Naming of Chiral Drugs: Should We Revisit?

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ABSTRACT

The purpose of standard nonproprietary, or generic, drug nomenclature is to provide a universally consistent and reliable name that facilitates safe and effective medication use in society. Naming that presents the drug inaccurately may result in erroneous prescribing and potentially puts the patient's health at risk. This paper tracks the historical record of guidelines for naming stereoisomer drugs both in the United States and on an international basis. We also examine the concordance of current nonproprietary (generic) names with the United States Adopted Names (USAN) stereoisomer naming guidelines currently in place. The USAN stereoisomer naming guidelines have changed throughout the years; however, the nonproprietary names of many drugs designated under previous guidelines have not been updated to reflect these changes. There is a need for key players such as the USAN Council, United States Pharmacopeia (USP), and the Food and Drug Administration (FDA) to come together to establish a practical, informative, and consistent set of guidelines for the naming of stereoisomer drugs. We acknowledge that the naming of stereoisomer drugs to provide useful information for clinicians is not simple, but the current state of affairs is inconsistent and unreliable, putting patient safety at risk. The purpose of the recommendations within this paper is to stimulate thinking and to improve the current stereoisomer naming guidelines, while reducing the future public health risk of continuing inconsistent stereoisomer drug naming practices.

I. INTRODUCTION

A nonproprietary, or generic, drug name can be rich with meaning and provide useful information to the manufacturer, the Food and Drug Administration (FDA), the prescriber, the pharmacist, and others. While the nonproprietary name may help prescribers choose the most appropriate treatment for a patient, lack of clarity or confusion created by an inconsistent generic name may potentially lead to harmful medication errors and adverse effects. FDA has reported that about ten percent of all

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medication errors result from drug name confusion.[1] "Confusion of drug names is a common system failure that results in potentially harmful medication errors."[2] Kenagy and Stein estimate, based on error reports from the Institute for Safe Medication Practices (ISMP), that confusion of drug names may be responsible for 10,000 or more patient injuries each year in the United States.[3]

Despite the lack of obvious meaning to the general public for assigned generic names, these nonproprietary names can provide abundant information to the knowledgeable user regarding the properties of a medication, such as the mechanism of action, effectiveness, or side effects.[4] While a drug's brand name may vary for different indications, dosage forms, or across different countries, the generic name usually remains consistent. A generic name, as defined[5] by the United States Adopted Names (USAN) Council—the organization primarily responsible for assigning generic names in the United States—should be useful to healthcare practitioners. Specifically, a generic name should be safe, educational, and internationally identifiable.[6] USAN Naming Guidelines state that "a name should not conflict, mislead or be confused with other nonproprietary [drug] names and with established trademarks."[7] In order to make generic drug names more useful, USAN defines and assigns word stems in their Naming Guidelines to simplify nomenclature.[8] For example, the generic name "valsartan" tells the practitioner that this drug is an angiotensin II receptor antagonist that is used to treat high blood pressure. This relationship of drug name to therapeutic activity is implied due to the suffix "-sartan," which is defined by the USAN Council as "an angiotensin II receptor antagonist."[9] Consequently, drugs with a generic name using the suffix "-sartan" will be expected to act by this mechanism. Other defined nomenclature stems include "-vastatin," indicating that the drug lowers cholesterol by inhibiting biosynthesis enzymes, and "-oxacin," indicating that the drug is a quinolone antibiotic.[10]

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1 Carol Rados, *Drug Name Confusion: Preventing Medication Errors*, 39:1 FDA CONSUMER 35, 35 (2005).

2 James M. Hoffman & Susan M. Proulx, *Medication Errors Caused by Confusion of Drug Names*, 26 DRUG SAFETY 445, 452 (2003).

3 Rachel Bryan, Jeffrey K. Aronson, Pius ten Hacken, Alison Williams & Sue Jordan, *Patient Safety in Medication Nomenclature: Orthographic and Semantic Properties of International Nonproprietary Names*, 10 PLOS ONE 1, 1 (2015); J.W. Kenagy & G.C. Stein, *Naming, Labeling, and Packaging of Pharmaceuticals,* 58 AM. J. HEALTH SYST. PHARM. 2033, 2035 (2001).

4 Guidance on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances, WORLD HEALTH ORG. 11 (2017), https://www.who.int/medicines/services/inn/FINAL_WHO_PHARM_S_NOM_1570_web.pdf?ua=1 [https://perma.cc/FZ4E-6R8K].

5 "By definition, nonproprietary names are entirely in the public domain and are not subject to trademark rights. A United States Adopted Name (USAN) is a nonproprietary name selected by the USAN Council to ensure safety, consistency and logic in the choice of names." *United States Adopted Names Naming Guidelines*, AMA (2019), https://www.ama-assn.org/about/united-states-adopted-names/united-states-adopted-names-naming-guidelines [https://perma.cc/22AJ-35QW].

6 *Id.*

7 *Id.*

8 *Id.*

9 *Id.*

10 *Id.*

Imagine the confusion that would ensue if a generic drug like valsartan was improperly designated with the suffix of "-vastatin" instead of "-sartan." The prescribing practitioner would likely assume the generic drug (inaccurately named valvastatin) is a cholesterol reducing agent instead of a medication to treat high blood pressure. Not only would this cause confusion to the healthcare professional, it may lead to prescribing errors or even patient harm. Currently, there are a number of generic drug names that have assigned USAN prefixes (e.g., ar-, es-, lev-, dex-, or rac-) related to the stereoisomeric form of a drug molecule. These stereoisomer prefixes, as defined by the USAN Council, imply that the drug molecule has a molecular structure which differs only in spatial arrangement. Proper and consistent use of these stereoisomeric prefixes can inform practitioners about the structural identity of the drug being prescribed. The practitioner can use the name to determine if the generic drug is a racemate or a single stereoisomer, identified in chiral drugs, and thus may have different therapeutic and safety properties. For example, the USAN Council defines the prefix "levo-" to mean the generic drug is an S-enantiomer and has levorotary optical rotation.[11] One would therefore assume that levocetirizine, a commonly used allergy medication, was named based on these criteria. However, levocetirizine is not an S-enantiomer. In fact, the S-enantiomer does not even have anti-allergy effects in the body.[12] If the practitioner was aware that the S-enantiomer is inactive for treating allergies and assumed that the generic name followed the USAN nomenclature guidelines, the practitioner might incorrectly tell a patient that this drug is not effective for treating allergies. Proper naming of chiral compounds is of great importance to public health because it can guide clinicians to prescribe safer and more effective medications for their patients. By assessing a generic drug's proper use of stereoisomeric prefixes, the prescriber can account for the stereochemical identity of a drug and appropriately adjust for safety and dosing issues. Drug names that are inconsistent with written guidelines are a threat to public health.

Within the current naming system there have been reported medication errors such as prescribing or dispensing citalopram instead of escitalopram and vice versa.[13] These stereoisomer drugs have similar indications in treating depression, but they differ in their effective dose range and their side effects. Generic name confusion can result in prescribing either too little or too much of a drug and may lead to serious side effects. If the healthcare professional that is prescribing or dispensing a specific medication is aware of the differing clinical profiles of the two stereoisomeric forms of a given drug, a proper name may greatly reduce the likelihood of significant errors.

From a public safety and regulatory standpoint, the standardization of stereoisomeric prefixes and their consistent use is critical to the safe and effective prescribing of drugs. When a USAN does not properly reflect the stereoisomeric form of a drug, the result may be concerning and confusing. In general, the USAN Council would not likely approve the suffix "-vastatin" in the generic name of a drug other than a cholesterol biosynthesis inhibitor. So, why does the prefix "levo-" not follow the same rigidity in nonproprietary name standardization that we see with other prefixes and suffixes? While currently there are a number of clear discrepancies in the

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[11] *Id.*

[12] Kathryn Blake & Hengameh Raissy, *Chiral Switch Drugs for Asthma and Allergies: True Benefit or Marketing Hype,* 26 PEDIATRIC ALLERGY IMMUNOLOGY & PULMONOLOGY 157, 160 (2013).

[13] Jeffrey K. Aronson, *Medication Errors Resulting from the Confusion of Drug Names*, 3 EXPERT OPINION ON DRUG SAFETY 167, 172 (2004).

nonproprietary names used with chiral drugs, we ask why these inconsistencies are not of more concern to FDA, drug manufacturers, USAN, physicians, pharmacists, and others. After all, many of the drugs that Americans consume on a daily basis are chiral entities which are not named in a consistent manner to reflect their chiral properties.

II. BACKGROUND

In 1848 Louis Pasteur, a French chemist, discovered chiral chemistry when he separated the two stereoisomers of sodium ammonium tartrate.[14] Pasteur's insights allowed him to create useful language in stereochemistry and the use of the prefixes levo- and dextro- in the names of optically active substances—terms which are still used today.[15] Chirality is an important aspect of a compound's molecular structural identity and may have important clinical ramifications. The importance of chirality was not fully realized until more than a century after Louis Pasteur's discovery. Chirality is now known to play a major role in the life of plants, animals, and humans, as well as in the agricultural, chemical, and pharmaceutical industries. Many chemical and biological compounds, including proteins, enzymes, carbohydrates, and hormones, have chiral properties.

Understanding the complexities of chiral compounds has important clinical and policy implications. One estimate from the early 2000s indicated that fifty-six percent of approved drugs on the U.S. market were chiral compounds, and about eighty-eight percent of those drugs were racemic mixtures, or racemates—equal proportions of both the left- and right-handed forms.[16] Not only are many prescription drugs chiral compounds, but some of the top selling prescription drug products in the recent past, such as Prilosec®, Zocor®, and Lipitor®, have chiral properties.[17] Over the years, the market has experienced a shift from racemic drug development to single stereoisomer drug development.[18] As medicine continues to advance, single-enantiomer drugs more accurately bind their targeted three-dimensional receptors. Because these protein receptors are typically stereoselective, it makes sense that the trend in drug development has shifted from racemic mixtures to single enantiomer molecules, as a single stereoisomer generally binds better to the desired receptor than its counterpart.[19] For example, Spravato® (esketamine) is a single stereoisomer of the widely used drug

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[14] Chiral molecules have left-handed and right-handed configurations due to their three-dimensional construction. These left- and right-handed forms are referred to as stereoisomers. KRZYSZTOF JOZWIAK ET AL., DRUG STEREOCHEMISTRY: ANALYTIC METHODS AND PHARMACOLOGY, THE EARLY HISTORY OF STEREOCHEMISTRY 7 (Irving W. Wainer & Dennis E. Drayer eds., 1988).

[15] Joseph Gal, *Louis Pasteur, Chemical Linguist: Founding the Language of Stereochemistry*, 102 HELVETICA CHIMICA ACTA (2019).

[16] Katharina M. Rentsch, *The Importance of Stereoselective Determination of Drugs in the Chiral Laboratory*, 54 J. BIOCHEMICAL BIOPHYSICAL METHODS 1, 9 (2002); Willi Walther & Thomas Netscher, *Design and Development of Chiral Reagents for the Chromatographic E.E. Determination of Chiral Alcohols*, 8 CHIRALITY 397, 401 (1996).

[17] Matthew Herper & Peter Kang, *The World's Ten Best-Selling Drugs*, FORBES, https://www.forbes.com/sites/matthewherper/2011/04/19/the-best-selling-drugs-in-america/#259dcd941993 [https://perma.cc/M7XQ-9T33].

[18] Hava Caner, Efrat Groner, Liron Levy & Israel Agranat, *Trends in the Development of Chiral Drugs*, 9 DRUG DISCOVERY TODAY 105, 107 (2004).

[19] W.H. Brooks, W.C. Guida & K.G. Daniel, *The Significance of Chirality in Drug Design and Developmen*t, 11 CURRENT TOPICS MED. CHEMISTRY 760, 770 (2011).

ketamine, and was recently approved as a nasal spray to treat drug-resistant depression.[20] Esketamine, the S stereoisomer, is more active and causes fewer side effects than the R stereoisomer.[21] Esketamine's Wholesale Acquisition Cost (WAC) is $1,105 per 100 mg,[22] compared to the WAC of regular ketamine, which can be purchased for roughly $1.17 per 100 mg.[23] It has been predicted that esketamine will have $1.3 billion in sales by 2024.[24] In terms of patent protection, some manufacturers have applied a technique called chiral switching that results in extension of the patent protection for stereoisomer drugs. Multiple published reviews and legal cases have prompted FDA to update its policies and regulations on this matter.[25] We will discuss this area and provide some examples—keeping in mind that this is not the primary focus of this Article.

Two of the most influential organizations involved in the naming of generic drugs are the American Medical Association (AMA) and the World Health Organization (WHO). These two organizations work together closely to standardize generic naming on an international basis. Nonproprietary (or generic) names possess standardized word stems (prefixes, suffixes, and infixes) that have meaning to healthcare providers and others. In the United States, a nonproprietary name application is typically submitted by a patent holder, or other intellectual property holder, to the USAN Council—an entity run by the AMA.[26] Nonproprietary names designated by the USAN Council are termed United States Adopted Names (USANs). The USAN Council consists of one individual from the following entities: FDA, the AMA, the American Pharmacists Association (APhA), the United States Pharmacopeia (USP), and one member-at-large.[27] After the initial formation of the council in 1961, six years later in

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[20] Esketamine is the left-handed (S stereoisomer) form of ketamine. Ketamine is the racemic mixture (or 50:50 blend) of both R and S ketamine stereoisomers.

[21] John Muller, Sahana Pentyala, James Dilger & Srinivas Pentyala, *Ketamine Enantiomers in the Rapid and Sustained Antidepressant Effects*, 6 THERAPEUTIC ADVANCES PSYCHOPHARMACOLOGY 185, 192 (2016).

[22] The Wholesale Acquisition Cost (WAC) per package of Spravato (NDC 50458-0028-03, 28 mg/0.2ml per unit, 3 units per package) is $928.38 as of May 13, 2020. This WAC per unit equates to $1,105.21 per 100 mg of Spravato (esketamine). *IBM Micromedex Red Book*, IBM, www.micromedexsolutions.com [https://perma.cc/P2GS-9H2J] (For search results for Spravato follow: "Other Tools" tab; then click: "Red Book" hyperlink; then search: Spravato).

[23] The Wholesale Acquisition Cost (WAC) per package of ketamine HCl (NDC 00143-9508-10, Hikma Pharmaceuticals USA Inc., 50 mg/1ml per unit, 10 units with 10 ml each per package) is $58.25 as of May 13, 2020. This WAC per unit equates to $1.17 per 100 mg of ketamine HCl as of May 13, 2020. *IBM Micromedex Red Book*, IBM, www.micromedexsolutions.com [https://perma.cc/P2GS-9H2J] (For search results for ketamine, HCl follow: "Other Tools" tab; then click: "Red Book" hyperlink; then search: ketamine HCl).

[24] Angus Liu, *Spravato*, FIERCE PHARMA (2019), https://www.fiercepharma.com/special-report/9-spravato [https://perma.cc/C7H8-Z7LN].

[25] Kyle Faget, *Why FDCA Section 505(U) Should Not Concern Us Greatly*, 15 MICH. TELECOMM. & TECH. L. REV. 453 (2009); Himanshu Gupta, Suresh Kumar, Saroj Kumar Roy & R.S. Gaud, *Patent Protection Strategies*, 2 J PHARM. & BIOALLIED SCI. 2, 7 (2010); Rebecca S. Yoshitani & Ellen S. Cooper, *Pharmaceutical Reformulation: The Growth of Life Cycle Management*, 7 HOUS. J. HEALTH L. & POL'Y 379 (2007).

[26] *USAN Negotiation Process*, AMA (2018), https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/usan/usan-process.pdf [https://perma.cc/XX8U-SDUJ].

[27] *USAN* Council, AMA (2019), https://www.ama-assn.org/about/united-states-adopted-names/usan-council [https://perma.cc/VZV2-BVXW].

1967, a liaison representative from FDA was appointed to serve on the USAN Council. In 1984, FDA announced that it would use the USAN as the established (or generic) name for the labeling and advertising of new single-entity drugs marketed in the United States.[28] During the USAN process for adopting a generic name, the Council must unanimously vote in favor of the suggested name before offering the proposed USAN to the applicant. The applicant then has the option to accept or decline the proposed USAN. If accepted, the name is then moved forward in the process and is submitted to the WHO for the designation of an International Nonproprietary Name (INN). If the applicant does not accept the proposed USAN, the Council will reconvene and introduce alternative USANs until the applicant accepts the proposed generic name.[29]

Because the purpose of a nonproprietary name is to have a globally consistent term designated for universal understanding, most USANs and INNs are the same. However, disagreements between the two organizations do sometimes occur. For example, the compound 4-[(1R)-2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol was designated with the USAN "levalbuterol" by the AMA; however, it was designated with the INN "levosalbutamol" by the WHO. There is currently no publicly available information on the reason behind the different generic names for this drug. When discrepancies occur between the two nonproprietary names, FDA typically follows the USAN designation, but if deemed necessary, it does have the right to change a given USAN.[30] For example, in 2009 FDA changed the nonproprietary names of botulinum toxin products (including Botox®) to ensure their safe use and reduce medication error risk.[31]

Both the AMA and WHO have published naming guidelines for USANs and INNs, respectively. Despite the close collaboration between the two organizations, and the overall goal to have matching USANs and INNs, the published guidelines are not identical, especially when it comes to stereoisomer naming guidelines.

The appropriate criteria for generic names involving stereoisomers has been a concern for several decades. In the 1980s and 1990s, multiple articles were published pointing out the inconsistencies of stereoisomer naming and the lack of clear and useful nomenclature. FDA, physicians, chemists, and various scientists have made a number of recommendations to improve the naming system for stereoisomers.[32] In

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[28] 21 C.F.R. § 299.4 (2018); Carmen Drahl, *Where Drug Names Come From*, 90 CHEMICAL & ENGINEERING NEWS 36, 37 (2012).

[29] *IBM Micromedex Red Book*, *supra* note 22.

[30] Liu, *supra* note 24.

[31] *FDA Gives Update on Botulinum Toxin Safety Warnings; Established Names of Drugs Changed*, PHARMA. ONLINE (2009), https://www.pharmaceuticalonline.com/doc/fda-gives-update-on-botulinum-toxin-safety-0001 [https://perma.cc/QR2H-Q4LF]; *Information for Healthcare Professionals: OnabotulinumtoxinA (Marketed as Botox/Botox Cosmetic), AbobotulinumtoxinA (Marketed as Dysport) and RimabotulinumtoxinB (Marketed as Myobloc)*, FOOD & DRUG ADMIN. (2009), https://wayback.archive-it.org/7993/20170112032330/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174949.htm [https://perma.cc/3NR5-Z5L2].

[32] Wilson H. De Camp, *Chiral Drugs: The FDA Perspective on Manufacturing and Control*, 11 J. PHARM. & BIOMEDICAL ANALYSIS 1167, 1172 (1993); Joseph Gal, *Stereoisomerism and Drug Nomenclature*, 44 CLINICAL PHARMACOLOGY & THERAPEUTICS 251, 253 (1988); Miklos Simonyi, Joseph Gal & Bernard Testa, *Sign of the Times: The Need for a Stereochemically Informative Generic Name System*, 10 TRENDS PHARMACOLOGICAL SCI. 349, 354 (1989); John Tomaszewski & Martha M. Rumore,

1992, a convention was held to discuss the regulatory requirements and the international standards and guidelines for naming chiral drugs. A plea was made to standardize the criteria for naming of chiral molecules "in the near future."[33] While the USAN stereoisomer naming guidelines have changed several times since their initial publication in 1993, the generic nomenclature of stereoisomers has not been comprehensively standardized after almost three decades. There is a lack of literature assessing whether the updated and current guidelines meet the needs of the current healthcare system. Furthermore, to our knowledge, there is no reliable source that has assessed and described all chiral drugs that have generic names that are inconsistently and incorrectly designated. The purpose of this paper is to explore how stereoisomer drugs are named, to identify some incorrectly named stereoisomer drugs, and to provide recommendations and discussion prompts to instigate needed change to the current stereoisomer naming conventions. In order to provide a clear understanding of stereoisomer drugs, the scientific, legal, and clinical implications are discussed briefly.

III. THE CHEMISTRY OF CHIRALITY

In order to understand how stereoisomers are named, understanding the chemistry behind the naming conventions is necessary. The following section provides a brief overview of chiral chemistry.

Stereocenters are defined as chiral atoms with four unique connecting constituent groups. Due to the three-dimensional construction of these chiral centers, they can take on either "left" or "right" configuration. Each chiral center can be characterized by its absolute configuration.[34] The absolute configuration of the center is determined by the identity of the adjacent groups. From heaviest to lightest groups, the center is designated "R" configuration if the atomic priority decreases in clockwise, right-to-left order when viewed along the carbon to the lowest priority bond. The center is designated "S" configuration if the atomic priority decreases in counterclockwise, left-to-right order when viewed along the carbon to the lowest priority bond.

Chiral molecules with a single stereocenter can therefore have two stereoisomers, R and S. The R and S pair are referred to as enantiomers, which are chemically identical, non-superimposable mirror images, differing only in the order of adjacent atoms around the chiral center. A racemic mixture (or racemate) is comprised of a 1:1 ratio of both R and S enantiomers.

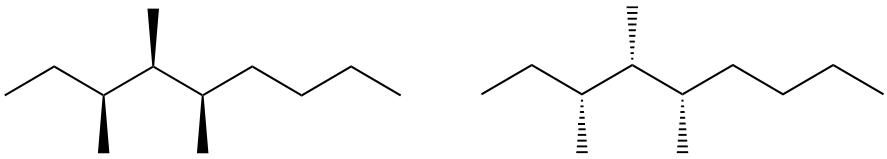
Small molecules often have more than one chiral center, resulting in a greater amount of possible stereoisomers. The maximum number of potential stereoisomers is equal to 2^n, where n is the number of the molecule's stereocenters. If the configuration of all chiral centers in one stereoisomer is switched (or inverted), the enantiomer is produced (e.g., Figure 1).

Stereoisomeric Drugs: FDA's Policy Statement and the Impact on Drug Development, 20 DRUG DEV. & INDUS. PHARMACY 119, 139 (1994).

[33] Michael Gross et al., *Regulatory Requirements for Chiral Drugs*, 27 DRUG INFO. J. 453, 457 (1993).

[34] Following the Cahn-Ingold-Prelog convention.

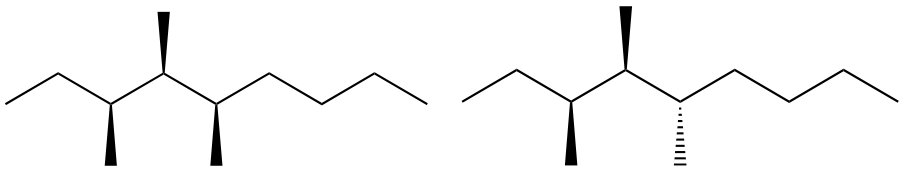
Figure 1. A Pair of Enantiomers



The wedges in the structure to the left represent groups (methyl substituents in this example) situated above the plane of the paper (which contains all of the atoms of the main chain in this representation), and the dashes in the structure to the right denote methyl groups oriented behind the plane of the paper. Because all three chiral centers have been inverted (i.e., wedges to dashes), these two molecules are enantiomers.

If some chiral centers remain the same and not all chiral centers are inverted, the resulting stereoisomer is a diastereomer (e.g., Figure 2).

Figure 2. Two Diastereomers



Because only one of the (three) chiral centers has been inverted, these two molecules are diastereomers.

Regardless of a chiral molecule's R/S configuration, stereoisomers are "optically active" and rotate plane-polarized light to either the left or the right. Molecules that rotate light to the right in clockwise order are "dextrorotary" compounds, from the Latin word "dexter," meaning "right." Molecules that rotate light to the left in counter-clockwise order are "levorotary" compounds, stemming from the Latin word "laevus," meaning "left." Dextrorotary molecules are often designated with "(+)-" and levorotary molecules are often designated with "(–)-" prefixes in chemical names to distinguish their optical activity.

IV. POLICY IMPLICATIONS OF CHIRALITY

A. Role of FDA and Chirality

In 1992, FDA released a guidance statement on stereoisomer drugs describing the benefits of pursuing a single enantiomer formulation versus a racemate. FDA guidance statement leaves the decision to develop either the racemate or a single stereoisomer up to the drug sponsor as long as the sponsor has a reason that is explained and justified.[35] Although both single enantiomer and racemate drugs may continue to be developed, thanks to a wide range of new technologies for chiral separation, more

[35] *Development of New Stereoisomeric Drugs*, FOOD & DRUG ADMIN. (1992), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-new-stereoisomeric-drugs [https://perma.cc/PD27-FGAF].

single enantiomers are being submitted as new drugs for approval.[36] According to FDA, development of racemic drugs creates complications with proper characterization of metabolism and distribution, acceptable manufacturing control of synthesis and impurities, appropriate clinical evaluation, as well as adequate pharmacologic and toxicologic assessment. In the clinical assessment of these products, if there is no difference between the toxicological profile of the single stereoisomeric product and its racemate, there is no need for further studies. On the other hand, if the single enantiomer is more toxic, the developers should seek out the reasons for the toxicity and how it impacts human dosing.[37]

B. Patent Protection Strategies Using Chirality

Chiral switches result in both racemic and single enantiomer products being in the market, and thus, improper naming could result in confusion about the clinical safety and efficacy of one form versus the other. If a chiral switch did not occur, there would be little to no opportunity for confusing the names or properties of the two forms. The single enantiomer versus the racemic form of a drug has been, at times, construed to provide the patent filer with a new invention, which in turn enabled the exclusive right to market or sell the drug in the granting jurisdiction. Thus, the sponsor filing for a patent on a single enantiomer after holding a patent on the racemic mixture could prevent others from commercially using the invention without permission across the span of two patent terms. One, however, must question whether the single enantiomer is "novel" if it was already known and present in a racemic mixture that was the subject of a previous patent. Patents and other forms of market exclusivity in the pharmaceutical industry prevent generic competition and prolong the economic lifecycle of a drug product.

Chiral switching is a procedure used to transform a racemic drug into its active single enantiomer formulation. This new enantiomeric drug may receive additional patent protection and the stereoisomer will be given a new generic name. The process of chiral switching allows drug manufacturers to apply for FDA approval of the enantiomer, before the expiration of the racemic mixture patent, while maintaining market exclusivity for the drug as a whole. An example of a successful chiral switch was the release of Nexium® (esomeprazole) while Prilosec® (omeprazole) was still patent-protected. Prilosec®, a blockbuster acid-reflux drug, had patent expiration in 2002, and before the patent expired, AstraZeneca released the single (S)-enantiomer, esomeprazole, which arguably exhibits superior clinical efficacy compared to its predecessor. This newly isolated stereoisomer compound, Nexium® or esomperazole, received an entirely new patent despite the fact that the stereoisomer, including the single (S)-enantiomer, was previously known, and it was again marketed for the treatment of acid reflux. Essentially, the switch from the racemate to the single stereoisomer has allowed this drug product to have a double patent life even though esomeprazole was a known entity and was embedded in the original omeprazole patent and related drug products. The drug company, AstraZeneca, was able to collect

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[36] A. Maureen Rouhi, *Chiral Business*, 81 CHEMICAL & ENGINEERING NEWS 45 (2003).

[37] *Development of New Stereoisomeric Drugs, supra* note 35.

monopoly prices and billions of dollars for twice the normal time period.[38] Table 1 shows other relevant chiral switch examples.

Table 1. Examples of Chiral Switches from Racemic to Enantiomer Drugs

Preceding Racemic Drug Name	Chiral Switch Drug Name	Chiral Switch Stereoisomer Absolute Configuration	Chiral Switch Drug Optical Rotation
Lansoprazole	Dexlansoprazole	R	(+)
Citalopram	Escitalopram	S	(+)
Modafinil	Armodafinil	R	(-)

C. Clinical Implications of Chirality

Single enantiomer drugs will become increasingly available to the practicing prescriber. There are at least four advantages to developing single enantiomers: (1) reduced dose administration; (2) improved assessment of dose-response relationships; (3) reduced pharmacokinetic and pharmacodynamic parameters; and (4) less toxicity from inactive enantiomers.[39] Atorvastatin, lisinopril, and simvastatin are just a few examples of widely used stereoisomer drugs. Especially in the case when both the single stereoisomer and the racemic drug form are available, it is critical for the generic name to clearly distinguish between the two. These two chiral forms may differ in their dosages, efficacies, side effect profiles, and even indications for use. The future naming of enantiomer drugs should be standardized to provide clear and consistent information to prescribers about the properties of each drug entity. In this way, drugs with meaningful chiral properties can be safely and effectively prescribed in a manner that will reduce the risk of medication errors.

Since the 1992 FDA statement on stereoisomers, many organizations have pointed out the benefits of using a single enantiomer drug in situations where both forms are not equally medically active or useful. One advantage of using a single enantiomer drug is that it may be more selective and may have a better therapeutic profile with fewer drug-drug interactions.[40] For example, S-warfarin interacts with metronidazole while the R stereoisomer does not.[41] If either stereoisomer of warfarin was ever marketed and named incorrectly, it may cause potential patient harm due to the metronidazole interaction.

It is important to ensure that the safety and efficacy data for a drug evaluated as a racemic mixture of stereoisomers are still valid if only one stereoisomer is used in the marketed drug product. Stereoisomers may differ significantly in their bioavailability, rate of metabolism, metabolites, excretion, potency, selectivity for receptors,

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[38] *Full-year and Q4 2018 Results*, ASTRAZENECA (2019), https://www.astrazeneca.com/content/dam/az/PDF/2018/full-year/Full-Year_2018_Results_announcement.pdf [https://perma.cc/B8UH-CENU].

[39] Brian E. Leonard, *An Introduction to Enantiomers in Psychopharmacology*, 16 HUM. PSYCHOPHARMACOLOGY S79, S80 (2001).

[40] Arnold H. Beckett, *Chirality and its Importance in Drug Development: What are the Issues?*, 19 BIOCHEMICAL SOC'Y TRANSACTIONS 443, 446 (1991); Neal M. Davies & Xiao Wei Teng, *Importance of Chirality in Drug Therapy and Pharmacy Practice: Implications for Psychiatry*, 1 ADVANCES PHARM. 242, 247 (2003).

[41] Milind Y. Nadkar et al., *Association of Physicians of India: Position Statement on Role of Chirally Pure Molecules in Clinical Practice,* 65 J. ASS'N PHYSICIANS INDIA 49, 52 (2017).

transporters and/or enzymes, and toxicity.[42] Identifying a drug as a racemate versus a single stereoisomer may be of clinical importance. For example, omeprazole is a racemic drug whose stereoisomers vary in therapeutic activity. S-omeprazole (known as esomeprazole) is more bioavailable than R-omeprazole; thus, the S stereoisomer provides greater body exposure.[43] Labetalol, a mixture of racemates, consists of multiple stereoisomers. One stereoisomer slows the heart rate, and a different stereoisomer causes vasodilation of blood vessels. If the clinician is not aware that these various stereoisomer drugs exist in multiple configurations, they may believe the properties are due to a single molecule, when in fact it is due to the existence of multiple stereoisomers with varying activities.[44]

Typically, a drug with both a marketed single enantiomer and a marketed racemate may have similar indications, although the appropriate dosing may differ. This difference may also affect the price of various drug products, especially if one form is off-patent while the other form of the drug is still patented. In today's health care system, clinicians often need to take drug affordability into consideration to assure that their patient can access the prescribed medication.

FDA plays a major role in assuring the safe and effective use of drugs, and through its involvement with the USAN Council, FDA has the opportunity and responsibility to make recommendations on the naming of chiral drugs that will provide clinicians with a consistent and accurate, yet informative, stereoisomer naming system.

V. USAN GUIDELINES FOR NAMING STEREOISOMER AND CHIRAL DRUGS OVER TIME

A. USAN Guidelines Before 1993

According to a historical archive of the USP Dictionary of USAN and the International Drug Names,[45] the USAN Council did not publish official stereoisomer naming guidelines until 1993.[46]

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[42] *Id.*

[43] Waheed Asghar, Elliot Pittman & Fakhreddin Jamali, *Comparative Efficacy of Esomeprazole and Omeprazole: Racemate to Single Enantiomer Switch*, 23 DARU J. PHARM. SCI. 50, 52 (2015).

[44] Gal, *supra* note 32.

[45] The historical archive used in this paper included the 1983, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, and 2000 editions of USP Dictionary of USAN and International Drug Names. Of note, in 1995 the official name changed from "USAN and the USP Dictionary of Drug Names" to "USP Dictionary of USAN and International Drug Names."

[46] UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 670, 673 (Mary C. Griffiths, Carolyn A. Fleeger & Lloyd C. Miller eds., 1982); UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 607, 612 (Mary C. Griffiths, Carolyn A. Fleeger & Lloyd C. Miller eds., 1987); UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 640, 640 (Mary C. Griffiths, Carolyn A. Fleeger & Lloyd C. Miller eds., 1988); UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 655, 660 (William M. Heller & Carolyn A. Fleeger eds., 1989); UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG *NAMES* 696, 696–97 (William M. Heller & Carolyn A. Fleeger eds., 1990); UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 712, 712–13 (Carolyn A. Fleeger ed., 1991); UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 745, 745–46 (Carolyn A. Fleeger 1992).

B. USAN Guidelines From 1993 to 1998

The first drug-related stereoisomer naming conventions were published in print in the 1993 USAN and the USP Dictionary of Drug Names.[47] From 1993 to 1998, the naming of stereoisomers was based on optical rotation only and was applied solely to drugs with previously designated racemate or stereoisomer USANs.

The guidelines from 1993 to 1998 were as follows[48]:

(1) For the racemic form of any compound, the "rac-"/"race-" prefix is used.
(2) For the levo form, the "lev-"/"levo-" prefix is used.
(3) For the dextro form, the "dex-"/"dextro-" prefix is used.

Figure 3 shows a graphical representation of the USAN naming guidelines published in the USAN and USP Dictionary of Drug Names from 1993 to 1998. These naming conventions may have been used prior to 1993 for many stereoisomer drugs, despite the lack of formally published naming guidelines at the time.

Figure 3. Published USAN Stereoisomer Naming Guidelines From 1993 to 1998

	Absolute Configuration	
Optical Rotation	R Stereoisomer	S Stereoisomer
Dextrorotary (+)	"Dex-"/ "Dextro-"	"Dex-"/ "Dextro-"
Levorotary (-)	"Lev-"/ "Levo-"	"Lev-"/ "Levo-"

C. USAN Guidelines From 1998 to Present

The current version of USAN stereoisomer naming guidelines was adopted in 1998 and was officially published in the 2000 Edition of the USP Dictionary of USAN and International Nonproprietary Names.[49] Starting in 1998, stereoisomers were no longer named solely based on optical rotation—the absolute configuration of the stereoisomer

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[47] UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 745, 745–46 (Carolyn A. Fleeger ed., 1992).

[48] UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 745, 745–46 (Carolyn A. Fleeger ed., 1993 ed. 1992); UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 781, 781–82 (Carolyn A. Fleeger ed., 1993); UNITED STATES PHARMACOPEIAL CONVENTION, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG NAMES 795, 804 (Carolyn A. Fleeger ed., 1994); UNITED STATES PHARMACOPEIAL CONVENTION, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG NAMES 825, 825–26 (Carolyn A. Fleeger ed., 1995); UNITED STATES PHARMACOPEIA, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG NAMES 845, 845–47 (Carolyn A. Fleeger ed., 1996); UNITED STATES PHARMACOPEIA, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG Names 867, 867–68 (Jean Ross Canada ed., 1997).

[49] UNITED STATES PHARMACOPEIA, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG Names 867, 877 (Jean Ross Canada ed., 1997). A footnote in the 2000 Edition of the USP Dictionary of USAN and International Drug Names states that the stereoisomer guidelines were officially adopted in 1998.

was added to the prefix designation criteria. Similar to the 1993 to 1998 guidelines, the naming guidelines only apply to stereoisomer drugs with a preceding USAN for the racemate version of the drug.[50]

The guidelines from 1998 to the present are as follows[51]:

(1) Levorotary (-), S stereoisomers require the prefix "lev-"/"levo-."
(2) Levorotary (-), R stereoisomers require the prefix "ar-."
(3) Dextrorotary (+), S stereoisomers require the prefix "es-."
(4) Dextrorotary (+), R stereoisomers require the prefix "dex-"/"dextro-."
(5) Racemic mixtures require the prefix "rac-"/"race-."

The current guidelines designate prefixes based on two criteria: absolute configuration and optical rotation. Figure 4 below shows a graphical representation of the current USAN naming guidelines.

Figure 4. Current USAN Stereoisomer Naming Guidelines, Used Since 1998

	Absolute Configuration	
Optical Rotation	R Stereoisomer	S Stereoisomer
Dextrorotary (+)	"Dex-"/ "Dextro-"	"Es-"
Levorotary (-)	"Ar-"	"Lev-"/ "Levo-"

VI. USAN GUIDELINES COMPARED TO INN GUIDELINES

Both the AMA and WHO have published naming guidelines for USANs and INNs, respectively. Despite the close collaboration between the two organizations, and the overall goal to have matching USANs/INNs, the published guidelines are not identical, especially when it comes to stereoisomer naming practices.[52]

Having different USAN and INN guidelines poses a problem with naming consistency and creates the real possibility of unnecessary clinical safety issues on a global basis. The most current version of INN naming guidelines was last updated and published in 2017 and follows the 1993 to 1998 USAN stereoisomer naming guidelines (which evaluate only optical rotation and not absolute configuration). Furthermore, the 2017 INN stereoisomer guidelines are identical to their 1997 version,

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[50] UNITED STATES PHARMACOPEIA, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG NAMES 1093, 1093–94 (2000).

[51] *United States Adopted Names Naming Guidelines*, AMA (2019), https://www.ama-assn.org/about/united-states-adopted-names/united-states-adopted-names-naming-guidelines [https://perma.cc/22AJ-35QW].

[52] *Id.*; *Guidance on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*, *supra* note 4.

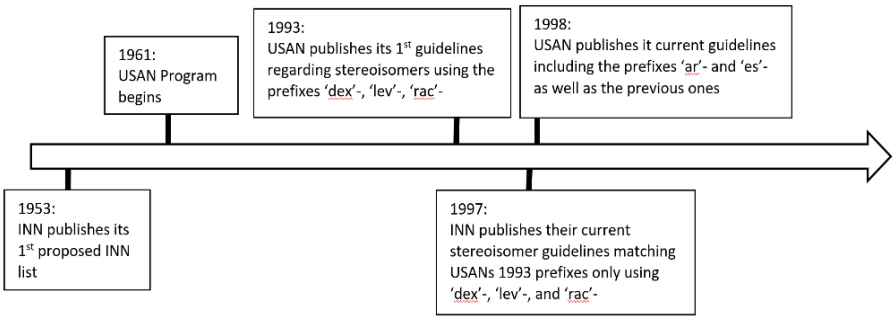
indicating that they have not been updated in over twenty years.[53] INN was contacted to comment on the observations made in this Article, and a staff person stated that the "restricted document on stereoisomers is being revised."

Despite the lack of INN guideline updates, there have been stereoisomer INNs that utilize the current USAN guidelines and name stereoisomers based on both absolute configuration and optical rotation protocol (i.e., they use "es-" and "ar-" prefixes). In other words, INNs with "es-" and "ar-" prefixes have been designated, despite the lack of guideline updates to include these prefixes to their protocol.

VII. TIMELINE OF USAN AND INN GUIDELINES

Figure 5 summarizes the overall timeline of influential INN and USAN nonproprietary naming events and changes to published stereoisomer guidelines.[54]

Figure 5. USAN and INN Stereoisomer Guideline Timeline, Showing the Initiation and Updates of Stereoisomer Guidelines



VIII. ASSESSMENT OF PAST AND CURRENT USAN GUIDELINES

Since INN has not updated the content of their guidelines for more than two decades and does not represent the most current naming protocol, this paper evaluates the accuracy of USAN naming only.

The USAN guidelines were assessed for chiral drugs by grouping them into the following: (A) stereoisomer drugs named before 1993; (B) stereoisomer drugs named between 1993 to 1998; (C) stereoisomer drugs named after 1998; (D) stereoisomer prefixes used for non-chiral drugs; and (E) diastereomer drugs. For each section,

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[53] UNITED STATES PHARMACOPEIA, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG Names 867, 877 (Jean Ross Canada ed., 1997); *Guidance on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*, *supra* note 4.

[54] UNITED STATES PHARMACOPEIAL CONVENTION, USAN AND THE USP DICTIONARY OF DRUG NAMES 745, 751 (Carolyn A. Fleeger ed., 1992); UNITED STATES PHARMACOPEIA, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG Names 867, 877 (Jean Ross Canada ed., 1997); UNITED STATES PHARMACOPEIAL CONVENTION, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG NAMES (2019); *Guidance on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*, *supra* note 4.

examples are included, and unless otherwise denoted, all information was gathered from the online 2019 USP Dictionary of USAN and International Drug Names.[55]

A. Stereoisomer Drugs Named Before 1993

Because USAN did not publish stereoisomer naming guidelines until 1993, the nonproprietary names given in Table 2 were not "incorrect" at the time of designation; however, they do not comply with the current USAN guidelines.

Table 2. USANs Adopted Before 1993 and Found to Be Inconsistent With Current USAN Guidelines

Designated USAN	**USAN Naming Date**	**Molecular Optical Rotation**	**Molecular Absolute Configuration**	**Nonproprietary Name Per Current USAN Guidelines**
Levamisole Hydrochlor-ide	1970	(-)	S	Levotetramisole
Dexchlorph-eniramine Maleate	1962[56]	(+)	S	Eschlorpheniramine Maleate

Levamisole hydrochloride, used to treat parasitic worm infections, is the levorotary S-enantiomer of tetramisole. Following current naming guidelines, the prefix "lev-" ought to be added to the preceding USAN; thus, levotetramisole would be the consistent USAN per today's guidelines, not levamisole. Furthermore, the example of dexchlorpheniramine maleate shows that the naming of stereoisomers before 1993 may have been following an unofficial guideline, as the naming appears consistent with the 1993 to 1998 USAN guidelines, though it does not comply with the current guidelines. Today, a drug with S absolute configuration and (+) optical rotation should be named with the prefix "es-," as shown in Table 2.

B. Stereoisomer Drugs Named Between 1993 and 1998

The 1993 version of the USP Dictionary of USAN and International Drug Names was the first edition to include stereoisomer naming guidelines in the Guiding Principles for Coining United States Adopted Names for Drugs section. The stereoisomer naming guidelines remained consistent in the 1993 to 1998 editions of the USP Dictionary of USAN and International Drug Names. However, because of the updated guidelines in 1998, not all nonproprietary names designated between 1993 and 1998 are consistent with today's naming convention, as seen in Table 3.

[55] UNITED STATES PHARMACOPEIAL CONVENTION, USP DICTIONARY OF USAN AND INTERNATIONAL DRUG NAMES (2019).

[56] 1962 is the listed INN date; no USAN data is available.

Table 3. USANs Adopted Between 1993 and 1998 Found to Be Inconsistent with Current USAN Guidelines

Designated USAN	**USAN Naming Date**	**Molecular Optical Rotation**	**Molecular Absolute Configuration**	**USAN Follows 1993 Guidelines**	**Nonproprietary Name Per Current USAN Guidelines**
Levalbuterol Hydrochloide[57]	1997	(-)[58]	R	Yes	Aralbuterol
Dexibuprofen	1997	(+)	S	Yes	Esibuprofen

From 1993 to 1998, stereoisomer prefixes were designated upon optical rotation alone. Prefixes under current guidelines, however, are designated based upon the optical rotation and absolute configuration. Both the levalbuterol hydrochloride and dexibuprofen USAN designations fail to include absolute configuration in their naming, rendering them inconsistent with today's guidelines.

C. Stereoisomer Drugs Named After 1998

Although the new stereoisomer naming guidelines were adopted by USAN in 1998, they have not been fully and consistently implemented into naming practice, as seen in Table 4.

Table 4. USANs Adopted After 1998 and Found to Be Inconsistent with Current USAN Guidelines

Designated USAN	**USAN Naming Date**	**Molecular Optical Rotation**	**Molecular Absolute Configuration**	**USAN Follows Current Guidelines**	**Nonproprietary Name Per Current USAN Guidelines**
Levocetirizine Dihydrochloride	2007[59]	(-)[60]	R	No	Arcetirizine

[57] The INN is levosalbutamol.

[58] *The Merck Index Search Results Albuterol Derivative: (R)-Form Hydrochloride*, https://www.rsc.org/merck-index [https://perma.cc/S4XR-KCPK] (Enter "Albuterol Derivative: (R)-Form Hydrochloride" in Quick Search textbox).

[59] INN was 1998.

[60] *See supra* note 58 (Enter "Cetirizine Derivative: (R)-Form Dihydrochloride" in Quick Search textbox).

Dexmed-etomidine Hydrochlo-ride[61]	1999	(+)[62]	S	No	Esmedetomi-dine

Despite levocetirizine dihydrochloride and dexmedetomidine hydrochloride being designated USANs after the adoption of the current stereoisomer naming guidelines, the generic names were most likely grandfathered in prior to their entry into the market. Specifically, levocetirizine dihydrochloride was given an INN in 1998, while the USAN was designated in 2007. The non-salt form of dexmedetomidine (not containing hydrochloride salt) was given its USAN in 1989, while the salt form of dexmedetomidine (dexmedetomidine hydrochloride) was designated in 1999. In both cases, a previous form of the drug was designated its nonproprietary name before the adoption of the current guidelines. Nonetheless, both levocetirizine hydrochloride and dexmedetomidine hydrochloride were designated USANs after current guidelines were established, and therefore do not follow the USAN Council's set precedents.

D. Stereoisomer Prefixes Used for Non-Chiral Drugs

Because prefixes "es-" and "ar-" were not adopted into stereoisomer guidelines until 1998, there are instances where these prefixes were given to non-chiral molecules before the adoption of the current guidelines.

Table 5. Certain USANs Given Stereoisomer Prefixes for Non-Chiral Molecules and Found to Be Inconsistent with Current USAN Guidelines

Designated USAN	**USAN Naming Date**	**Why Nonproprietary Name is Incorrect**
Aripiprazole	1997	Not chiral[63]
Estazolam	1990	Not chiral[64]

As seen in Table 5, one might assume that both aripiprazole and estazolam are stereoisomer drugs; however, they are in fact non-chiral molecules. Although these drugs were named before the current adoption of stereoisomer naming guidelines, the current guidelines state that stereoisomer prefixes ought to be reserved for chiral forms only. Furthermore, there is no mention of non-chiral molecules being named with these prefixes prior to the adoption of the 1998 guidelines. The only way to tell that these molecules are not named properly is by a structural analysis of the molecule to recognize that they are not chiral compounds, and thus not stereoisomers.

E. Diastereomer Drugs

Some drugs have more than one chiral center; however, the current USAN naming protocol treats all chiral drugs as if they have a single stereocenter. Current USAN

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[61] The non-salt dexmedetomidine was designated a USAN in 1989.

[62] *See supra* note 58 (Enter "Dexmedetomidine Derivative: Hydrochloride" in Quick Search textbox).

[63] Per current USAN Naming Guidelines, stereoisomer prefixes ("ar-," "lev-," "dex-," "es-," "rac-") ought to be reserved for chiral molecules only.

[64] Per current USAN Naming Guidelines, stereoisomer prefixes ("ar-," "lev-," "dex-," "es-," "rac-") ought to be reserved for chiral molecules only.

guidelines do not define which center is used when naming a diastereomer drug. When all chiral centers of a molecule have the same configuration (i.e., three R chiral centers), this lack of distinction is irrelevant, as the given prefix would be the same for each center. However, when there is a mixture of R and S centers in a single molecule, the given prefix renders itself meaningless, as the molecule's multiple configurations may contradict the assigned prefix.

Table 6. USAN Adopted for Diastereomer Drug Found to Be Inconsistent with Current USAN Guidelines

Designated USAN	**USAN Naming Date**	**Molecular Optical Rotation**	**Molecular Absolute Configuration Center 1**	**Molecular Absolute Configuration Center 2**	**Nonproprietary Name Per Current USAN Guidelines**
Levomilnacipran Hydrochloride	2011	N/A	S	R	N/A

As seen in Table 6, levomilnacipran hydrochloride was designated a USAN in 2011, and has two chiral centers, one S and one R. By simply analyzing the nonproprietary USAN designated prefix, it would be assumed that the molecule is an S (-) stereoisomer, which is not the case. A USAN representative was asked how USAN determined that the name of a diastereomer, such as levonordeferin, should use the "lev-" prefix. The USAN representative responded by saying that often the nonproprietary names are based on proprietary information from the company so that the details must be kept confidential.[65] The current USAN guidelines do not describe how molecules with multiple chiral centers are to be named if the centers do not have the same configuration.

IX. LIMITATIONS

A limitation of this analysis is the omission of a systematic review to determine the true number of stereoisomer USANs that are not named in concordance with the current naming guidelines. This task was beyond the scope of this Article for multiple reasons described in this section.

For consistency, we initially aimed to gather both optical rotation and absolute configuration data from the online USP Dictionary of USAN and International Drug Names to evaluate the number of USANs that are not in agreement with current guidelines. We discovered that the USP Dictionary of USAN and International Drug Names does not label optical activity for all stereoisomers, either online or in print. Esomeprazole, esketamine, levobupivacaine, and levocarnitine, in addition to levalbuterol hydrochloride, levocetirizine dihydrochloride, dexmedetomidine, and

[65] E-mail from Gail Karet, USAN (ama-assn.org), (June 3, 2019, 7:07 PM) (on file with author) ("Oftentimes companies provide us with proprietary information that is used in the deliberations, and we therefore need to maintain confidentiality.").

levomilnacipran, are just some of the instances when optical rotation data was omitted in the USP Dictionary of USAN and International Drug Names.

Another limitation of this analysis was unstandardized methods for designating optical activity. There are many factors that may impact the magnitude and direction of a molecule's optical activity, such as the pH, wavelength, temperature, and solvent.[66] For example, chloramphenicol is dextrorotatory in ethanol solvent, but levorotatory in ethyl acetate solvent.[67] Some examples of inconsistent USANs according to the present guidelines have been highlighted in this paper. Most of these examples were evaluated using optical activity data obtained from USP Dictionary of USAN and International Drug Names; however, it is unknown if standard conditions are required for their listed optical activity. When the optical activity was not presented in the USP Dictionary of USAN and International Drug Names, the Merck Index was used, and it lists optical rotation data in varying conditions. Without conducting a full chemistry literature review to obtain optical rotation under standardized conditions, it would not be possible to evaluate the true percentage of correctly named USANs based on the present naming guidelines.

X. ISSUES TO BE ADDRESSED

The following rhetorical questions raise issues that need to be addressed in order to improve the consistency of naming stereoisomer drug products using the USAN naming guidelines. We acknowledge the intricacies of this task and recognize that there is no clear or perfect solution. We respect the expertise of the USAN Council, the USP, FDA, and the INN Programme. Our aim is not intended to criticize these bodies, but rather to raise important issues with respect to nonproprietary names for stereoisomers and the consistency of nonproprietary names currently in use. The goal is to promote quality discussion and to simplify and improve the current naming system with respect to stereoisomers.

A. How Can USAN and INN Naming Guidelines Become More Consistent?

The purpose of nonproprietary names is to reduce medication confusion and to have globally consistent terms that will reduce therapeutic misunderstandings. We call for USAN and INN to reflect this goal of international consistency and to update their most recent naming guideline protocols to reflect how each organization currently designates stereoisomer nonproprietary names. We recommend USAN and INN create a committee which convenes regularly to assure the most up to date version of naming guidelines have been published. The USAN and INN should provide a list, which is readily available to the public, of drug products that are named differently between by the two organizations.

As the term "nonproprietary" implies, a generic name is not owned by any one individual, organization, or corporation. Rather, it is intended to be a universal term established to avoid the confusion and misunderstandings that may occur because of trademarked proprietary names.

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[66] Miklos Simonyi, Joseph Gal & Bernard Testa, *Sign of the Times: The Need for a Stereochemically Informative Generic Name System*, 10 TRENDS PHARMACOLOGICAL SCI. 349, 354 (1989).

[67] *Id.*

We call for the transparency of nonproprietary naming. Since nonproprietary names are not patent protected, why is it that the naming procedures are confidential information? Furthermore, it is important for the relevant organizations (i.e., the USP, USAN Council, and INN Programme) to be transparent and to identify the sources used when creating and updating stereoisomer naming guidelines.

B. Are Healthcare Professionals Aware That Some USAN Nonproprietary Names for Stereoisomers are Inconsistent With Current USAN Naming Guidelines?

Due to the revision of USAN naming guidelines over the years, there are a number of USAN nonproprietary (generic) names currently in use today that are not consistent with current USAN naming guidelines. Because the nonproprietary name sometimes implies meaningful clinical information about a stereoisomer, it is essential to educate providers and practitioners on the history of stereoisomer naming guidelines and on the meanings that can or cannot be implied by certain naming prefixes, suffixes, or infixes.

We call for the USAN Council to publish a complete timeline of stereoisomer naming guidelines, including major protocol changes. This will provide transparency to clinicians, showing that the current USAN guidelines were not always in use, and that prefix meanings have changed over time. Additionally, clinical information related to the stereoisomer and enantiomer properties of a drug molecule should be consistently and accurately reported in the package insert for all approved drug products.

C. How Can One Identify USAN Nonproprietary Names That Are Inconsistent With Current USAN Naming Guidelines?

We call for the USAN Council to conduct and publish a systematic review of all USAN nonproprietary names to evaluate their consistency with current USAN naming guidelines, for both stereoisomer and non-stereoisomer drugs. Furthermore, we recommend that the USAN Council identify and publish a list of drugs that are named inconsistently by USAN and INN guidelines. Additionally, if optical rotation continues to be used as part of the generic drug naming criteria, we call for public standardization of conditions to be used when determining the optical rotation of a drug molecule.[68] Finally, we believe it is important for the USAN Council to update all future editions of the USP Dictionary of USANs and International Drugs with optical activity for all relevant chiral molecules.

D. What Organizations Should be Involved in Creating a Consistent Naming System?

Because some USAN nonproprietary names are inconsistent with current USAN naming guidelines, it begs the question: should we retrospectively change nonproprietary names to reflect current USAN naming conventions? If healthcare providers are to look at nonproprietary names as a source of accurate information, it

[68] Not all molecules are soluble in the same solvent, and solubility is required for optical rotation experimentation to be conducted. A single standardized condition may not be possible for all drugs for this reason; however, it would be possible, for example, to enforce the optical rotation assay to be conducted at room temperature, at a specified wavelength in the most possible polar solvent to create consistency among reported optical rotations.

may be worthwhile to assess the feasibility of changing nonproprietary names that are inconsistent with current USAN naming guidelines. The USAN Council has not previously had participation of chemists and members from the Institute for Safe Medication Practices (ISMP) provide their insights in naming drug products. Chemists have a deep understanding of drug structures and aspects of their chemical features that may influence the generic naming of stereoisomer drugs. The ISMP has the primary goal of preventing drug errors and has published guidelines for choosing appropriate drug names, as well as a "list of confused drug names" and a list of "look-alike drug names and products." These guidelines are actively monitored and applied in various clinical settings and they are routinely updated. We call for the creation of a stereoisomer naming task force (consisting of practicing physicians, pharmacists, chemists, USAN, FDA, ISMP, USP, and INN members) to review the possibility of adjusting previously designated USAN nonproprietary names to reflect current USAN naming guidelines. The task force could also consider other alternatives for managing previously designated nonproprietary names that are no longer consistent with current USAN naming guidelines. We acknowledge that this is a large task that will be challenging and may initially provide as much confusion as clarity during a transition period. However, with inconsistent USAN nonproprietary names currently in use for some stereoisomers, there is already confusion and inconsistency in the meaning of these names. We believe that it is critical to raise this question, to start the discussion, and to begin the transition.

E. How Do We Avoid Inconsistent USAN Nonproprietary Names in the Future?

Although there are many previously given USAN nonproprietary names that are inconsistent with current USAN guidelines, the future of stereoisomer naming should not continue to create inconsistency. The inherent purpose of nonproprietary (generic) naming guidelines for stereoisomers is to provide a clear, consistent protocol for naming all stereoisomers, and the current USAN naming guidelines do not currently accomplish this goal.

We call for a stereoisomer naming task force, described above, to review the current USAN naming guidelines. Although the naming of stereoisomers is a complicated effort, we are confident that a panel of experts can prepare USAN guidelines for naming stereoisomers that will increase the clarity, value, ease of use, and inclusion of all stereoisomers. For example, the current stereoisomer USAN guidelines do not address how to name diastereomers. Perhaps it would be wise to adjust the USAN naming guidelines to assess both the optical rotation and the first chiral center of a molecule.[69] Or, perhaps, it would be wise to revert to the 1993 to 1998 protocol and only evaluate stereoisomers based on their optical rotation, thus simplifying the naming convention.

Since the implementation of the USAN stereoisomer naming guidelines in 1993, stereoisomer prefixes have remained solely designated for drugs with preceding USAN nonproprietary names. In their 1992 statement, FDA described the advantages of enantiomer drugs over racemates. Because enantiomer and diastereomer molecules are becoming more prevalent as the first form of a drug molecule introduced in the

[69] Per standard chemical (IUPAC) nomenclature, chiral centers are given a numerical designation based on its location on the molecule. If all stereoisomers, including diastereomers, are named based on the first listed chiral center, the process would be standardized.

U.S. market, it may be beneficial to designate nonproprietary names for stereoisomers that indicate the stereochemical properties of the drug entity without respect to any previously assigned USAN nonproprietary names.

One option to consider would be to assign new USAN nonproprietary names to all stereoisomers (whether or not they have a preceding USAN nonproprietary name), based solely on their documented optical activity. This would indicate to healthcare practitioners that a drug is a stereoisomer and that there may be relevant clinical features of a drug based on its stereochemistry. Even though the number of newly approved racemate products has decreased over time, it is of importance that the prefix "rac-" be applied to the racemate drugs in the market as well as to future drug entities. A simple, yet highly valuable step, would be the explicit identification of racemate, stereoisomer, and diastereomer forms of a drug in the drug product's approved FDA package insert. The package insert should also disclose the optical rotation of the drug molecule and the conditions under which optical rotation was assessed. In addition, the package insert should report all relevant clinical features of the drug molecule related to its chiral form.

XI. CONCLUSION

The switch from the previous USAN stereoisomer naming convention (pre-1998) to the current USAN stereoisomer naming guidelines (post-1998) has added confusion to the drug naming protocol for stereoisomers. Aside from a mention in the 2000 Edition of the USP Dictionary of USAN and International Drug Names, the current guidelines (both print and online) do not acknowledge that previous guidelines existed. This makes it unlikely that clinicians would know about the previous guidelines, or that they have been amended, unless the clinician laboriously examined a historical archive of the multiple previous versions of the USP Dictionary of USAN and International Drug Names. Without an explicit statement in the archival literature of when and how the guidelines have changed, it would not be intuitive to assume that "lev-" or "dex-" ever had a different meaning than they do now. For example, "lev-" in 1995 meant only levorotary optical rotation; however, "lev-" currently means levorotary optical rotation and S absolute configuration. Because both prefixes "lev-" and "dex-" once had different meanings, the connotation of the prefix is trivial without proper explanation of the guideline changes. Furthermore, before 1993 there were no published guidelines, so it is unknown exactly what protocol was being followed prior to 1993 or what meaning "lev-" or "dex-" held.

Another source of confusion regarding the current stereoisomer guidelines is the fact that "lev-" and "dex-" are common chemistry prefixes that refer to optical rotation only. To someone with an advanced chemistry background, but not in pharmaceuticals, the prefix "lev-" and "dex-" refer solely to optical rotation and are shortened from "levorotary" and "dextrorotary," respectively. Because "lev-" and "dex-" now are applies to drug names based on absolute configuration and optical activity, these prefixes may mislead chemists.

FDA has the power and position to lead change and to encourage the AMA, the APhA, the USAN Council, and the USP to reassess current stereoisomer naming guidelines. Considering that FDA has a dedicated team within the Center for Drug Evaluation and Research responsible for proprietary name review, drug naming is

clearly of paramount importance.[70] As nonproprietary names generally are, or should be, globally consistent, it is arguably even more important to review generic names in addition to brand names, considering there is generally only a single nonproprietary name. FDA has gone to great lengths within the past few decades to ensure the safe use of drugs and to reduce drug errors. By taking on this initiative to update stereoisomer naming guidelines, they will continue to ensure that practitioners are at a low risk of prescribing errors and are better able to provide optimal patient care.

The goal of the USAN Council, which is also followed and supported by FDA, is to provide useful, informative, and simple nonproprietary drug names. The simplicity prevents confusion and assures that naming is consistent, which, in turn, provides clinicians with the necessary tools to identify the best possible drug options for their patients. Considering that more than one-half of the drugs currently on the market are chiral, the clinical implications of stereochemistry ought to be accurately reflected in nonproprietary (generic) naming of drugs. It is time for stereoisomer naming guidelines to accurately and consistently inform clinicians, improve patient care, and be beneficial to the global delivery of healthcare.

In summary, the assignment of nonproprietary names should be reflective of their stereochemical properties. USAN guidelines for designating nonproprietary names prior to 1998 were substantially different from the current USAN guidelines so that older generic names are not always consistent with current naming conventions. The current USAN guidelines are not always followed when designating new nonproprietary names for drugs with important stereochemistry features, and, at times, the names adopted may result in confusion and inconsistent or even misleading information about the properties of a drug molecule. Nonproprietary names, and their adoption guidelines, should be aligned so that FDA, USP, and healthcare practitioners can accurately infer the stereochemical properties of the drug from the assigned generic name. If nonproprietary naming guidelines are not going to be consistently followed, it begs the question: "Why even bother with naming guidelines?"

[70] *How FDA Reviews Proposed Drug Names*, FOOD & DRUG ADMIN., https://www.fda.gov/media/72409/download [https://perma.cc/VE8S-2MC5].