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Biosimilar Nomenclature: Can We Achieve the Truth, the Whole Truth, & Nothing but the Truth?

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I. INTRODUCTION

Urban legend attributes the following quote to Albert Shanker, the very outspoken past president of the American Federation of Teachers: "When school children start paying union dues, that's when I'll start representing the interests of children."

As always, it's a question of priorities — and whose priorities. Today that same issue has arisen in the debate over biosimilar nomenclature.

The issue for drug compendia, regulators in charge of pharmacovigilance programs, is (among other things) interoperability.

According to *Inside Health Policy:*

> "While some say an easy solution is to simply add a suffix to distinguish a biosimilar from the innovator product, the compendia group told FDA any change is a change, and regardless of the simplicity of the change, the associated coding would also have to shift. First data bank and two other databanks are sold to stakeholders who assemble them and put overlays on them and then the data are used for different purposes, including for reimbursement."[1]

Unfortunately change is not always easy. But as management guru W. Edwards Deming warned, "Change is not required. Survival is not mandatory."

Assigning differential naming to biosimilar products will certainly prove challenging to the various constituents of the drug compendia community — but it will be crucial for pharmacovigilance. In the real world, how can we not have separate names when there are going to be four categories of products?

Based on comparative analytical data, FDA will characterize its assessment of biosimilarity into one of four levels -- not similar, similar, highly similar or highly similar with a fingerprint-like similarity — depending on the type, nature and extent of any structural and functional differences revealed.

Additional pharmacologic studies would be required to show that the identified difference is "within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product." FDA said only products in the top two tiers would meet the statutory requirement for analytical similarity under the Biologics Price Competition and Innovation Act of 2009. Products in the top two tiers would then only require "targeted and selective animal and/or clinical studies to resolve residual uncertainties" to demonstrate biosimilarity. In addition, these data could be used to extrapolate clinical data for additional indications.

Giving credit where credit is due, the good people at the United States Pharmacopeia understand that interoperability is important, but that naming (per USP) is more of a philosophical issue. That's why they support differentiation via discrete numerical suffix.

Per *Inside Health Policy:*

> The drug compendia stakeholders told a group of 13 FDA drug policy experts, including drug center chief Janet Woodcock, that changing the traditional naming process would require that each piece of the compendia process be individually rebuilt in order to ensure patient safety and restore functionality to the system. Doing so, while possible, would be difficult and could lead to confusion, errors and misunderstanding, creating a "very real risk to patients," according to slides presented at the May 2 meeting and a June 6 follow-up letter, obtained by Inside Health Policy.[2]

The argument that differential naming is bad for patient safety is pure Orwellian Newspeak — specifically "blackwhite, "The ability to accept whatever "truth" the party puts out, no matter how absurd it may be — no matter the lack of supporting data. When it comes to biosimilar nomenclature, it's urgent that we keep our priorities straight. And that means keeping patient safety, not interoperability challenges, at the top of the agenda. Fortunately, White Oak trumps blackwhite.

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POLICY RECOMMENDATIONS

- Insist that the FDA require differential nomenclature for all biosimilar products.
- Require physician notification for all patients switched from an innovator medicine to any biosimilar product.
- Develop more robust and frequent pharmacovigilance programs for biosimilars.
- Expand post-marketing surveillance to gain better "real world" perspectives on the therapeutic outcomes of both naïve and switched patients using biosimilar medicines.

II. BACKGROUND

Biosimilar drugs offer the very real possibility of providing patients with quality alternative medicines and enhanced treatments at better prices. But bringing biosimilar drugs to patients depends on achieving a transparent, predictable, competitive marketplace, protected by strong intellectual property and regulatory systems — and keeping patient safety and therapeutic outcomes at the center of the conversation.

Physicians live in the real world where cost concerns of patients, insurance companies and the government chaff against the freedom to practice the art and science of patient-centered care.

Wanting something to be true (whether a "magic pill" for a nation's budgetary woes or a "risk-free" way to reduce a patient's medical expenses) should not cloud the judgment of lawmakers or physicians or regulators. But the blinders of cost-containment on the one hand, and easy profits on the other, must never be permitted to obscure the twin therapeutic pillars of safety and efficacy.

It's always important to begin a discussion of biosimilars by reminding ourselves that there is no such thing as a *generic biologic*. "Big" molecules are more than just larger versions of "small" ones.

Biologics are created from living organisms and are not as simple to replicate as traditional drugs like aspirin and antihistamines. *Biosimilar safety* means something different than *generic drug* safety.

At Dr. Janet Woodcock's (the Director of the FDA's Center for Drug Evaluation and Research), recent Energy & Commerce Subcommittee on Health she was asked if the FDA's decision to allow differential labeling for generic drugs also included biosimilars.

Per Dr. Woodcock, "This rule does not apply to that because those would be under the Pubic Health Service Act — and they're not considered generics, so that's a separate issue."[3]

Some see it as a nod and a wink that the agency is going to allow biosimilars to have the same name and labeling language as innovators. I disagree for two reasons:

- Dr. Woodcock was precisely correct in stating that generic drugs and biosimilars are two distinct things. Biosimilars are not generic drugs.
- The fact that the FDA has made distinct generic drug labeling such an important policy initiative certainly does not send a signal that they will view biosimilars in a more *laissez faire* manner. *Au contraire*.

Per FDA guidance[4], to establish that two protein products are both similar and interchangeable, the sponsor of a follow-on product will need to demonstrate through *de novo* clinical trials that repeated switches from the follow-on product to the referenced product (and vice versa) have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity.

For many follow-on proteins — and in particular the more complex proteins — there is a significant potential for repeated switches between products to have a negative impact on patient safety and clinical effectiveness.

It is for these reasons that we must focus on bioequivalence, bioavailability and their impact on immunogenicity.

Careful consideration of the advantages and disadvantages of biosimilar drugs should be the guiding principle for all involved as we first ensure to "first do no harm." When it comes to biosimilar drugs, the most important issues facing global drug regulators are the scientific and technical factors related to a determination of biosimilarity and interchangeability — and they are not the same thing. As an article in the Journal of Infection so aptly stated, "Nothing is more expensive than treatment failure."[5]

III. MAJOR ISSUES IN DISPUTE

Efforts to derail biosimilar pharmacovigilance are contrary to the public health and require rebuttal.

Some generics manufacturers, payers, and national chain drug stores have interwoven half-truths, out of context comments and just plain misinformation to build a fatuous argument dressed up as support for patient safety. But the actual patient and safety communities are firmly on the polar opposite side – in favor of safety, choice, and transparency.

The insurance-industry driven effort claims that distinguishable names for biologics "could lead to patient and prescriber confusion, increasing the possibility of medication errors."[6] Unpacking that a bit, biologics are complex therapies that are made from living cells and prescribed for patients with difficult-to-target, debilitating and life-threatening health conditions such as cancer, diabetes, MS, lupus, Crohn's disease and rheumatoid arthritis. There are no generics for them but it is expected that the closest thing — biosimilars — will soon enter the US marketplace. What the insurers are essentially saying is that, a biosimilar that relates to a biologic should have exactly the same name as that biologic.

In the case of biologics and biosimilars, even minute differences between products can cause individual patients to respond differently even though each product is considered safe and effective. Of greatest concern is immunogenicity, which carries a significant risk for all biologics. Because of the size and complexity of the biologic molecule, patients can experience unwanted immune reactions; these reactions can occur months after a patient begins taking the medicine and it is often difficult to know if it is due to the reaction to the medicine or simply the progression of the patient's condition.

As John Adams said, "Facts are pesky things." And facts that don't reinforce your cognitive mapping are pesky things. But that does not change the fact that nothing deserves truth and accuracy more than the public health.

Here are some of the more egregious myths shared by the aforementioned group of compendia stakeholders along with the facts to debunk them.

MYTH
Distinguishable naming for every biologic, biosimilar and interchangeable biologic could confuse both providers and patients, and have the unintended effect of slowing the uptake of these cost saving drugs.

FACT
The patient and safety communities, as well as many physician organizations have weighed in on the same issue, and have come out on the opposite side — in favor of transparency, so that patients can know which medication is being put into their bodies and the whole system can quickly connect the dots to stem negative impact when an adverse event occurs. The scope of patient-focused organizations that have come out in support of distinguishable naming is so broad, it covers virtually every single American family.

MYTH
While it is important to gather data that allows providers to better understand how biologics and biosimilars are performing among various patient groups and to assist in the tracking of adverse events, the current mechanisms in place (e.g., National Drug Code, lot number, brand name, manufacturer, etc.) are sufficient.

Traditional naming structures do a good job of tracking post market issues (NDC, lot number, brand name, manufacturer, etc.).

FACT
Other, complementary tracking systems do and should exist, however non-proprietary names are the backbone of pharmaceutical tracking within payment systems, not necessarily for tracking and tracing adverse events (AEs). The National Drug Code, or NDC, system provides a unique 10- or 11-digit set of numbers for each medication, however payers do not universally use NDC codes.

A lot number alone is not sufficient enough to identify a product and its manufacturer. It is only useful when it is accompanied by an identifier that is linked to the manufacturer. While having brand names is useful for tracking and tracing AEs, they are not always used when prescribing or reporting AEs.

Additionally, there is a lack of standard use in medical benefit setting where the majority of biologics are administered and NDCs are not necessarily present in patient records. When are entered there are many instances in patient care where NDC codes have been inaccurately entered.

Current approaches and systems do not allow for adequate collection of data relating to patient subpopulations, such as women, minorities and people with specific genetic problems; depending on the level of additional clinical research that will be required to bring a biosimilar to market, it is very likely there is much we won't know about how a biosimilar might uniquely impact these subpopulations. Distinguishable names for biosimilars support the patient advocate and medical community's vital post-approval learning curve to determine which medicines are best for patient subpopulations.

The clarity from distinguishable non-proprietary names will:

- Enable better safety monitoring.
- Promote timeliness in managing adverse events if they occur.
- Provide physicians with more information to understand which products are likely to be more effective in specific patient subpopulations.

MYTH
Requiring distinguishable names would segregate the safety data for brand and biosimilar products, making it more difficult to detect rare AEs across classes of products.[7]

FACT
The 2013 study referenced in this assertion did in fact find that 96.2% of adverse events could be traced back to biosimilars if either the brand name OR INN or company name were available. However, "…products for which only the INN was available were considered non-identifiable, except for epoetin zeta, for which product the International Non-Proprietary Name (INN) differs from the innovator (epoetin alfa)," (pgs. 619-620). This is precisely why there needs to be distinguishable INN/ USAN names: so that products that can only be identified by INN/USAN (United States Adopted Names) can still be traced. Furthermore, the 2013 study cited actually found that 1 out of every 10 (90.4%) adverse events related to biosimilars can't be traced back to a specific product if the biosimilar was given concomitantly or interacted with another medication.

MYTH
The World Health Organization (WHO) has already established a global naming convention, known as the International Non-proprietary Names (INN) system.

FACT
The INN system was established in the 1950's to identify active ingredients in small molecule chemical compounds, well before highly complex biologics were developed.

Unlike traditional pharmaceutical medicines (small molecule, chemical entities), where the active ingredient of a generic and the originator compound are identical, the active ingredient for biologics (large molecule) is complex, and a biosimilar will not be an exact replica.

WHO has not announced how it may alter its existing INN program to effectively serve biologics including biosimilars, however the organization's published deliberations on the issue indicate change is likely:

"Compared to a small chemical entity, biotherapeutic proteins are large and complex, with four levels of structure (primary, secondary, tertiary and quaternary). The complexity of their structure is often further augmented by glycosylation and other molecular modifications, whose variability can impact on bio-activity. There are already several different naming policies for Similar Biotherapeutic Products (SBP) amongst individual regulatory authorities and in some cases, alternative interpretation of INN policy has led different authorities to assign different non-proprietary names for the same product. If prescribers rely on regulatory authority names, this will lack global consistency and could lead to different SBPs having the same name in different countries.

Four approaches are suggested on how to deal with this situation:

- Continue with the status quo
- Treat all SBPs as unique products and provide them with a unique INN
- Create a biosimilar 'identifier' to be used for all SBPs (and not just glycosylated ones), e.g. use the original INN and add a fantasy code suffix
- Encourage regulatory authorities to provide an 'identifier' under the guidance of WHO"

"The last two approaches fulfill the need for a unique identifier of a biosimilar and it would be preferable for the WHO to perform this (i.e. the third option); if regulatory authorities are involved (fourth option), there is no guarantee that a name will be accepted and adopted globally. The naming of SBPs needs to be

addressed globally and soon while the number of registered SBPs remains relatively small and with the INN programme being the best forum to achieve this."[8]

MYTH
Changing the traditional naming process would require that each piece of the compendia process be individually rebuilt in order to ensure patient safety and restore functionality to the system.

FACT
Comparing biologics to small molecule products that share identical active ingredients *misses the crucial point that biosimilars are not generics*. If the proper use of biosimilars requires modernizing the existing system of safety alerts, then it is imperative to do so.

Existing INN's for small molecule medicines and their generic counterparts do not need new naming conventions, only biologics. This significantly reduces the alleged burden on the system.

As medicine and technology evolves, so should our naming and coding process. Patient therapies should be precise and traceable every step of the way; the cost of implementing computer upgrades should never be presented as an obstacle to ensuring the safety of patients.

MYTH
There is already a precedent for shared names that has not resulted in any known issues and are used effectively in EU, Canada, Australia and Japan.

FACT
The non-proprietary naming system in Europe (INN) has mainly been used for first-generation biosimilars, as second-generation products have only recently been approved for marketing in the EU. Historical data that is collected from first generation biologics will be largely irrelevant and will not provide an accurate picture of potential pitfalls as complex second generation biologics enter the marketplace.

Canada has one biosmilar on the market and has stated that it will likely follow guidance issued by WHO as it establishes its naming nomenclature system for biosimilars. Australia and Japan have established their own systems to biosimilars naming, both of which take a distinguishable naming approach. The Australian system includes a shared INN and suffix and early evidence indicates successful entry and uptake.

Often left unmentioned is the well-documented situation in Thailand, which resulted from the use of shared non-proprietary names. From the Citizen Petition filed January 7, 2014 by Johnson & Johnson with the FDA:

> "Between 2004 and 2007, despite our switch to coated stoppers, adverse event reporters worldwide reported 15 cases of erythropoietin antibody-mediated PRCA (*pure red cell aplasia*) in patients with chronic kidney disease who had been administered subcutaneous epoetin alfa. Of these 15 cases, 11 occurred in Thailand. The Thai market included multiple epoetin alfa products and hospitals and pharmacists frequently switched patients among them, often with incomplete documentation. Despite an extensive investigation, we were unable to determine which product(s) were responsible for the PRCA in the Thai patients because we could not determine which epoetin alfa product(s) a patient had received or which of several products that a patient had received had caused the problem.
>
> In Thailand, several different erythropoietins were used, some of which shared the same nonproprietary name, and records did not reliably identify which specific product a patient

had received. These factors confounded our ability to identify the product(s) responsible for the safety signal. To our knowledge, the product(s) responsible for the increased rate of PRCA in Thailand has never been identified."[9]

In the early 2000s, Thailand used non-distinguishable names for biological treatment of treat certain diseases, which lead to a dramatic increase in incidences of blood-related adverse events. Some of the products shared the same non-distinguishable name and records did not reliably identify which specific biosimilar a patient had received. These factors confounded the ability to identify the product responsible for the safety signal…When patients are switched between or among products, it can be difficult or impossible to identify the product responsible for an adverse event…contributing to the inability to identify the responsible product for cases of PRCA in the Thailand situation was the common practice of switching patients among the multiple epoetin alfa products available. And even where records identified which product(s) a patient received, it was often impossible to determine the particular product responsible for the PRCA because many patients had received more than one product."

In order to prevent another life-threatening adverse event, more expensive registries were ultimately required in Thailand to better track these products and related outcomes.

MYTH
Distinguishable names would be contrary to sound economic healthcare policy and congressional intent in the Biologics Price Competition and Innovation Act (BPCIA)."

FACT
The patient and safety communities, as well as many physician organizations have weighed in on the same issue, and have come out on the opposite side — in favor of transparency, so that patients can know which medication is being put into their bodies and the whole system can quickly connect the dots to stem negative impact when an adverse event occurs. In the views of these stakeholders:

- "If untraceable biosimilars become the norm and should the hypothesis of biotherapeutic equivalency not prove to be correct it would likely cause significant morbidity and mortality and thus irreparably damage this market and consumer and practitioner confidence in this class of products."[10]
- Distinguishable names can prevent delays in determining the cause of an AE by creating a more expeditious route back to the origin of the problem and may avoid the recall of an entire class of biologics (which would be necessary if the specific medicine causing the adverse effect could not be readily identified.)."[11]

Additionally, Australia opted for distinguishable codes for all biologics, and they appear to be experiencing successful rollout and uptake of biosimilars.

MYTH
The incident surrounding ado-trastuzumab[12] shows the risk of confusion with prefixes and can cause patient safety concerns.

FACT
Safety and quality experts concluded that the lesson learned by the ado-trastuzumab incident is not that prefixes present a patient safety risk but instead that strong coordination is needed between FDA, USAN,

National Library of Medicine (NLM), USP, Compendia, and Health Information Technology (HIT) stakeholders regarding naming for all biologics, including biosimilars.

MYTH
Applying different names for the same biological drug ingredients:

- Introduces confusion and unnecessary complexity
- Is contrary to historical FDA practice and policy
- Is opposed by virtually all pharmacy association stakeholders because it conflicts with normal pharmacy practice — employing an electronic database to recognize products by identifiers
- Is unnecessary for product recall or other patient safety considerations
- Undervalues the ability of existing systems (NDC- and Lot- based recalls) and new regulatory structures (track and trace) to provide adequate safeguards

FACT
The patient and safety communities, as well as many physician organizations have weighed in on the same issue, and do not believe distinguishable naming would introduce confusion and complexity, nor do they believe distinguishable names would hinder product recalls. They have come out on the opposite side — in favor of transparency, so that patients can know which medication is being put into their bodies and the whole system can quickly connect the dots to stem negative impact when an adverse event occurs.

Due to the fact that the FDA will characterize its assessment of biosimilarity (based on comparative analytical data) into one of four levels — not similar, similar, highly similar or highly similar with a fingerprint-like similarity — it will become even more critical to provide transparency as to which biologic or biosimilar is being prescribed. Additional pharmacologic studies would be required to show that the identified difference is "within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product." FDA said only products in the top two tiers would meet the statutory requirement for analytical similarity under the Biologics Price Competition and Innovation Act of 2009.

The American Society of Health-System Pharmacists stated in a February 27, 2014 letter to the FTC that "… we do not oppose the addition of suffixes (e.g., alpha, beta) to the INN name if experts believe this approach is needed to facilitate pharmacovigilance."

The Hematology/Oncology Pharmacy Association (HOPA) has stated its support for distinguishable naming in a published position paper: "Health care providers, patients, manufacturers, and regulatory agencies must be able to identify that a product is biosimilar to the original branded medication, and they must be able to associate the medication with the appropriate therapeutic class to assure appropriate prescribing. Naming is important to avoid prescribing and dispensing errors. Further, biosimilars must be able to be easily tracked to monitor safety and quality. Pharmacists are uniquely positioned to understand the important role that naming will have in ensuring appropriate medication substitutions take place when biosimilars are used."

IV. IMPACT OF POLICY RECOMMENDATIONS

In a letter submitted to FDA Commissioner Margaret Hamburg, The National Organization for Rare Diseases) NORD asks that the agency give serious consideration to the concerns of the rare disease community when

setting policy regarding official names for biologics, including biosimilars. NORD President and CEO Peter L. Saltonstall writes,

> With over 7,000 rare diseases identified and 30 million Americans affected, the patient population represented by NORD is extraordinarily heterogeneous, the letter notes. Without thoughtful and consistent naming protocols for biologics, there is the potential for significant confusion among treatment options and increased adverse events, both of which could jeopardize patient safety. Distinguishable naming of all biologics is imperative for health care professionals to deliver the degree of customized care that is routinely required for patients with complicated, uncommon and less well-studied diseases. Every patient deserves the care best suited for their medical situation and most likely to give them the best outcomes. Biologics are often the most advanced and effective treatments for patients we represent and everyone in the treatment continuum should be able to readily identify the specific drug product a patient was given.

V. CONCLUSIONS

Those who view distinctive biosimilar nomenclature naming as either contrary to safety or anti-competitive are addressing these issues through a single dimension. And it just isn't that simple.

With all of these considerations, it stands to reason that the name of biologics and biosimilars should be similar, not the same. But rather than taking my word for it, consider these important viewpoints:

"Distinguishable names…will enable the gathering of sufficient data to ultimately allow providers to fully understand how all biologics — including biosimilars — are performing for minorities. This will lessen the inevitable confusion and assure optimum medical care in the use of biosimilars among minority populations." – From a June 10, 2014 letter to FDA signed by 22 of the leading U.S. organizations focused on minority health, including the National Alliance for Hispanic Health, National Hispanic Medical Association and National Medical Association.

"…For millions of female patients, any potential increase or decrease in effectiveness of a biologic, along with side effects and adverse reactions, will only be discovered after the treatment is approved and under active use…As states across the country look to the FDA for guidance on issues surrounding biosimilarity, interchangeability, and therapeutic substitution, the agency's views on sex and genomic-based differences will be crucial…Distinguishable names will enable the gathering of sufficient data to ultimately allow providers to fully understand how all biologics — including biosimilars — are performing for both men and women." – From a May 20, 2014 letter to FDA spearheaded by the Society for Women's Health Research and signed by 45 other leading U.S. organizations focused on women's health.

As acknowledged by WHO and regulatory bodies of every developed nation, biologics are not chemical compounds (e.g., statins) — they're infinitely more complicated. When it comes to biosimilars, we need to be extremely thoughtful about how we set policy and strike a balance that promotes health and safety, rather than forcing a binary response that is driven by profits rather than patients.

Claude Debussy said, "Music is between the notes." And the same can be said for biosimilarity. We now have many thoughtful guidance documents but, in many respects, it's just theory. And just as the case with music theory, the words on the page are one thing—but when talented performers sit down at different pianos in disparate venues the results are both similar and unique.

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