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HISTORY OF MEDICINE

How Do Drugs Get Named?

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Abstract

Since the 1960s, the United States Adopted Names Program has been assigning generic (nonproprietary) names to all active drug ingredients sold in the United States. Pharmaceutical names are assigned according to a scheme in which specific syllables in the drug name (called stems) convey information about the chemical structure, action, or indication of the drug. The name also includes a prefix that is distinct from other drug names and that is euphonious, memorable, and acceptable to the sponsoring pharmaceutical firm. Drug names are the product of complex, multiparty negotiations in which the needs and desires of various stakeholders (patients, pharmaceutical firms, physicians, pharmacists, other health care professionals, and US and international regulators) must be balanced.

Overview of Generic Naming

The assignment of generic names to pharmaceuticals in development is an important prerequisite to marketing a drug. The United States Adopted Names (USAN) Program, which assigns generic (nonproprietary) names to all active drug ingredients in the United States, is the result of a long-time partnership between the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA). These 3 organizations are the sponsoring partners and receive support from the US Food and Drug Administration (FDA).

In the United States, the FDA recognizes the USAN as the legal name for the active drug ingredient, and the USAN appears in the titles of monographs published by the USP that define the standards, properties, and characteristics of marketed drugs. With few exceptions (eg, prophylactic vaccines and mixtures not named by the USAN Council), a drug cannot be marketed in the United States without a USAN. Consequently, the USAN assignment is a necessary step in drug development before a drug can be brought to the US market, and assignment of a USAN is required for a new drug before patients can have access to it.

Outside the United States, the World Health Organization (WHO) publishes recommended International Nonproprietary Names (INN) for active drug ingredients, but

the INN is not a substitute for a USAN. The USAN and the INN programs work together to ensure that generic names are the same inside and outside the United States. Consequently, the generic names inside and outside the United States differ only rarely, and these differences can potentially be very important. An example of a drug with 2 names is the substance known as acetaminophen inside the United States and as paracetamol internationally,[1,2] although these 2 names predate the inception of the USAN Program.

Firms usually begin the process of obtaining a nonproprietary name by filing a submission with the USAN Program or the WHO when a drug is in phase I or phase II clinical trials. Most prefer to complete generic name assignments by the time they are ready to publish papers about the drug so that they can use the name instead of a manufacturer code in publications. The USAN must be assigned before conducting premarketing labeling negotiations with the FDA.

The USAN Council is committed to patient safety, facilitating communication among health care professionals and patients, and access to prescription medications. The USAN Council is, therefore, aware of the importance of coining names that will not be confused with other drug names, compromise patient safety, or mislead health care professionals and patients about the action or use of a new drug substance. The USAN Council is also mindful of concerns that high drug costs can limit patients' access to them and, accordingly, must weigh this possibility against the possibility that pharmaceutical companies may choose not to develop drugs that they believe will not be profitable when they make their nomenclature decisions. Because the USAN name includes information about a drug's structure, action, or planned use, the name can potentially affect how a drug is perceived by physicians, pharmacists, pharmacy benefits managers, or the investment community. These perceptions can affect drug pricing and which drugs companies choose to advance in clinical trials.

USAN Program History

The USAN Program originated with the AMA's Council on Pharmacy and Chemistry, which was created in 1905 to evaluate drugs and to try to eliminate quackery in medications.[3] In 1938, the Food, Drug, and Cosmetic Act established federal regulatory authority over drugs, including requiring proof of safety,[4] but the AMA's Council on Pharmacy and Chemistry (renamed the Council on Drugs in 1957[5]) continued to evaluate drugs, and the AMA had laboratory facilities for this purpose. From 1907 through 1964, the AMA published an annual volume called *New and Nonofficial Remedies (NNR)*, renamed *New and Nonofficial Drugs (NND)* in 1958.[3,5] The AMA also published *Epitome of the United States Pharmacopeia and National Formulary* annually between 1907 and 1955.[3] Both AMA publications listed drugs by name along with information about their properties, use, or efficacy. In 1962, the Food, Drug, and Cosmetic Act was amended to give the FDA the authority to approve—or not approve—a drug based on evidence of efficacy as well

as safety in the wake of the thalidomide tragedy.[6] After passage of this law, the AMA continued to publish information on drugs.

Until 1963, the AMA's Council on Drugs did not adopt the position that drugs should be labeled so that patients would know what they were taking, and when it did adopt this position, it expressed the belief that patients should sometimes not be informed what was in their medications.[7] Several circumstances under which it was better for patients not to know the identity of their medicines were described: when patients were taking opioids or barbituates, when they might try to "out-guess the doctor" and make decisions themselves, or if patients regarded medications as "magical potions." The Council favored labeling as a general practice, but recommended that prescription pads include boxes for "yes" or "no" to indicate whether the drug should be labeled, with the default being labeling.

Meanwhile, the AMA's future partners in USAN were conducting their own nomenclature activities. The American Pharmaceutical Association, later renamed APhA, began publishing the *National Formulary* in 1888.[8] The USP, which incorporated in 1900, was tasked with publishing reference standards for strength, quality, and purity in the Pure Food and Drug Act of 1906.[9,10] The USP published compendia of monographs describing these standards, with the drug name as the monograph title.

On July 22, 1960, the AMA, the USP, and industry representatives met at the USP Conference on Nonproprietary Names for Drugs to discuss not only nonproprietary names for drugs but also to review a proposal to transfer nomenclature to a single entity. Concerns were raised that the existing system did not require selection of a nonproprietary name for each drug, that there was no central list of names, and that there was no legal requirement that all firms use the same name for a substance.

In a proposal to the AMA dated November 7, 1960, the USP called the program that later became USAN a "cooperative program for the selection of non-proprietary names of drugs." The draft of the proposal stated, "The American Medical Association will maintain and expand, as necessary, its present facilities for receiving proposals of nonproprietary names from all sources, will process these proposals and initiate and conduct such negotiations expeditiously as may be appropriate to settle upon a tentative name for all new drug entities." The USP committed to adopting the selected names as USP monograph titles and to publishing lists of the names.

The founders sought to achieve industry cooperation and preferred not to involve the federal government in nomenclature. A July 15 memorandum sent by the USP's Lloyd Miller to participants shortly before the USP Conference on Non-Proprietary Names for Drugs stated, "The industry seems to have no special preference as to what agency acts as a clearing-house. There is a desire, however, to keep the name selection program

separate from processing the FDA new drug applications. The FDA has not been disposed heretofore to concern itself very much with nonproprietary names."

Following these discussions, the AMA-USP Nomenclature Program was established in June 1961.

In 1963, the APhA joined the AMA and the USP in sponsoring the committee's nomenclature efforts. The partners agreed the council would include 3 representatives from each of the sponsoring organizations and a member at large. The committee was renamed the USAN Council, and the selected names were to be known as USAN. The USP agreed to adopt USAN as USP monograph titles, and the APhA, through its Committee on National Formulary, agreed to adopt USAN as *National Formulary* titles. In 1967, the agreement was further amended, and a representative from the FDA was added to the council. It was agreed that AMA staff would maintain all contacts in connection with the process of selecting and negotiating names. The USAN Council would—and still does—function independently of the FDA and is not an FDA advisory body.

What USAN Names

Over 10 000 drugs have received nonproprietary names since the WHO, AMA, USP, and APhA began assigning names to drugs,[11] and they are listed in online databases such as the *USP Dictionary of USAN and International Drug Names*.[1] In 2018, the USAN program named 198 substances. The number of USAN adoptions fluctuates from year to year but has grown steadily over the past 20 years.

By reviewing the chemical information published on the statements of adoption for each compound, it is possible to determine what types of substances were named (Table 1). Of all the drugs named in 2018, 112 (57%) were chemical substances (organic molecules) or their salts or esters intended as drugs for human use. The USAN Program named 76 substances (38%) that were biological in nature, including gene therapies, cell therapies, oligonucleotides, monoclonal antibodies and antibody drug conjugates, and other proteins or peptides. Biologic drugs tend to be expensive, and the path for approval of generic versions of these products is different than for small molecules.[12]

Table 1. Types of Substances Named by United States Adopted Names Program, 2018

Type of Substance	Number Named
Antibody-drug conjugates	1
Cell therapies	6
Chemical substances, organic molecules	83
Salts or Esters of chemical substances	29
Gene therapies	9
Inorganic salts or solid-state compounds	1
Monoclonal antibodies	41
Oligonucleotides	10
Peptides	3
Polymers	8
Proteins (not monoclonal antibodies)	6
Other types of substances	1
Total	198

The USAN Program publishes the planned therapeutic indication that the firm discloses when it applies for a name on the statement of adoption (see Table 2). In 2018, 71 substances (36%) named were intended for use as antineoplastics (ie, oncology drugs that attack tumors). Other popular indications for new substances named include neurologic conditions such as Parkinson's disease (22 substances or 11%), infectious diseases (18 substances, or 9%), and rare, inherited disorders such as Crigler-Najjar syndrome or Fabry disease (24 substances, or 12%). Relatively few drugs (or none) were named for common conditions affecting large numbers of patients, such as diabetes, depression, or high blood pressure.

Table 2. Planned Therapeutic Indications of Substances Named by the United States Adopted Names Program, 2018

Indication	Number Named
Anti-infectives	17
Antineoplastic compounds, oncology	72
Arthritis	1
Contact lens polymers	6
Analgesic	3
Cardiovascular indications other than high cholesterol	5
Cholesterol (high cholesterol)	1
Dermatology	3
Diabetes and related metabolic disorders	0
Diagnostic agent	1
Gastroenterology	1
Genetic disorders (eg, lysosomal storage disorders)	23
Gynecologic	2
Hepatology	2
Immunomodulatory indications (eg, psoriasis)	10
Muscular dystrophy and muscular conditions	5
Neurologic indications (eg, Parkinson's, Alzheimer's)	22
Ophthalmology indications	3
Psychiatric indications (eg, depression, schizophrenia)	2
Respiratory indications (eg, asthma, cystic fibrosis, COPD)	6
Urology	2
Veterinary pharmaceuticals	3
Other indications	5
Multiple indications	3
Total	198

Developing new drugs for common conditions for which drugs already exist poses challenges. Pharmaceutical companies are for-profit entities that seek to maximize returns and minimize potential risks, and developing new drugs is a high-risk enterprise. Although there has been some debate about the exact cost of developing a drug, the most widely disseminated recent estimate is that it costs about $2.6 billion to bring a drug to market.[13] Although failure rates vary according to the therapeutic class, most drugs that enter clinical trials fail.[14] Thus developing new drugs that target existing mechanisms and are differentiated from existing products in a clinically meaningful way can be challenging.[15] Consequently, pharmaceutical companies might find it more financially viable to develop drugs when there is less competition from low-cost therapies.

It is not clear whether firms' focus on oncology and rare diseases or on expensive biologic drugs—potentially with less emphasis on developing affordable drugs for conditions affecting many people (eg, diabetes, high blood pressure)—restricts access to adequate care. If low-cost prescription drugs already available to treat common chronic conditions are adequate, new treatments, which tend to be more expensive than older drugs, might not be needed.

What Names Mean

In naming drugs, the most important considerations are avoiding drug names that are too similar to existing names—and therefore might compromise patient safety—and making sure the drug name communicates accurate information about the action or use of the substance. Over time, the USAN and INN nomenclature scheme has developed into a system for classifying new pharmaceuticals.

Many of the oldest drugs were named by shortening the systematic chemical name for the compound. However, the AMA-USP Nomenclature Committee quickly realized that a different way of naming drugs was needed and published a list of guiding principles to systematize nomenclature and move away from names derived from the chemical name of a substance.[16] At that time, the AMA-USP Nomenclature Committee recognized 3 difficulties with chemically derived names: (1) the use of chemical syllables led to "complex, unmanageable" names for large classes of chemically related drugs; (2) common, chemically derived syllables (eg, di-, chlor-, meth-) were so overused that names were becoming less distinctive; and (3) some chemical compounds were so complex that the names derived from the proper chemical name were not meaningful to physicians.

Consequently, most USAN now include a stem. A stem consists of syllables—usually at the end of the name—that denote a chemical structure, indication, or action at a specific receptor. For example, in the name imatinib, the -tinib stem refers to the drug's action as a tyrosine kinase (TYK) inhibitor. Occasionally, a substem is used to further classify a

drug. Thus, -citinib refers to drugs inhibiting a specific family of TYK inhibitors, the Janus kinases. There are currently over 600 stems and substems that have been defined for classes of drugs.[17]

A 1- or 2-syllable prefix at the beginning of each name differentiates each drug from other members of the same class. The most important concern in choosing a prefix is patient safety—specifically, reducing the risk of medication errors, which are a common and long-standing problem in medical practice.[18,19] For this reason, the USAN Council avoids prefixes that will create new names that are too similar either to other drugs in the same stem class or to names in other stem classes that might look or sound similar to the new name. This means comparing drug names against lists of names for existing drugs. The USAN Program carefully screens prefixes using searches of databases of existing drug names[1,11] and Phonetic and Orthographic Computer Analysis (POCA) software.[20] The USAN Program, as much as possible, also avoids creating new drug names that begin and end with letters shared with existing generic or trade names for drugs or that have been found to have strong conflicts with other names in the POCA analysis. An analyis of trade-name pairs prone to look alike-sound alike medication errors found that these pairs often had shared strings of 3 or more letters in the prefix and POCA scores that indicated a conflict.[21]

Balancing the Needs of Firms and Patients

As with any complex multiparty negotiation, there can be disagreements. The USAN Council's focus on patient safety, access to new drugs, and communicating necessary information about drugs through the generic name is sometimes in conflict with the desires of pharmaceutical companies to create either a certain message about their drugs through the generic name or a positive image for their substances. While this desire on the part of companies is understandable, the USAN Council prioritizes patient safety and access to affordable drugs.

The class to which a drug is assigned can indirectly affect a company's decisions about whether or not to continue developing it. Sometimes there are financial benefits if a drug is assigned to a specific drug class, and assignment to an undesirable drug class (often one in which there have been safety problems) might adversely affect drug development. Because pharmaceutical firms are in business to generate profits for their investors, they tend to develop more drugs in classes that they believe are commercially viable.

The USAN can also affect how a drug is perceived by payers or pharmacy benefits managers, who may be reluctant to list a "me-too" drug in their formulary but may accept an expensive drug if it is a first-in-class therapy because it is perceived as offering added value that justifies a higher price. For a small biotech firm, a first-in-class drug may be perceived as more valuable by investors or by larger, more established pharmaceutical firms looking to acquire the rights to develop and market new drugs.

Firms might therefore request assignment of a new stem to indicate a drug is first in class. First-in-class drugs can achieve a larger market share, but the second or third member of a class can be a successful product if it improves on the first product in a clinically significant way.[22,23,24]

The USAN Council must therefore be mindful of how firms' desires for a drug to be named a specific way might affect access to medications and how much those medications cost. Assignment of a new stem is rare, occurring only after the council determines that a drug is truly novel and does not fit into any existing group. Unnecessary assignment of a new stem could lead insurers and patients to pay more for drugs similar to older, less-expensive products, indirectly affecting patients' access to drugs. Similarly, an unfavorable nomenclature decision for the firm, if it contributes to a company's decision to discontinue a developmental drug, might affect patient access.

Conclusions

For decades, assignment of a USAN has been a key step in the development and marketing of a new active pharmaceutical ingredient, because a substance cannot be marketed in the United States without a name. The primary goals of the USAN Council are to facilitate the safe use of medications by assigning names that are unlikely to result in medical errors and to ensure that drug names are reflective of what physicians, pharmacists, and patients need to know about each substance. The USAN can affect how payers, health care professionals, patients, and the investment community perceive a drug—and therefore patients' access to drugs.

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