 123, but they don't know the exact recipe used to grow the cells and get them to produce Biologic Drug 123. So they develop their own "cell line" to reverse engineer the biosimilar of Biologic Drug 123. While they

All of these scenarios could give clinicians the idea that biosimilars have a different clinical effect from the original biologic drug. That is incorrect, and it was not the intent of the laws passed to allow biosimilar approval. Different nonproprietary names should only be used for products that achieve approval as original biologic drugs, not drugs approved as biosimilars. The entire purpose of regulatory biosimilar approval is to ensure that the biosimilar has comparable clinical effects, using a similar biologic protein, but at a more affordable cost.

can get the amino acids - the building blocks of biologics—to exactly match those used in Biologic Drug 123, there's a catch: the protein their cell created might be slightly different in "shape" than the one in Biologic Drug 123. However, to be approved as a biosimilar, the clinical benefits must be proven to not differ.

The scientists at Biosimilar Company ABC can use different techniques to get the protein to closely resemble the shape of Biologic Drug 123. But it's almost impossible to get the biosimilar to take the same identical form as Biologic Drug 123. Even though the drugs will act the same way when given to a patient, the varying protein shape means they will always be slightly different in the way they look but not necessarily in the way they act. Variability in shape is also seen in Biologic Drug 123 from one manufacturing batch to the next.

A biosimilar must be as safe and effective as the original biologic. For example, Hospira's clinical trials on biosimilars earned approval from the European Union and Australian regulatory authorities because they met key safety and effectiveness tests of similarity to the orginal biologic.

BREAKING DOWN THE INN

It may seem obvious that drugs must be properly identified in order for healthcare professionals to prescribe the right product and for patients to know they are taking what the doctor ordered. But in a complex, global industry that speaks a multitude of languages, communicating exactly which drug should be taken—and whether the often more affordable and just as effective generic version is permissible—can be challenging.

To highlight just how important a name can be in the pharmaceutical world, let me share an example from my personal experience. During my years as a practicing physician, I was on vacation in a major European country when I got a bad headache. So I stopped in a local pharmacy to get the common pain reliever known as acetaminophen. But when I asked the pharmacist for the drug, he did not know what I was talking about. I said I was looking for a pain reliever, and the pharmacist offered ibuprofen. I like to stay away from taking ibuprofen because I can have a mild asthmatic reaction to the drug. Plus I knew that acetaminophen was a globally available drug—it seemed impossible that it would not be available in a European pharmacy. But after some back and forth, it became clear we were not communicating. I gave up and took the ibuprofen.

Later, I discovered what the problem was: acetaminophen is the rare example of a drug that has a different nonproprietary name in the United States versus Europe. What we call acetaminophen is known as paracetamol in Europe and other countries. But even though I was a physician, specializing in internal medicine, I was not familiar with this different name. Upon inquiry with several of my medical and lay colleagues, they were not aware that the "generic name", i.e. the INN, of acetaminophen was known differently in Europe. This captures just a fraction of the challenge a clinician or the general public can face when drugs do not share nonproprietary names in the global marketplace.

Drugs generally have two names that are important to patients and clinicians: the brand name and the INN. While many generic versions of drugs have their own brand name, a global system was established

through various regulatory bodies, including the WHO, to make sure drugs with the same active ingredients had a standard "nonproprietary" name. That way, health professionals knew what drugs they were prescribing, regardless of whether they are the original brand name product or the generic that followed it. And patients got the drugs they were prescribed.

This has held true for biologic drugs up to now, even though the biologic products made by the same manufacturer can have slightly different versions of the same molecules. By giving original biologics the same INN, even with this slight variation, the WHO and other bodies acknowledged there will be some level of variability in biologic drugs, but the slightly different shapes will still deliver similar clinical benefits. In addition, since biosimilar approval began in the European Union in 2006, several of these drugs have been approved with the same INN as the original biologic.

A familiar example is the proprietary name for a common pain medicine—Advil™—and its nonproprietary name, ibuprofen. While there are many generic versions of Advil on the shelves, they must use different brand names than "Advil." But when you look at the fine print, you will see that they all share the same nonproprietary name of ibuprofen. The name "ibuprofen" has become so well known that many generics don't have a brand name at all—they simply state the nonproprietary name as the form of identity of the drug. Of course, the product has other unique identifiers such as the manufacturer name and lot number. We will touch upon those other unique identifiers later in this paper.

The nonproprietary name helps pharmacists and other healthcare professionals identify what the expected clinical activity of the active ingredient is, no matter what language they speak.

In traditional "small molecule" drugs, both original and generic versions of a drug share the same nonproprietary name. This is a practice that has been and should continue with biologic drugs and their biosimilar versions. Changing this well-established practice would lead to unnecessary confusion for clinicians and patients worldwide. It could also end up compromising patient safety, as doctors and clinicians will have to essentially memorize names of dozens (if not hundreds) of versions of drugs with comparable clinical effects.

In the United States, Congress passed legislation as part of the Affordable Care Act (ACA) in 2010, giving the FDA the authority to approve biosimilars as long as manufacturers prove they have comparable clinical results.[7] This does not mean it is easy to get a biosimilar approved. Though several biosimilars are available to the public in the European Union, Australia and New Zealand, the FDA has yet to greenlight a biosimilar in the United States, largely because patents or exclusivity on original biologic products have not yet expired.

And while several countries already have biosimilar drugs available for public use, there is not yet consensus on how to name biosimilars versus original, or "reference," biologic drugs. That has created a rift among regulatory bodies around the globe.

Some regulatory bodies, including those in Japan and Australia, are already adding a prefix or a suffix to the nonproprietary name of the biosimilar drug.[8,9] Original biologic manufacturers argue that an additional unique identifier beyond the already present unique identifiers of brand name, manufacturer, National Drug Code (NDC)—a 10-digit ID number assigned to the medication in the United States—and lot number is needed because the biologic and its biosimilar version are not identical.

Not only does that proposition defeat the purpose of the FDA's approval process, which establishes that biosimilars are as safe and effective as compared to the original biologic, but it also calls into question giving any biologic drug, even if it is produced by the original manufacturer, the same INN. That's because even if a biologic is produced in exactly the same way, by the same manufacturer, using the same tools, over time slight changes start to appear, particularly if manufacturing changes are introduced. These changes, known in the industry as "drift," are quite common.

Or as Christian Schneider, a respected Danish pharmaceuticals regulator, put it recently, "Non-identicality is a normal feature of biotechnology."[10] In fact, biologic products differ enough that whenever an original biologic manufacturer changes its production methods, whether it is as small as changing the supplier of cell growth materials or as significant as using an

entirely new manufacturing site, the manufacturer must prove to the FDA, the European Medicines Agency (EMA) and other international regulatory authorities that its biologic drugs still meet the same physiochemical characteristics and biologic activity of the product prior to the change and will still produce comparable clinical outcomes.[11]

So if we start to change the INN for biosimilar drugs because they are not "identical" to the biologics they are following, shouldn't we also change the INN for original biologics every time a shift in the profile of that drug occurs? For example, this comes into play when a new manufacturing site is used to make the drug or when a manufacturer changes the equipment that is used to make that drug, since the drug doesn't always identically match the profile of the original biologic before the change.

Of course, this extreme example would create an incredibly unwieldy situation for pharmacists, doctors and patients. Doctors would be forced to remember several different INNs for the same drug. It is not the prescribers' job to remember a vast array of terminologies for the same drug. Simplicity ensures compliance and fewer errors. It is physicians' job to take care of the patient. But if we go the way of changing an INN every time a drug differs slightly in chemical make-up (but not in clinical effect), then we will create problems in the future that will have significant clinical impact. INNs cannot be owned by a company making a specific product—that is not the intent of this naming system.

TRACKING BIOSIMILARS RELIES ON MORE THAN ONE MARKER

A common argument for giving a biosimilar a different INN is that it will help improve the tracking of any potential safety incidents, or, in technical terms, pharmacovigilance. If a biosimilar has a different INN from the original biologic, goes the argument, then the FDA and other health regulators will know exactly which product a patient received.

There is a serious flaw with this argument, and Hospira has the data to counter this claim from information we receive from our pharmacovigilance process on our biosimilar products currently on the market in Europe. **Our data show that patients and healthcare professionals include the brand name of the biosimilar product when reporting an event in the vast majority of cases. They do not use the INN alone.**

Hospira introduced biosimilars in the European Union in 2008. Since late 2008, more than **99 percent of the post-market reports received by Hospira regarding our Retacrit biosimilar were successfully identified as Hospira's product without the need for INN differentiation**. Less than one percent could not be attributed to any brand.[12] For Hospira's

Hospira biosimilar Retacrit™ in the Eurpean Union, 2008-2013

Nivestim biosimilar, the rate of post-marketing reports that successfully identified Hospira's product was more than 95 percent.

As these data show, it is possible to have robust safety data without requiring a biosimilar to have a different INN. Patients and clinicians use the biosimilar's brand name when identifying a drug the vast majority of the time when reporting any incidents.

Moreover, there are several other important markers that clinicians and pharmacists use to identify exactly which drug was prescribed to a patient and can be tracked in event reporting. To improve drug safety tracking, the critical improvement needed is not with INN names, but with automated, electronic tracking systems that can directly track which drug was taken by whom. Already, U.S. pharmacists are required by their state boards of pharmacies and by payers to record the NDC when dispensing a drug. This is helpful information when reporting and tracking adverse events.

Biologic products are typically dispensed in a very controlled manner, often inside a hospital or doctor's office or by specialty pharmacies. In other words, these are not the oral drugs that patients would typically fill at their neighborhood pharmacy. Biologics are primarily injectable drugs that are often administered by a healthcare professional. And, while there are some biologic drugs that are self-administered outside the health professional setting, these biologic drugs are dispensed by specialty pharmacies that have a record of which drug was dispensed to which patient. So comparing event reporting of future biosimilars to small molecule oral drugs that patients get at their local pharmacy, as some have done, is like comparing apples to oranges. The situations are very different.

In addition to having a robust data collection system in place, Hospira and other makers of biosimilar products will be required, as is customary with original biologics, to conduct rigorous U.S. post-marketing safety evaluations. This has already been done in the European Union, to ensure that our products continue to be monitored while in the marketplace.

BIOLOGIC NAMES HAVE HISTORY

The history of biologic names is also significant to this debate. In the past, adding a prefix or a suffix to the nonproprietary name of a biologic signaled that there were significant differences between products, not the "minor differences" the FDA will allow between an original biologic and its biosimilar version.[13]

Take, for example, biologics such as interferons. These proteins are used to treat a wide variety of diseases. To signal which interferon biologic should be used to treat a specific illness, the suffix "alfa" or "beta" is added to the INN. For example, "interferon alfa" is used to help patients with hepatitis or melanoma, while "interferon beta" is used in therapies treating multiple sclerosis. The key is that interferon alfa and interferon beta are actually different molecules at the molecular level and at the clinical effect level. An original biologic and a biosimilar, by contrast, have very slight differences at the molecular level, and are deemed to be comparable at the clinical level.

From this example, one can see how a clinician would read a suffix added to the INN and think that the biosimilar did a completely different thing than the original biologic. If "alfa" and "beta" in an INN signal that a drug should be used to treat diseases as different as hepatitis and multiple sclerosis, why wouldn't you think the same applies for other suffixes?

So how confusing can a few extra letters be? Imagine you are a doctor intending to prescribe a biologic drug to help cancer patients. One such product that accomplishes this is called "filgrastim." Another product, "pegfilgrastim," is essentially filgrastim with a molecular modification that allows it to work much longer, meaning it is dosed differently and patients have to take it much less frequently. If you see that there are five new versions of the drug you want to prescribe in an e-Prescribing system, all with different prefixes before "filgrastim," it wouldn't be surprising if you assumed that meant the drugs with the added prefix letters had been made in a significantly different manner that achieve a substantially different clinical effect, like the difference between filgrastim and pegfilgrastim.

Or what if you are the pharmacist? You go to your computer to fill an order of "filgrastim" and see there is a handful, or maybe even dozens, of different versions of that INN. Given the history of biologic naming, it again would not be surprising if you assumed that an added prefix or suffix means the drug has a substantially different clinical effect.

The issue became even more complex in 2012. A pharmaceutical company submitted to the FDA for approval a biosimilar that was already on the market in Europe. However, the pharmaceutical company decided to submit the biosimilar through the FDA process used to approve an original biologic, known as the Biologics License Application (BLA), or the 351(a) pathway, instead of the biosimilar pathway.

The FDA approved the drug as a brand new application, but also added a prefix to the INN used for the original biologic. This FDA approval doesn't set precedent or indicate the future action of biosimilar naming. Instead, it reflects the fact that the drug was approved as an original biologic and not as a biosimilar. Nonetheless, some have incorrectly interpreted the assignment of a prefix to the name of this drug approved via the original biologic pathway as setting a precedent for future biosimilar naming.

It's also important to remember that biologics and their similar versions have already shared INNs for more than 40 years. The following chart is just a small sample of the biologic products that have been routinely and safely used around the globe under the same INN.[14]

The bottom line: adding prefixes and suffixes to biologic products historically means that something is clinically different with a drug. That is not the case with biosimilars, which are approved by regulatory agencies to have similar clinical results as a brand name biologic drug.

SIMILAR BIOLOGIC PRODUCTS THAT HAVE SHARED INNs

Brand Name	INN	Use	Manufacturer	Approval year
Avonex®	Interferon Beta-1A	Treats multiple sclerosis	Biogen	1996
Rebif®			Serono inc.	2002
Betaseron®	Interferon Beta-1B	Treats multiple sclerosis	Bayer Healthcare	1993
Extavia®			Novartis	2009
Asellacrin™	Somatropin	Growth hormone	EMD Serono	1976
Crescormon®			Genentech	1979
Accretropin™	Somatropin Recombinant	Growth hormone	Cangene	2008
Bio-Tropin®			Ferring	1995
Genotropin®			Pharmacia and Upjohn	1995
Humatrope®			Eli Lilly	1987
Norditropin®			Novo Nordisk	2000
Nutropin®			Genentech	1993
Omnitrope®			Sandoz	2006
Saizen®			EMD Serono	1996
Serostim®			EMD Serono	1996
Tev-Tropin®			Ferring	1995
Valtropin®			LG Life	2007
Zorbitive®			EMD Serono	2003

INTERNATIONAL STATE OF CONFUSION

Without an international standard on naming biosimilars, individual countries or regions of the world have been left to make their own rules. The disparate rules among the countries that have approved biosimilars will lead to even greater confusion among clinicians and patients given the interconnected world we live in and how information flows freely between countries.

The following list explains the different standards countries have established for naming biosimilars:

- **European Union:** For nearly a dozen years the EU has used the same system for naming biologics. There are no formal rules for biosimilar drugs, but in general they are given a unique brand name and share the same nonproprietary name with the original biologic.[15]

- **Australia:** The Australian drug regulatory body in July released initial draft guidance that requires a suffix be added to a word following the biosimilar. The suffix must start with the letters "sim" (to signify the word "similar"), and can end with any letters the biosimilar company chooses. For example, a biosimilar for the drug "infliximab" would be called "infliximab simfam."[16]

- **Japan:** Japanese regulators require that biosimilars have nonproprietary names that are followed by the word "Follow-on" and the brand name should be followed by the letters "BS" for biosimilar.[17]

- **United States:** The legislation giving the FDA the authority to approve biosimilars did not include directions on how biosimilars should be named.

CONCLUSION

We have the scientific knowledge necessary to create affordable, life-saving drugs for a global population. One of the many things needed for biosimilars to be successful is to follow the naming standards that are already globally established to facilitate the adoption of more affordable, life saving biosimilar drugs.[18]

The evidence is clear. In the EU and Australia, Hospira biosimilar products save patients 25 to 30 percent when compared to the original biologic drug.[19] Biosimilar drugs could deliver savings of up to $20 billion a year in the United States alone, according to estimates.[20] Savings have already been realized in Europe since biosimilars were first approved. And, since original biologic drugs are typically among the highest-cost therapies used, the savings have been significant.

If we allow biologics and their biosimilars to have different nonproprietary names, it means patients and clinicians will not realize the full extent of these consequential savings. Instead, clinicians' therapeutic plans will become harder to execute, potentially putting patient safety at risk by causing confusion as to how the different drug names translate into therapeutic effect.

The international community should not change the rules governing naming. Using the same nonproprietary name for generic and brand name small molecule drugs is a successful foundation that biologics and biosimilars should build off of, not dismantle a successful 40-plus-year history.

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