International Nonproprietary Names (INN) for pharmaceutical substances*

S. Kopp-Kubel

WHO has a constitutional mandate to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products" (1) is the basis for many of its activities, such as those concerned with the International Nonproprietary Names (INN), Good Manufacturing Practices, the International Pharmacopoeia, the WHO Certification Scheme and many others. The unit responsible for and specifically dealing with the selection of International Nonproprietary Names for pharmaceutical substances falls under the WHO Division of Drug Management and Policies.

Trade-marks and nonproprietary names

Most products available on the market are identified by a trade-mark. This is also true in the pharmaceutical field. In many countries trade-marks, also called brand-names, are used when prescribing, dispensing, selling, promoting or buying a medicament. Trade-marks are usually selected by the owner of the product and registered in national trade-mark or patent offices. They are private property and can be used only with the consent of the owner of the trade-mark (2, 3). In most cases brand-names are chosen for a finished pharmaceutical product, i.e., for one or various active drug substances in a defined dosage form and formulation. Therefore, pharmaceutical preparations containing the same active drug substance are frequently sold under different brand-names or trade-marks, not only in different countries, but even within the same country (Fig. 1).

Nonproprietary names, also called generic or common names, are intended to be used as public property without restraint, i.e., nobody owns any rights on their usage. These names are usually designated by national or international nomenclature commissions.

Although both trade-marks and INNs may appear similar to an outsider, there is in fact a big difference. Firstly, trade-marks identify the final drug product, whereas nonproprietary names stand for the active pharmaceutical, or medicinal substance—although drug products are often prescribed and put on the market under their nonproprietary names. Second, the selection of a nonproprietary name follows established rules so that the name itself communicates to the medical and pharmaceutical health professional the therapeutic or pharmaceutical group to which the active drug substance belongs.

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History

The rapid industrial expansion from the beginning of this century led to the development of a large number of synthetic drug substances. While in the past most products used were of natural origin and known by simple names, the introduction of synthetic substances provided the opportunity for patent protection and the use of trade-marks. These short names were attractive since compounds could otherwise only be described by a systematic or chemical name. A systematic chemical name may be developed following the guidelines of international bodies, including the International Union for Pure and Applied Chemistry (IUPAC). However, these names were usually long and difficult to retain. Therefore national nomenclature bodies and the international nomenclature programme were formed to develop simple generic names (Fig. 2).

The INN programme, which falls under WHO’s constitutional mandate of setting norms and standards for pharmaceutical products, was started in 1953 when Member States passed a resolution at the World Health Assembly. A procedure for the selection of recommended international nonproprietary names for pharmaceutical substances was developed together with general principles for guidance in devising INNs for pharmaceutical substances. At the start of this programme the experts coordinated the activities of existing national nomenclature bodies. Many substances had already well-established names, e.g., acetaminophen/paracetamol. A single name had to be chosen.

Naming of new substances was coordinated from the outset, in order to have only one single name worldwide. Secretaries or representatives of all the major national nomenclature committees (e.g., in France, Japan, United Kingdom and the USA) are practically ex officio members of the INN Committee (Fig. 3). This approach has proved successful in ensuring that national and generic names are identical (Fig. 4).

Selection process

How are INNs selected? A request for an INN is usually submitted on a form to the World Health Organization. In certain countries, where national nomenclature commissions exist, this is done through the corresponding national nomenclature authority, e.g., in the USA it is through the United States Adopted Names (USAN) Council. Precise information on the chemistry, pharmacological action and use, as well as suggested nonproprietary names, and the name and address of the manufacturer should be provided on the form.

Each name proposed by the originator of such a request is then examined and a name selected. All members of the WHO Expert Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated to select nonproprietary names have to agree to the name, which is then first published as a proposed INN. During a four-month period, any person can put forward comments, or lodge a formal objection to a name, e.g., on grounds of similarity to a trade-name. If no objection is raised, the name will be published a second time as a recommended INN.

The primary principle for selection is that an INN should be:
- distinctive in sound and spelling;
- not too long;
- not liable to confusion with other names in common use.

Usually an INN consists of a random, fantasy prefix and a common stem; substances belonging to a group of pharmacologically related substances show their relationship by the use of a common stem.
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Fig. 2. Various common names for the same substance (paracetamol).

Sometimes sub-stems are established to differentiate between different related groups of substances, e.g., -olol for β-adrenoreceptor antagonists and anti-hypertensives, -teplase for tissue-type-plasminogen activators, and -uplase for urokinase-type-plasminogen activators. The following examples show the components that make up an INN:

Fig. 3. INNs, the key to one name worldwide.

### INN

<table>
<thead>
<tr>
<th>INN</th>
<th>Prefix</th>
<th>Substem</th>
<th>Stem</th>
</tr>
</thead>
<tbody>
<tr>
<td>apafant</td>
<td>a</td>
<td>pafant</td>
<td></td>
</tr>
<tr>
<td>isbogrel</td>
<td>isbo</td>
<td>grel</td>
<td></td>
</tr>
<tr>
<td>daltroban</td>
<td>dal</td>
<td>troban</td>
<td></td>
</tr>
<tr>
<td>duteplase</td>
<td>du</td>
<td>tepl</td>
<td>ase</td>
</tr>
</tbody>
</table>

Examples of some common stems are:

- **-arol** anticoagulants, dicoumarol derivatives
- **-teplase** tissue-type-plasminogen activator
- **cef-** antibiotics, cefalosporanic acid derivatives
- **-dil** vasodilators
- **-grel**, **-grel** platelet aggregation inhibitors
- **-irudin** hirudin derivatives
- **-poetin** erythropoietin type blood factors
- **-troban** thromboxane A₂-receptor antagonists, antithrombotic agents

Examples of INNs of the -grel- and -grel series for platelet aggregation inhibitors are: anagrelide, camonagrel, clopidogrel, dazmegrel, furegrelate, isbogrel, itazigrel, midazogrel, nafagrel, nicogrelate, oxagrelate, ozagrel, pamicogrel, pirmagrel, ridogrel,

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rolafagrel, sarpogrelate, satigrel, sunagrel, trifena-grel.

In addition to the above principles, certain rules have been established to allow the use of INNs internationally, i.e., in various languages. For example, the letters “h” and “k” should be avoided; “e” should be used instead of “ae” and “oe”, “i” instead of “y”, and “t” and “f” instead of “th” and “ph”.

**Publication and use**

All newly selected names are published, after informing the originator of the request, in the journal *WHO Drug Information* which is published by WHO. Two proposed and one recommended lists are published per year. The lists are trilingual, English, French and Spanish, including also Latin INNs.

All INNs are published in a cumulative list, which is updated periodically (4). At present, some 6525 INNs have been published.

Nonproprietary names are intended to be used in pharmacopoeias, labelling, advertising, drug regulation, scientific literature, and as product names, e.g., for generics.

**Protection**

During the past few years INN common stems have been increasingly introduced in trade-marks. This hampers the selection of new nonproprietary names within the established system. Given the fact that all INNs should be distinctive from existing INNs and trademarks, this practice causes difficulties when selecting a new name. In addition it causes confusion to health professionals and may be the source of serious errors in prescribing and dispensing.

Based on recommendations made by the WHO Expert Committee on the Use of Essential Drugs, a resolution (WHA46.19) was adopted during the 46th World Health Assembly in 1993, requesting Member States to:

— “enact rules or regulations, as necessary, to ensure that international nonproprietary names... are always displayed prominently;
— to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than trade-marks, to promote and market multisource products introduced after patent expiration;
— to develop policy guidelines on the use and protection of international nonproprietary names, and to discourage the use of names derived from INNs, and particularly names including INN stems in trade-marks.”

**Recent developments in drug nomenclature**

When requesting selection of an INN the manufacturer has often not yet finalized the precise indications for the therapeutic use of the compound. A name is usually requested during the development phase of a new compound, which means that the request is generally submitted to WHO during the clinical trials phase. A name is, however, needed as soon as an application for registration of a product is forwarded to the national authorities. This means that the naming process is closely related to new scientific developments in the pharmaceutical field. External expertise is often needed for specific questions concerning new therapeutic groups and new types of products.

During the last few years the selection process has become more complex. New receptors and pharmacological actions are being discovered more and more frequently. This means in many cases that new stems have to be created. However, there is sometimes a structural relationship to existing molecules and experts have to decide whether an existing stem may be used or whether a new one must be established. Fibrinogen receptor antagonists are a recent example. These substances act as platelet aggregation inhibitors for which the stem -grel existed for several years. The nomenclature experts now have to decide whether the same stem should be used for the fibrinogen receptor antagonists or whether the group of new molecules is so important that a new stem needs to be established.

On the other hand, a new mode of action is sometimes discovered for an existing substance. If further substances are developed with a similar mode of action, the question arises whether a new stem is needed, which would mean modifying the “old” name for the first compound in the series. For example, alfibylline and pentoxifylline are N-methylxanthine derivatives and the stem -ylline was therefore chosen for their names. These substances have now been found to suppress also the tumour necrosis factor-α (5). The experts decided to retain the stem -ylline in this case, since the “new” action was nevertheless based on the typical xanthine-mediated inhibition of phosphodiesterase.

New approaches to naming pharmaceutical substances may be needed in the near future because of increasing research using molecular design. “Simple”

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*Examples of recently published INN lists: List 71 of proposed INNs in *WHO Drug Information*, 1994, 8(2); List 34 of recommended INNs in *WHO Drug Information*, 1994, 8(3); and List 72 of proposed INNs in *WHO Drug Information*, 1994, 8(4).*
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derivatives of known compounds are becoming less frequent. Chemistry based on receptor structure and molecular design focuses more on synthesizing compounds to fit receptor bindings sites. This will mean that nomenclature will have to move in the same direction. Chemical relationship will need to be looked at from a different standpoint, and the pharmacological activity might have to be considered in almost all cases as a basis for assigning a given substance to a group.

Substances produced by biotechnology are another challenge for the nomenclature committee (6). New schemes and concepts need to be developed on a worldwide basis. One example is the scheme for common stems for naming monoclonal antibodies, as shown below.

I. General stem: -mab

II. Sub-stems for source of product:
  human: -u-
  rat: -a-
  hamster: -e-
  primate: -i-
  mouse: -o-
  chimeras: -xi-

III. Sub-stems for disease or target group:
  bacterial: -ba(c)-
  cardiovascular: -ci(r)-
  immunomodulator: -li(m)-
  viral: -vi(r)-

and for tumours:
  colon: -co(l)-
  testis: -go(t)-
  ovary: -go(v)-
  mammary: -ma(r)-
  melanoma: -me(l)-
  prostate: -pr(o)-
  miscellaneous: -tu(m)-

Whenever there is a problem in pronunciation, the final letter of the sub-stems for diseases or targets may be deleted, e.g. -co(l)-, vi(r), li(m), etc.

IV. Prefix: The prefix should be random, e.g., the only requirement is to contribute to a euphonious and distinctive name.

V. Second word: If the product is radiolabelled or conjugated to another chemical, such as a toxin, identification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation. For monoclonals conjugated to a toxin, the tox- stem must be included as part of the name selected for the toxin.

Examples of INNs are: altumomab, balimomab, biciromab, dorlimomab aritox, imciromab, maslimomab, nebacumab, satumomab, sevirumab, telimomab aritox, tuvirumab, etc.

References