WHO/ PHARM S/NOM 1570
Distr.: GENERAL
ENGLISH ONLY

GUIDELINES ON THE USE OF INTERNATIONAL NONPROPRIETARY NAMES (INNs) FOR PHARMACEUTICAL SUBSTANCES

Programme on International Nonproprietary Names (INN)
Division of Drug Management & Policies
World Health Organization
Geneva

GUIDELINES ON THE USE OF INTERNATIONAL NONPROPRIETARY NAMES (INNs) for Pharmaceutical Substances

Table of contents

List of Annexes

Information on the INN Programme and the INN request form
are available on INTERNET:
http://www.who.ch/programmes/dmp/innmain.htm

1. General introduction

The present guidelines on the use of INNs are intended as a general explanation of the INN selection process. They have been developed for drug regulatory authorities for use in the marketing authorization/ registration of products, drug manufacturers who are requesting new INNs and those using INNs, patent authorities/offices, trade-mark attorneys and trade-mark specialists, scientists, teachers, health professionals, as well as any person interested in nomenclature.

1.1 General information on the INN system

An International Nonproprietary Name (INN) identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.

The INN system as it exists today was initiated in 1950 by a World Health Assembly resolution WHA3.11 and began operating in 1953, when the first list of International Nonproprietary Names for pharmaceutical substances was published. The cumulative list of INNs now stands at some 7000 names designated since that time, and this number is growing every year by some 120 - 150 new INNs.

Since its inception, the aim of the INN system has been to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance. The existence of an international nomenclature for pharmaceutical substances, in the form of INNs, is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide.

As unique names, INNs have to be distinctive in sound and spelling, and should not be liable to confusion with other names in common use. To make INNs universally available they are formally placed by WHO in the public domain, hence their designation as "nonproprietary". They can be used without any restriction whatsoever to identify pharmaceutical substances.

Another important feature of the INN system is that the names of pharmacologically-related substances demonstrate their relationship by using a common "stem". By the use of common stems the medical practitioner, the pharmacist, or anyone dealing with pharmaceutical products can recognize that the substance belongs to a group of substances having similar pharmacological activity. For example all iodine-containing contrast media are given the prefix *io-*, while all ß-adrenoreceptor antagonists the suffix *-olol*. The use of stems is described later in more detail.

The extent of INN utilization is expanding with the increase in the number of names. Its wide application and global recognition are also due to close collaboration in the process of INN selection with numerous national drug nomenclature bodies. The increasing coverage of the drug-name area by INNs has led to the situation whereby the majority of pharmaceutical substances used today in medical practice are designated by an INN. The use of INNs is already common in research and clinical documentation, while

the importance of the programme is growing further due to expanding use of generic names for pharmaceutical products.

The names which are given the status of an INN are selected by the World Health Organization on the advice of experts from the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The process of INN selection follows three main steps:

- a request/application is made by the manufacturer or inventor,
- after a review of the request a proposed INN (prop. INN) is selected and published for comments,
- after a time-period for objections has lapsed, the name will obtain the status of a recommended INN (rec. INN) and is published as such.

The procedures relating to each of these steps are described in the present document in full detail.

INNs are selected in principle only for single, well-defined substances that can be unequivocally characterized by a chemical name (or formula). It is the policy of the INN programme not to select names for mixtures of substances, while substances that are not fully characterized are included in the INN system in exceptional cases only. INNs are not selected for herbal substances (vegetable drugs) or for homoeopathic products. It is also the policy of the INN programme not to select names for those substances that have a long history of use for medical purposes under well-established names such as those of alkaloids (e.g. morphine, codeine), or trivial chemical names (e.g. acetic acid).

The INN is usually designated for the active part of the molecule only, to avoid the multiplication of entries in cases where several salts, esters, etc. are actually used. In such cases, the user of the INN has to create a modified INN (INNM) himself ; *mepyramine maleate* (a salt of *mepyramine* with *maleic acid*) is an example of an INNM. When the creation of an INNM would require the use of a long or inconvenient name for the radical part of the INNM, the INN programme will select a short name for such a radical (for example, *mesilate* for *methanesulfonate*).

Names of pharmaceutical preparations, such as used in pharmacopoieal monograph titles, usually consist of two elements, the first designating the active substance (an INN is used here), and the other designating the dosage form of the product. Rules for creating such names fall outside the INN programme and are not discussed here.

In the process of INN selection, the rights of existing trade-mark owners are fully protected. If in the period of four months following the publication of a proposed INN, a formal objection is filed by an interested person who considers that the proposed INN is in conflict with an existing trade-mark, WHO will actively pursue an arrangement to obtain a withdrawal of such an objection or will reconsider the proposed name. As long as the objection exists, WHO will not published it as a recommended INN.

With the growing number of INNs and trade-marks, the possibility of conflicts between the two has gradually increased, even with full protection of the rights of existing trade-marks. The main source of conflict is usually an attempt by a manufacturer to propose a new trade-mark containing stems established in the INN programme. If protection is granted to such a name, this may diminish the freedom of the INN programme in selecting further INNs in the same series of substances. To prevent such occurrences, the matter was taken up in a resolution of the World Health Assembly *WHA46.19*. This issue is discussed in more detail in section 4.

Further background information on the INN programme may be found in Annex 1.

1.2 Use of INNs

Nonproprietary names are intended for use in pharmacopoeias, labelling, product infromation, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. Their use is normally required by national or, as in the case of the European Community, by international legislation. As a restult of ongoing collaboration, national names such as British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN) and United States Accepted Names (USAN) are nowadays, with rare exceptions, identical to the INNs.

Some countries have defined the minimum size of characters in which the generic nonproprietary name must be printed under the trade-mark labelling and advertising. In several countries the generic name must appear prominently in type at least half the size of that used for the proprietary or brand-name. In some countries it has to appear larger than the trade-mark name. Certain countries have even gone so far as to abolish trade-marks within the public sector.

To avoid confusion, which could jeopardize the safety of patients, trade-marks cannot be derived from INNs and, in particular, must include their common stems. As already menitoned the selection of further names within a series will be seriously hindered by the use of a common stem in a brand-name.

2. Elements in the INN system

2.1 Proposed INNs

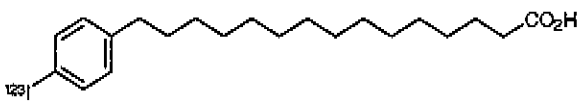
The selection of a new INN relies on a a strict procedure. Upon receipt of an INN request form, the WHO Secretariat examines the suggested names for conformity with the general rules, for similarities with published INNs and potential conflicts with existing names, including published INNs and trademarks. A note summarizing the result of these checks is added and the request is subsequently forwarded to the INN experts for comments. Once all experts agree upon one name, the applicant is informed of the selected name.

Newly selected, proposed INNs are then published in *WHO Drug Information*, which indicates a deadline for a 4-month objection period. This period is allowed for comments and/or objections to the published names to be raised. The reasons for any objection must be stated clearly and these will be evaluated by the experts for further action. Users are invited to refrain from using the proposed name until it becomes a recommended INN, in order to avoid confusion should the name be modified.
Two lists of proposed INNs are published yearly. An example is set out below.

acidum iocanlidicum (^{123}I)

iocanlidic (^{123}I) acid	15-(*p*-[^{123}I]iodophenyl)pentadecanoic acid *radiodiagnostic agent*
acide iocanlidique (^{123}I)	acide 15-(4-[^{123}I]iodophényl)pentadécanoïque *produit à usage radiodiagnostique*
ácido iocanlídico (^{123}I)	ácido 15-(*p*-[^{123}I]iodofenil)pentadecanoico *agente de radiodiagnóstico*

$C_{21}H_{33}{}^{123}IO_2$ 74855-17-7



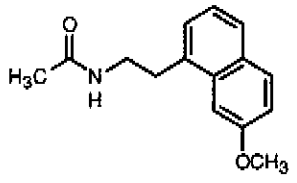
2.2 Recommended INNs

The final stage of the selection process is the recommended INN. Once a name has been published as a recommended INN it will not normally be modified further and is ready for use in labelling, publications, on drug information. It will serve to identify the active pharmaceutical substance during its life-time worldwide. Since the name is available in the public domain it may be used freely. However, it should not be registered as a trademark since this would prevent its use by other parties (see also chapter 4.).

Recommended INNs are published in the *WHO Drug Information* as a consequence of the objection procedure applied to proposed INNs (see 2.1 above). As from 1997, two lists of proposed INNs are published yearly and as from list 37 of recommended INNs, graphic formulae are also included for better identification of the substances.

An example of an entry in the list may be found below:

agomelatinum	
agomelatine	*N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide
agomélatine	*N*-[2-(7-méthoxynaphtalén-1-yl)éthyl]acétamide
agomelatina	*N*-[2-(7-metoxi-1-naftil)etil]acetamida
	$C_{15}H_{17}NO_2$



2.3 Names for radicals and groups

During the 1975 meeting on Nonproprietary Names for Pharmaceutical Substances the experts discussed the issue of INNs for salts and esters and noted that requests had frequently been received for INNs for salts, esters, or combination products of substances for which INNs already existed. At that time, the experts decided that INNs for the simple salt and esters should be devised from the INN in conformity with normal chemical practice.

Some of the radicals and groups involved are, however, of such complex composition that it makes it inconvenient to use the chemical nomenclature. It was thus decided that in such cases, shorter nonproprietary names are selected for these inactive moieties and published in proposed lists under the title "Names for Radicals and Groups". Separate names for salts and esters derived from this procedure are not published. If a "radical and group name" is used in conjunction with an INN, they are referred to as International Nonproprietary Name (Modified) or INNM.

A comprehensive list of radicals and groups may be obtained from the Distribution and Sales unit or the INN Secretariat (*INNs: Names for radicals and groups, combined summary list, WHO/PHARM S/NOM 1506, updated regularly*).

2.4 Modified INNs (INNMs)

In principle, INNs are selected only for the active part of the molecule which is usually the base, acid or alcohol. In some cases, however, the active molecules need to be expanded for various reasons, such as formulation purposes, bioavailability or absorption rate. In 1975 the experts designated for the selection of INN decided to adopt a new policy for naming such molecules. In future, names for different salts or esters of the same active substance should differ only with regard to the inactive moiety of the molecule. For example, *oxacillin* and *ibufenac* are INNs and their salts are named *oxacillin sodium* and *ibufenac sodium*. The latter are called modified INNs (INNMs).

Before the existence of this rule, some INNs were published for salts. In such cases, the term "modified INN" may also be used for a base or acid. For example, *levothyroxine sodium* was published as an INN and *levothyroxine* may thus be referred to as an INNM.

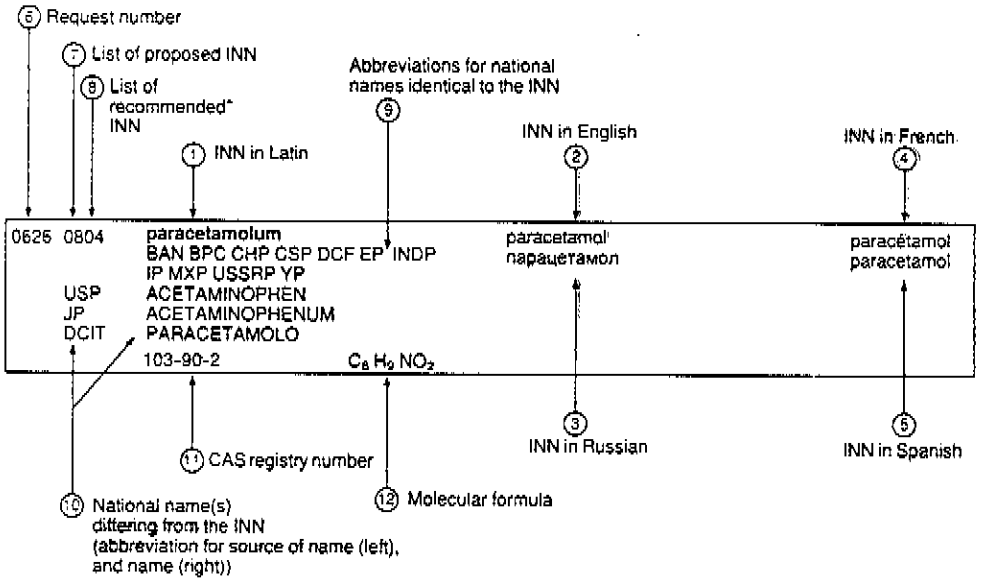
Please see also chapter 2.4 for radicals and groups (see also 2.4) which are used in conjunction with INNs and which are also referred to as INNM.

2.5 Cumulative list

All names selected as proposed and recommended INNs are published in a *Cumulative list*, which is updated periodically. The generic names are presented in alphabetical order by Latin name. Each entry includes:

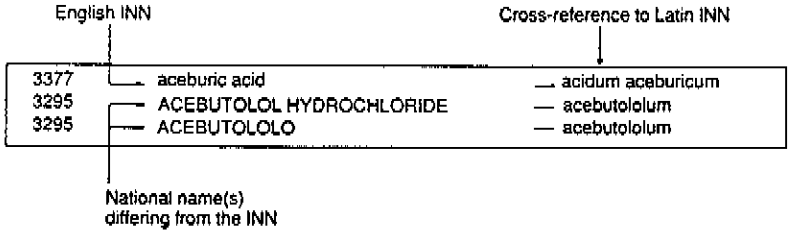
- equivalent nonproprietary names: in Latin, English, French, Russian and Spanish;
- a reference to the INN list in which the name was originally proposed or recommended, or last amended;
- reference to names of substances that have been abandoned or never been marketed;
- reference to national nonproprietary names;
- reference to pharmacopoeial monographs or similar official references;
- reference to names issued by the International Organization for Standardization (ISO);
- reference to the Convention of Psychotropic Substances, if applicable;
- reference to the List of Narcotic Drugs under International Control, if applicable;
- the molecular formula;
- its Chemical Abstracts Service (CAS) number.

The layout for information contained in the *Cumulative list* of INNs is as follows:



* An asterisk in place of a recommended list number signifies that an objection has been raised to the proposed name.

Note: Cross-references are provided for entries corresponding to (a) English, French and Spanish INN that appear in different alphabetical positions from the Latin INN and (b) national names that differ from the INN. Entries for (a) are printed in lower-case letters (as in the example of aceburic acid, below) while entries for (b) are printed in capitals (as in the examples of ACEBUTOLOL HYDROCHLORIDE and ACEBUTOLOLO).



3. Principles for selection of INNs

3.1 General rules

General rules were established at the beginning of the INN programme in order to guide the members of the INN committee and to allow health professionals to understand the rationale for a number of new names. At first, some countries used shortened chemical names as generic names, but this system was found to be very limited, since many molecules contain similar elements and groups, such as phenol, chlor, methyl or benzene-rings, in their chemical structures. In addition, a name that indicates relationship to a group of pharmacological similarly-acting substances is more meaningful to users.

In its Twentieth Report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds over the years. The current version of the *General principles for guidance in devising international nonproprietary names for pharmaceutical substances* is reproduced in Annex 2.

3.2 Use of stems

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. Sometimes sub-stems are established to differentiate between different related groups of substances, e.g. *-olol* for b-adrenoreceptor antagonists and antihypertensives, *-teplase* for tissue-type-plasminogen activators and *-uplase* for urokinase-type-plasminogen activators.

A list of common stems used in the selection of INNs may be found in Annex 3.

3.3 Stereoisomers

An INN for a new chemical entity does not routinely specify the stereoisomeric state of the molecule in the nonproprietary name. If the stereochemistry has been determined, then this information is presented in the chemical name(s) to identify the substance. An INN can, therefore, identify the racemic mixture (e.g. ibuprofen, tetramisole), the *levo-* isomer (e.g. amifostine, lofentanil, prenalterol, remoxipride, quadazocine), or the *dextro* form (e.g. butopamine). Subsequently if an INN is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing INN:

(a) For the *levo* form, the *lev-/levo-* prefix is used, e.g. levocarnitine, levamisole.
(b) For the *dextro* form, the *dex-* prefix is used, e.g. dexamisole, dexibuprofen.
(c) For the *racemic* form, the *rac-/race-* prefix is used, e.g. racepinefrine.

3.4 Radioactive compounds

A name for a drug substance containing a radioactive atom should list, in the following order:

(1) the name of the substance containing the radioactive atom,
(2) the isotope number,
(3) the element symbol, and
(4) the name of the carrier agent, if any,

e.g. cyanocobalamin (^{60}Co), technetium (^{99m}Tc) bicisate, technetium (^{99m}Tc) sestamibi.

3.5 Specific groups of biological compounds

Because of the complexity of certain new types of pharmaceutical products, such as compounds produced by biotechnology, general rules are not always easily formulated. Some of these substances may already have descriptive names assigned by other institutions such as the *International Union of Biochemistry (IUB), International Union of Pure and Applied Chemistry* (IUPAC), *Joint Commission on Biochemical Nomenclature* (JCBN). These names may not be suitable as INNs.

Annex 4 summarizes nomenclature schemes for groups of biological compounds
(for details and examples please also see document WHO/PHARM S/NOM 15: *The use of common stems in the selection of international nonproprietary names (INN) for pharmaceutical substances,* updated regularly).

4. Protection of INNs

Lists of both proposed and recommended INNs are sent together with a *note verbale* by the Director-General to WHO Member States (at present 191), to national pharmacopoeia commissions and to other bodies designated by Member States. In his *note verbale,* the Director-General of the World Health Organization requests that Member States should take such steps as are necessary to prevent the acquisition of proprietary rights on the name, including prohibiting registration of the name as a tradename.

Over the years, the need to maintain the integrity of the INN system has become urgent. This is reflected in the following extract from the Fifth Report of the WHO Expert Committee on the Use of Essential Drugs which met in November 1991[1]:

> **"The procedure for selecting INNs allows manufacturers to contest names that are either identical or similar to their licensed trade marks. In contrast, trade mark applications are disallowed, in accordance with the present procedure, only when they are identical to an INN.A case for increased protection of INNs is now apparent as a result of competitive promotion of products no longer protected by patents. Rather than marketing these products under generic name, many companies apply for a trade mark derived from an INN and, in particular, including the INN common stem. This practice endangers the principle that INNs are public property; it can frustrate the rational selection of further INNs for related substances, and it will ultimately compromise the safety of patients by promoting confusion in drug nomenclature."**

These concerns were debated during the sixth International Conference of Drug Regulatory Authorities (ICDRA), in Ottawa, in October 1991.

Based on recommendations made by the WHO Expert Committee on the use of Essential Drugs the resolution WHA46.19 on *Nonproprietary Names for pharmaceutical substances* was adopted in May, 1993 during the Forty-sixth World Health Assembly requesting Member States to:

> ■ ***"enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic nam used in the labelling and advertising of pharmaceutical products are always displayed prominently;***
> ■ ***to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than on 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 established INN stems as trade-marks."***

In the Director General's *note verbale* attention is drawn to this resolution concerning the use and protection of International Nonproprietary Names (INNs).
The full text of the resolution is reproduced in Annex 5.

As a matter of principle, it may thus be recommended that trade marks should not be derived from INNs. In particular, the intentional incorporation of meaningful INN stems in trade marks should be avoided.

Similarly, inclusion of elements from biochemical nomenclature (like *-feron* from interferon, or *-leukin* from interleukin) in trade marks in anticipation is discouraged since these elements are likely to be utilized as stems within the INN nomenclature. Their inclusion in trade marks could pre-empt the logical development of the INN nomenclature.

[1] WHO Technical Report Series, No. 825, 1992.

In accordance with resolution WHA46.19, registration of an INN together with a firm's name is perfectly acceptable, as long as it does not prevent another manufacturer from using the same approach.

5. How to apply for an INN

5.1 Procedure for selection of INNs

The selection of INNs is based on the *Procedure for selection of international nonproprietary names for pharmaceutical substances.* The text adopted is set out in World Health Assembly resolution WHA3.11 [Text adopted by the Executive Board of WHO in resolution EB15.R7 (*Off. Rec. Wld Health Org.*, 1955, **60**, 3) and amended by the Board in resolution EB43.R9 (*Off. Rec. Wld Hlth Org.*, 1969, **173**, 10).]. The application/request form for INN is attached as Annex 6 in its updated version.

In countries with national nomenclature commissions, applications for international nonproprietary names should be made through the national authorities (addresses - see Annex 7). In countries without a national nomenclature commission, requests for INNs may be forwarded directly to WHO. Applications for INNs should be addressed to:

Secretary of the INN Programme
Quality Assurance - INNs
Drug Management and Policies
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
***Internet:* koppkubels@who.ch**
***Fax* : +41 22 791 07 46**
***Tel.* : +41 22 791 36 36/36 60**

5.2 INN request form

Before a suggested name can be evaluated by the INN Secretariat, complete information must be provided on a request form to facilitate uniform handling of the data and to assure that pertinent items have not been omitted. It is important that the information is as comprehensive as possible. If parts of this information are missing or explanations are unclear or incomplete, the INN Secretariat will request the applicant to furnish the missing data. This can result in delay because selection of an INN requires the availability of all relevant information to the INN experts.

The following explanations will help applicants to complete the INN form. If additional information is needed, an applicant may contact the INN Secretariat at the World Health Organization, DMP/QAS, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland. (Telephone: +41/22/791 36.36/36.60. Facsimile: +41/22/ 791.07.46. Internet: *koppkubels@who.ch*).

Suggested names in order of preference

An applicant may make 3 suggestions for an INN relating to the acid, base or alcohol of a specific chemical entity under investigation. The suggested name should be a single word and not inconveniently long.

Nonproprietary names are developed by a system that relates compounds with chemical, pharmacological or therapeutic similarity. Therefore, whenever justified, the suggested name must incorporate the established common stem. A list of stems may be found in the document entitled *The use of common stems in the selection of international nonproprietary names (INN) for pharmaceutical substances (WHO/PHARM S/NOM 15)* which is updated regularly.

Occasionally stems require modification. For example, some drugs inhibit a-adreno-receptors as well as ß-adrenoreceptors and exhibit a specific structural variation from the "*-olol*" prototype. Accordingly, for this type of drug, the stem was modified by one letter to "*-alol*". This change introduces a nuance in the

naming of related groups of drugs that may not be apparent to every observer but would be understood by someone familiar with the naming conventions of the ß-adrenoreceptor antagonists and related compounds. The important point is that similar compounds have a common element in the name that imparts useful information.

It is imperative that the newly suggested name does not conflict with existing chemical names, other nonproprietary names or trade-marks. Therefore, the INN Secretariat requests the applicant to verify the absence of conflicts with existing chemical names, common names for insecticides, other nonproprietary names, and trade-marks. Some firms routinely perform exhaustive searches for possible conflicts with a suggested INN and for pharmacologically and chemically related compounds with already assigned INNs; the INN Secretariat would appreciate receiving this information to avoid search duplication.

Chemical name and description

Chemical information should be as complete and as current as possible. Information on stereochemistry should be included if known. The chemical names will be in accordance with the nomenclature rules of the International Union of Pure and Applied Chemistry (**IUPAC**) as interpreted by the Chemical Abstracts Service (8th collective period); the Chemical Abstracts Index names in their current style may also be included as additional information. The chemical name provided by the manufacturer is reviewed for accuracy and to confirm that its construction follows accepted chemical nomenclature rules.

A description is used to identify a substance that is insufficiently defined to be assigned an IUPAC and CAS chemical name. This description will be superseded by the chemical name when the drug substance is fully characterized.

Precautions are taken to ensure confidentiality of the material submitted to WHO, but an applicant should not attempt to obtain an INN before all patent procedures are completed and until full chemical information can be made available to WHO.

Graphic formula

Without a graphic formula, it may be difficult to determine if an INN already exists. In addition, the graphic formula is necessary to relate the new drug to existing compounds in the same chemical family. Guidelines for drawing structures may be found in the document entitled *Graphic representation of chemical formulae in the publications of International Nonproprietary Names for pharmaceutical substances (WHO/PHARM/95.579)*, available from the INN Secretariat upon request.

Molecular formula

A one-line molecular formula constructed in accordance with accepted chemical practices should be supplied. The molecular formulas should be given in the following manner, e.g. $C_{21}H_{28}N_2$.

Chemical Abstracts Service (CAS) registry number

If a CAS registry number has been assigned to a new compound before it is submitted to the INN Secretariat, the number should be included on the form. If no number has yet been assigned, the manufacturer should obtain the CAS registry number from Chemical Abstracts Services for publication in the INN lists. Proof of the entry will be required.

Tradenames (known or contemplated)

If a trade-mark has been issued for the drug, it should be entered on the form. List any national or international trade-marks (and manufacturers) and the name of the country where the trade-mark is registered.

Any other name or code

Sometimes, long before a nonproprietary name or a trade-mark has been selected for a new compound, it may acquire a trivial name that has been used in the laboratory and scientific literature. The INN Secretariat would like to be made aware of such names but requests manufacturers not to create, use, or in any way encourage the creation of trivial names for new drugs. The fact that a trivial name has become accepted in the literature will not ensure its adoption as a nonproprietary name and may only cause confusion when an official nonproprietary name is selected. It is therefore recommended to use codes before the publication of a recommended nonproprietary name and indicate these on the request form to the INN Secretariat as an additional reference.

Principal therapeutic use(s) and posology

It is important to know the therapeutic category for the new compound as such information may determine the stem selected for the nonproprietary name. Pertinent reprints presenting evidence of the claimed therapeutic use should be included with the application (for terminology, please see *Pharmacological Action and Therapeutic Use of Drugs, a list of terms*, English/French/Spanish, 1996 (*PHARM/96.320*).

Pharmacological action

The pharmacological action should be explained in as much detail as possible, since it may also influence the stem selected for the compound. Again, pertinent reprints must be included to support the claimed action (for terminology, please see above).

Verso side of request form

Date of clinical trial

As a general guide, the development of a drug should progress up to the point of clinical trials (phase II) before an application is submitted to the INN Secretariat for name selection. An approximate date when clinical trials began is requested. The intent of this request is to assure that clinical trials are under way. It is the belief that if a drug has entered clinical trials, there is a reasonable expectation that it will be marketed and thus the name selected will have been developed for that need and purpose.

In case the development is stopped, the manufacturer should inform the INN Secretariat as soon as possible, in order to halt the selection process.

Availability of suggested names

The originator of the INN request confirms with his signature that the suggestion is made on the understanding that, insofar as is known, none of the suggested names are either registered or pending registration.

Permission to publish the CAS registry number

The applicant herewith confirms that the CAS registry number sent to the INN Secretariat is correct and may be used in the INN lists.

Additional comments

This section allows the applicant to give additional comments and/or information.

6. References for supporting material

Documents:

- *The use of common stems in the selection of international nonproprietary names (INN) for pharmaceutical substances* (WHO/PHARM S/NOM 15) INN Programme, WHO, Geneva - *updated regularly*
- *Graphic representation of chemical formulae in the publications of international nonproprietary names (INN) for pharmaceutical substances* (WHO/PHARM/95.579), INN Programme, WHO, Geneva
- *Pharmacological Action and Therapeutic Use of Drugs, list of terms*, English/French Spanish, 1996, (*PHARM/96.320*), WHO, Geneva
- *INNs: Names for radicals and groups, combined summary list*, WHO/PHARM S/NOM1506, INN Programme, WHO, Geneva - *updated regularly*
- *Definition of INNs for Substances Prepared by Biotechnology*, PHARM S/NOM 1348,INN Programme, WHO, Geneva

Publications:

- *Cumulative List of INNs, No. 9*, 1996, WHO, Geneva
- *WHO Drug Information* (quarterly journal published by the World Health Organization)

ANNEX 1

Background information on the INN Programme

The activities of national nomenclature commissions are coordinated in order to achieve international standardization in nomenclature under the auspices of WHO according to *article 2a* and *2u* of its constitution (adopted in 1946 in New York):

"In order to achieve its objective, the functions of the World Health Organization shall be:

(a) to act as the directing and coordinating authority on international health work; ...
(u) to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products; ..."

The WHO programme on the selection of international nonproprietary names (INN) emerged really as an extension of the WHO programme on the unification of pharmacopoeias and the preparation of the International Pharmacopoeia requested by the very first World Health Assembly in July 1948 in resolution *WHA1.27*. The meeting of an Expert Committee on Unification of Pharmacopoeias in 1949 studied the preparation of general rules for nomenclature, and drew up a plan that was adopted in 1950 by a resolution of the World Health Assembly (*WHA3.11*).

The World Health Organization's (WHO) international nomenclature programme was thus established in 1953 when Member countries adopted a resolution at the World Health Assembly officially initiating the programme on International Nonproprietary Names (**INN**) for pharmaceutical substances [French : **D**énominations **C**ommunes **I**nternationales]; [Spanish : **D**enominaciones **C**omunes **I**nternacionales - **DCI**].

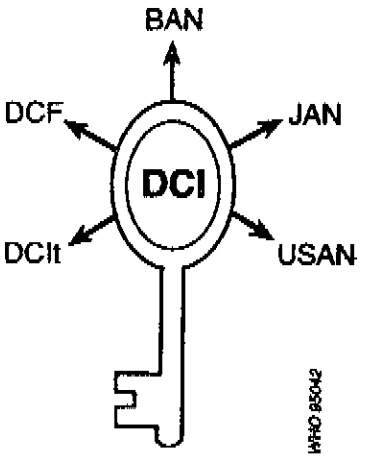
The official "Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances" and the "General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances" on which the whole programme is based were adopted by the Executive Board in 1955 in resolution *EB15.R7*. The Procedure has remained unchanged -- except for the replacement of the words "INNs for Pharmaceutical Preparations" by "*INNs for Pharmaceutical Substances*" (res. *EB43.R9*). However, the General Principles have evolved and revisions were regularly approved in the reports of the Sub-Committee meetings submitted to the Executive Board. Since 1969 the Director-General is authorized by the Executive Board to make such revisions of the General Principles as may seem desirable in the light of advances in science and of experience as may be suggested by the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated to deal with the selection of nonproprietary names (INN experts) in accordance with the above-mentioned Procedure (res. *EB37.R9*).

From 1950 onwards the programme was dealt with by the Sub-Committee of the Expert Committee on the Unification of Pharmacopoeias. The first task of the Sub-Committee was to establish contacts with national pharmacopoeia commissions that had already established programmes on the unification of drug nomenclature as those carried out under the *Comité de Nomenclature* of the *Commission permanente de la Pharmacopée Française*, the Nomenclature Committee of the British Pharmacopoeia Commission, the Council of Drugs of the American Medical Association in the USA and the Nomenclature Committee of the Nordic Pharmacopoeia Council in the Scandinavian countries. The purpose of these contacts was to coordinate the activities of such existing national nomenclature programmes.

Between 1950 and 1966 the Sub-Committee met 16 times. The earlier meetings were concerned with developing the Procedure and the General Principles and the first list of proposed INNs was only published in 1953. In 1967 the Sub-Committee became the Expert Committee on Nonproprietary Names for Pharmaceutical Preparations and later the Expert Committee on Nonproprietary Names for Pharmaceutical Substances. This Expert Committee only met in 1967, 1968, 1970 and 1975. In the other years, and since 1976, the meetings were held in a less formal way and

referred to as Consultations on the Selection of INNs. The justification for this less formal approach is that the main report of the Committee consists of the officially published INNs selected during its meetings.

The composition of the INN meetings over almost 40 years has been characterized by a great stability. The average number of participants is 6-8 experts, mostly people with responsible positions in - or secretaries of - national nomenclature commissions, and only some 30 people have been involved over the years. At present the Expert group is composed of experts from France, Indonesia, Japan, Nigeria, Poland, Spain, the United Kingdom and USA.



BAN: British Approved Name
DCF: Dénomination Commune Française
DCIt: Denominazione Comune Italiana
JAN: Japanese Accepted Name
USAN: United States Approved Name

WHO Bulletin OMS. Vol 73 1995

ANNEX 2

General principles for guidance in devising International nonproprietary names for pharmaceutical substances

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, "f" should be used instead of "ph", "t" instead of "th", "e" instead of "ae" or "oe", and "i" instead of "y"; the use of the letters "h" and "k" should be avoided."

When devising an INN it is important to be aware of possible language problems . Since the name is used worldwide, not only should certain letters be avoided, but experts need to be aware of unsuitable connotations in the major languages spoken in the world.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use. [1]Where a stem is shown without any hyphens it may be used anywhere in the name.

Latin	***English***	
-acum	-ac	anti-inflammatory agents of the ibufenac group
-actidum	-actide	synthetic polypeptides with a corticotropin-like action
-adolum	-adol }	analgesics
-adol-	-adol-}	analgesics
-astum	-ast	antiasthmatic, antiallergic substances not acting primarily as antihistaminics
-astinum	-astine	antihistaminics
-azepamum	-azepam	diazepam derivatives
-bactamum	-bactam	b-lactamase inhibitors

[1] An extensive listing of stems is contained in the working document WHO/PHARM S/NOM15 which is regularly updated and can be requested from the INN Secretariat, WHO, Geneva.

Latin	*English*	
bol	bol	steroids, anabolic
-buzonum	-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
-cain-	-cain-	antifibrillant substances with local anaesthetic activity
-cainum	-caine	local anaesthetics
cef-	cef-	antibiotics, cefalosporanic acid derivatives
-cillinum	-cillin	antibiotics, derivatives of 6-amino- penicillanic acid
-conazolum	-conazole	systemic antifungal agents, miconazole derivatives
cort	cort	corticosteroids, except prednisolone derivatives
-dipinum	-dipine	calcium channel blockers, nifedipine derivatives
fibratum	-fibrate	clofibrate derivatives
gest	gest	steroids, progestogens
gli-	gli-	sulfonamide hypoglycaemics
io-	io-	iodine-containing contrast media
-ium	-ium	quaternary ammonium compounds
-metacinum	-metacin	anti-inflammatory substances, indometacin derivatives
-mycinum	-mycin	antibiotics, produced by *Streptomyces strains*
-nidazolum	-nidazole	antiprotozoal substances, metronidazole derivatives
-ololum	-olol	b-adrenoreceptor antagonists
-oxacinum	-oxacin	antibacterial agents, nalidixic acid derivatives
-pridum	-pride	sulpiride derivatives
-pril(at)um	-pril(at)	angiotensin-converting enzyme inhibitors
-profenum	-profen	anti-inflammatory substances, ibuprofen derivatives
prost	prost	prostaglandins
-relinum	-relin	hypophyseal hormone release-stimulating peptides
-terolum	-terol	bronchodilators, phenethylamine derivatives
-tidinum	-tidine	histamine H_2-receptor antagonists
-trexatum	-trexate	folic acid antagonists
-verinum	-verine	spasmolytics with a papaverine-like action
vin-	vin-)	vinca alkaloids
-vin-	-vin-)	vinca alkaloids

ANNEX 3

LIST OF COMMON STEMS USED IN THE SELECTION OF INNs

STEM	*DEFINITION* ***substem, if available***
-ac	anti-inflammatory agents, ibufenac derivatives
-actide	synthetic polypeptides with a corticotropin-like action
-adol or -adol-	analgesics
-adom	analgesics, tifluadom derivatives
-afenone	antiarrhythmics, propafenone derivatives
-aj-	antiarrhythmics, ajmaline derivatives
-aldrate	antacids, aluminium salts
-alox	antacids, aluminium derivatives
-amivir see *vir*	
andr or -stan- or -ster-	steroids, androgens
-anserin	serotonin receptor antagonists (mostly 5-HT_2)
-antel	anthelminthics (undefined group)
-apine	see *-pine*
-arabine	arabinofuranosyl derivatives
-arit	antiarthritic substances, acting like clobuzarit and lobenzarit (mechanism different from anti-inflammatory type substances, e.g. *-fenamates* or *-profens*)
-arol	anticoagulants, dicoumarol derivatives
arte-	antimalarial agents, artemisinin related compounds
-ase	enzymes; *-dismase* (superoxide dismutase activity), *-pase* (lipase) *-teplase* (tissue plasminogen activators), *-uplase* (urokinase-type-plasminogen activators)
-ast	antiasthmatic, antiallergics, not acting primarily as antihistaminics; *-lukast (* leukotriene receptor antagonist); *-trodast* (thromboxane A_2 receptor antagonists, antiasthmatics)
-astine	antihistaminics
-azenil	benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)
-azepam	diazepam derivatives
-azepide	cholecystokinin receptor antagonist
-azocine	narcotic antagonists/agonsists related to 6,7-benzomorphan
-azoline	antihistaminics or local vasoconstrictors, antazoline derivatives
-azosin	antihypertensive substances, prazosin derivatives
-bactam	b-lactamase inhibitors
-bamate	tranquillizers, propanediol and pentanediol derivatives
barb	hypnotics, barbituric acid derivatives
-bendazole	anthelminthics, tiabendazole derivatives
bol	anabolic steroids
-bradine	bradycardic agents

STEM	***DEFINITION*** ***substem, if available***
-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
-cain-	Class I antiarrhythmics, procainamide and lidocaine derivatives (antifibrillants with local anaesthetic activity)
-caine	local anaesthetics
calci	Vitamin D analogues/derivatives
-carbef	antibiotics, carbacepham derivatives
-carnil	benzodiazepine receptor antagonists/agonists (carboline derivatives)
-cavir	see *vir*
cef-	antibiotics, cefalosporanic acid derivatives
cell- or cel- or -cell-	cellulose derivatives *cell-ate* (cellulose ester derivatives); *-cellose* (cellulose ether derivatives)
-cic	hepatoprotective substances with a carboxylic acid group
-cidin	naturally occurring antibiotics (undefined group)
-cillin	antibiotics, 6-aminopenicillanic acid derivatives
-citabine	nucleoside antiviral or antineoplastic agents, cytarabine or azarabine derivatives
-clone	hypnotic tranquillizers
-cog	blood coagulation factors; *(-)eptacog* (blood coagulation VII); *(-)octocog* (blood coagulation factor VIII); *(-)nonacog* (blood coagulation factor IX)
-conazole	systemic antifungal agents, miconazole derivatives
cort	corticosteroids, except prednisolone derivatives
-crinat	diuretics, etacrynic acid derivatives
-crine	acetylcholinesterase inhibitors, tacrine derivatives
-cromil	antiallergics, cromoglicic acid derivatives
-curium	see *-ium*
-cycline	antibiotics, tetracycline derivatives
-dan	cardiac stimulants, pimobendan derivatives
-dapsone	antimycobacterials, diaminodiphenylsulfone derivatives
-dermin	see *-ermin*
-dil	vasodilators
-dipine	calcium channel blockers, nifedipine derivatives
-dismase	see *-ase*
-dopa	dopamine receptor agonists, dopamine derivatives, used as antiparkinsonism/prolactin inhibitors;
-dox	antibacterials, quinoline dioxide derivatives
-dralazine	antihypertensives, hydrazinephthalazine derivatives
-drine	sympathomimetics; *-frine*: sympathomimetic, phenethyl derivatives
-dronic acid	calcium metabolism regulator, pharmaceutical aid
-ectin	antiparasitics, ivermectin derivatives
-entan	endothelin receptor antagonists
-eptacog	see *-cog*

STEM	***DEFINITION*** ***substem, if available***
erg	ergot alkaloid derivatives
-eridine	analgesics, pethidine derivatives
-ermin	growth factors; *-dermin* (epidermal growth factors); *-fermin* (fibrinoblast growth factors); *-nermin* (tumour necrosis factor); *-sermin* (insulin-like growth factors)
estr	estrogens
-etanide	diuretics, piretanide derivatives
-exakin	see *-kin*
-exine	mucolytic, bromhexine derivatives
-fenamic acid	anti-inflammatory, anthranilic acid derivatives *-fenamate* ("*-fenamic acid*" derivatives)
-fenin	diagnostic aids; (phenylcarbamoyl)methyl iminodiacetic acid derivatives
-fenine	analgesics, glafenine derivatives - (subgroup of fenamic acid group)
-fentanil	narcotic analgesics, fentanil derivatives
-fermin	see *-ermin*
-fiban	fibrinogen receptor antagonists (glycoprotein IIb/IIIa receptor antagonists)
-fibrate	clofibrate derivatives
-flapon	5-lipoxygenase-activating protein (FLAP) inhibitor
-flurane	general inhalation anaesthetics, halogenated alkane derivatives
-formin	antihyperglycaemics, phenformin derivatives
-fos (-vos)	insecticides, anthelmintics, pesticides etc., phosphorous derivatives
-fos- or fos-	various pharmacological categories belonging to -fos (other than above)
-fradil	calcium channel blockers acting as vasodilators
-frine	see *-drine*
-fungin a	ntifungal antibiotics
-fylline	*N*-methylated xanthine derivatives
gab	gabamimetic agents
gado-	diagnostic agents, gadolinium derivatives
-gatran	thrombin inhibitor, antithrombotic agents
gest	steroids, progestogens
-giline	MAO-inhibitors type B
-gillin	antibiotics produced by *Aspergillus* strains
gli	antihyperglycaemics, sulfonamide derivatives
-golide	dopamine receptor agonists, ergoline derivatives
-gramostim	see *-stim*
-grastim	see *-stim*
-grel- or -grel	platelet aggregation inhibitors
guan-	antihypertensives, guanidine derivatives
-icam	anti-inflammatory, isoxicam derivatives
-ifene	antiestrogens, *clomifene* and *tamoxifen* derivatives
-ilide	Class III antiarrhythmics, sematilide derivatives
imex	immunostimulants

STEM	***DEFINITION*** ***substem, if available***
-imod	immunomodulators, both stimulant/suppressive and stimulant
-imus	immunosuppressants (other than antineoplastics)
io-	iodine-containing contrast media
-io- or iod-	iodine containing compounds other than contrast media
-iptan	serotonin ($5HT_1$) receptor agonists, sumatriptan derivatives
-irudin	hirudin derivatives
-isomide	antiarrhythmics, disopyramide derivatives
-ium	quarternary ammonium compounds; *-curium* (curare-like substances)
-izine	diphenylmethyl piperazine derivatives; *-rizine* (antihistaminics/cerebral (or peripheral) vasodilators)
-kacin	antibiotics, kanamycin and bekanamycin derivatives (obtained from *Streptomyces kanamyceticus*);
-kalant	potassium channel blockers
-kalim	potassium channel activators, antihypertensive
-kef-	enkephalin agonists
-kin	interleukin type substances; *-nakin* (Il-1 derivatives) *-leukin* (Il-2 derivatives) *-plestim* (Il-3 derivatives) *-exakin* (Il-6 derivatives)
-kinra	interleukin receptor antagonists; *-nakinra* (Il-1 receptor antagonists)
-kiren	renin inhibitors
-leukin	see *-kin*
-lipastat	see *-stat*
-lukast	see *-ast*
-mab	monoclonal antibodies (for details please see page .....)
-mantadine	adamantane derivatives; *-mantine, -mantone*
-meline	cholinergic agents, arecoline derivatives
-mer	polymers
-mesine	sigma receptor ligands
-mestane	aromatase inhibitors
-metacin	anti-inflammatory, indometacin derivatives
-micin	antibiotics obtained from various *Micromonospora*
-monam	monobactam antibiotics
-morelin	see *-relin*
-mostim	see *-stim*
-motine	antivirals, quinoline derivatives
-moxin	monoamine oxidase inhibitors, hydrazine derivatives**not part of definition
-mustine	antineoplastic, alkylating agents, (b-chloroethyl)amine derivatives
-mycin	antibiotics, produced by *Streptomyces strains*
nab	cannabinol derivatives
-nakin	see *-kin*

STEM	*DEFINITION* ***substem, if available***
-nakinra	see *-kinra*
nal-	narcotic antagonists/agonists related to normorphine
-nercept	tumor necrosis factor antagonist
-nermin	see *-ermin*
nic	nicotinic acid or nicotinoyl alcohol derivatives
-nicate	antihypercholesterolaemic and/or vasodilating nicotinic acid esters
-nidazole	antiprotozoals, metronidazole derivatives
nifur-	5-nitrofuran derivatives
-nixin	anti-inflammatory, anilinonicotinic acid derivatives
-nonacog	see *-cog*
-octocog	see *-cog*
-olol	b-adrenoreceptor antagonists; *-alol*: aromatic ring -CH-CH2-NH-R related to -olols
-olone	steroids other than prednisolone derivatives
-opamine	dopaminergic agents dopamine derivatives used as cardiac stimulant/antihypertensives/diuretics
-onide	steroids for topical use, acetal derivatives
-(o)nidine	antihypertensives, clonidine derivatives
-orex	anoretics
orphan	narcotic antagonists/agonists, morphinan derivates; *-orphine, -orphinol, orphone*
-oxacin	antibacterials, nalidixic acid derivatives
-oxan(e)	benzodioxane derivatives
-oxanide	antiparasitics, salicylanides and analogues
-oxef	antibiotics, oxacefalosporanic acid derivatives
-oxetine	antidepressants, fluoxetine derivatives
-pafant	platelet-activating factor antagonists
-pamide	diuretics, sulfamoylbenzoic acid derivatives
-pamil	coronary vasodilators, verapamil derivatives
-parcin	glycopeptide antibiotics
-parin	heparin derivatives including low molecular mass heparins
-penem	analogues of penicillanic acid antibiotics modified in the five-membered ring
-peridol	see *-perone*
-peridone	see *-perone*
-perone	tranquillizers, neuroleptics, 4'-fluoro-4-piperidinobutyrophenone derivatives; *-peridol* (antipsychotics, haloperidol derivatives); *-peridone* (antipsychotics, risperidone derivatives)
-pidem	hypnotics/sedatives, zolpidem derivatives
-pin(e)	tricyclic compounds; *-apine* (psychoactive); *-cilpine* (antiepileptic); *-dipine (see -dipine)* *-zepine* (antidepressant/neuroleptic); *-oxepin, -oxopine, -sopine, -tepines*
-piprazole	psychotropics, phenylpiperazine derivatives
-pirox	antimycotic pyridone derivatives
-planin	antibacterials (*Actinoplanes* strains)

STEM	*DEFINITION* ***substem, if available***
-platin	antineoplastic agents, platinum derivatives
-plestim	see *-stim*
-plon	pyrazolo[.]pyrimidine derivatives, used as anxiolytics, sedatives, hypnotics
	-poetin erythropoietin type blood factors
	-porfin benzoporphyrin derivatives
-pramine	substances of the imipramine group
-prazole	antiulcer, benzimidazole derivatives
pred	prednisone and prednisolone derivatives; *-methasone* or *-metasone, -betasol*
-pressin	vasoconstrictors, vasopressin derivatives
-pride	sulpiride derivatives
-pril(at)	angiotensin-converting enzyme inhibitors
-prim	antibacterials, trimethoprim derivatives
-profen	anti-inflammatory agents, ibuprofen derivatives
prost	prostaglandins; *-prostil* (prostaglandins, anti-ulcer)
-prostil	see *-prost*
-quinil	benzodiazepine receptor partial agonists (quinoline derivatives)
-racetam	amide type nootrope agents, piracetam derivatives
-relin	prehormones or hormone-release stimulating peptides: *-morelin* (growth hormone release-stimulating peptides); *-tirelin* (thyrotropin releasing hormone analogues)
-relix	hormone-release inhibiting peptides
-renone	aldosterone antagonists, spironolactone derivates
-restat (or -restat-)	see *-stat*
retin	retinol derivatives
-ribine	ribofuranil-derivatives of the *pyrazofurin* type
rifa-	antibiotics, rifamycin derivatives
-rinone	cardiac stimulants, amrinone derivatives
-rizine	see *-izine*
-rozole	aromatase inhibitors, imidazole-triazole derivatives
-rubicin	antineoplastic antibiotics, daunorubicin derivatives
sal	salicylic acid derivatives: *-sal-, salazo-, -salazine/-salazide, -salan*
-sartan	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
-semide	diuretics, furosemide derivatives
-sermin	see *-ermin*
-serpine	derivatives of *Rauwolfia* alkaloids
-setron	serotonin receptor antagonists (5-HT_3) not fitting into other established groups of serotonin receptor antagonists
som-	growth hormone derivatives
-spirone	anxiolytics, buspirone derivatives
-stat (or -stat-)	enzyme inhibitors: *-lipastat* (pancreatic lipase inhibitors); *-restat* or *-restat-* (aldose-reducing inhibitors);

STEM	*DEFINITION* ***substem, if available***
	-vastatin (antilipidemic substances, HMG CoA reductase inhibitors)
-steine	mucolytics, other than bromhexine derivatives
-ster-	androgens/anabolic steroids: *-testosterone, -sterone, -ster-, -gesterone, -sterone, sterol, ster,* *-(a)steride* (antineoplastics)
-stim	colony stimulating factors: *-grastim* (granulocyte colony stimulatory factor (G-CSF) type substances; *-gramostim* (granulocyte macrophage colony stimulating factor (GM-CSF) type substances); *-mostim* (macrophage stimulating factors (M-CSF) type substances); *-plestim* (interleukin-3 analogues and derivatives)
sulfa-	anti-infectives, sulfonamides
-sulfan	antineoplastic, alkylating agents, methanesulfonates
-tecan	antineoplastics, topoisomerase I inhibitors
-tepa	antineoplastics, thiotepa derivatives
-teplase	see *-ase*
-terol	bronchodilators, phenethylamine derivatives [previously *-prenaline* or *-terenol*]
-terone	antiandrogens
-tiazem	calcium channel blockers, diltiazem derivatives
-tide	peptides and glycopeptides (for special groups of peptides see *-actide, -pressin, -relin, -tocin)*
-tidine	histamine H_2-receptor antagonists, cimetidine derivatives
-tirelin	see *-relin*
-tizide	diuretics, chlorothiazide derivatives
-tocin	oxytocin derivatives
-toin	antiepileptics, hydantoin derivatives
-trexate	folic acid analogues
-tricin	antibiotics, polyene derivatives
-triptyline	antidepressants, dibenzo[*a,d*]cycloheptane or cyclopheptene derivatives
-troban	thromboxane A_2-receptor antagonists; antithrombotic agents
-trodast	see *-ast*
trop	atropine derivatives
-uplase	see *-ase*
-uracil	uracil derivatives used as thyroid antagonists and as antineoplastics
-uridine	uridine derivatives used as antiviral agents and as antineoplastics; also *-udine*
-vastatin	see *-stat*
-verine	spasmolytics with a papaverine-like action
vin- or -vin-	vinca alkaloids
vir	antivirals (undefined group): *-amivir* (neuraminidase inhibitors); *-cavir* (carbocyclic nucleosides); *-virsen* (antisense oligonucleotides)
-virsen	see *vir*

STEM	*DEFINITION* ***substem, if available***
-vudine	antiviral; antineoplastics, zidovudine derivatives
-xanox	antiallergic respiratory tract drugs, xanoxic acid derivatives
-zafone	alozafone derivatives
-zepine	see *-pine*

Explanatory note:
The hyphens indicate the position of the stem, prefix, infix or suffix, within the INN. In the event that the hyphen is absent, the stem may be used in any position within the name.

The following common stems have been discontinued:

STEM	*DEFINITION*
mer- or -mer-	mercury-containing drugs, antimicrobial or diuretic (deleted from General Principles in List 28 prop. INN)
mito-	antineoplastics, nucleotoxic agents (deleted from General Principles in List 24 prop. INN)
-ol	alcohols and phenols (deleted from Generla Principles in 14th report)
-quine, quin	quinoline derivatives (deleted from General Principles in List 28 prop. INN)
-stigmine	anticholinesterases (deleted from General Principles in List 24 prop. INN)

ANNEX 4

Specific groups of biological compounds

Peptides, glycopeptides, proteins and glycoproteins (general approach)

The INN experts have adopted the following general scheme for the naming of peptides/proteins:

1. selection of a *stem* for the main compound, e.g. *-poetin* (for erythropoietin derivatives), *-irudin* (for hirudin derivatives), *-cog* (for blood coagulation factors);
2. designation of *subgroups* by expanding the stem, e.g. *-eptacog, -octacog;*
3. selection of a *random prefix* for compounds with differences in aminoacid sequence;

In addition for *glycosylated compounds:*

4. selection of a Greek letter spelt out as a second part of a two-word name for glycosylated compounds with identical amino acid sequence and different glycosylation pattern.

Blood coagulation factors

The following stems, infixes and suffixes, have been selected up to date for recombinant blood coagulation factors:

blood coagulation factors:	*-cog*
factor VII :	*(-)eptacog*
factor VIII :	*(-)octocog*
factor IX :	*(-)nonacog*

A prefix will be necessary if the amino acid sequence does not match that of the naturally occurring material. In accordance with the general policy, *alfa, beta,* etc., will be added for the glycoproteins. When the additional statement "activated" is needed, i.e. for the blood coagulation factor VIIa, it should be spelt out in full and added in parenthesis after the name.

Colony stimulating factors

A general stem for all colony stimulating factors was selected and substems for the various categories were designated:

colony stimulating factors : *-stim*

combination of two different types of colony stimulating factors:	*-distim*
granulocyte colony stimulating factor (G-CSF) type substances :	*-grastim*
granulocyte macrophage colony stimulating factor (GM-CSF) type substances :	*-gramostim*
macrophage stimulating factor (M-CSF) type substances :	*-mostim*
interleukin-3 analogues and derivatives:	*-plestim*

Enzymes

The common stems for enzymes, in general, is *-ase.* Substems are referring to the origin of the substances, e.g. tissue plasminogen activator and urokinase-type plasminogen activators.

enzymes : *-ase*

enzyme with superoxide dismutase activity :	*-dismase*
tissue-type plasminogen activators :	*-teplase*
urokinase-type plasminogen activators :	*-uplase*

Further examples of enzymes may be found in *WHO/PHARM S/NOM 15*

Erythropoietins

In the case of erythropoietins it was decided to select *epoetin* together with a Greek letter to differentiate between compounds of the same amino acid sequence as human erythropoietin which vary in the glycosylation pattern. INNs with different amino acid sequence will be named using the *-poetin* stem and a random prefix.

erythropoietin type blood factors : *-poetin*

Growth factors

The general stem assigned for growth factors is *-ermin*. Substems allow distinction between the various types of growth factors, for example epidermal growth factors, fibrinoblast growth factors and insulin-like growth factors.

When selecting a name for tumor necrosis factors (TNF) these were also classified as growth factors.

growth factors : *-ermin*

epidermal growth factors :	*-dermin*
fibrinoblast growth factors :	*-fermin*
tumor necrosis factors (TNF):	*-nermin*
platelet-derived growth factor:	*-plermin*
insulin-like growth factors :	*-sermin*
transforming growth factor:	*-termin*

Growth hormones

The characteristic stem for this group of compounds is the prefix *som-*. For substances other than human, suffixes are added to indicate the species specificity of the structure are as follows:

growth hormones: *som-*

bovine-type substances :	*-bove*
porcine-type substances:	*-por*
salmon-type substances :	*-salm*

Hirudin analogues

Hirudin is a well-established name for an anticoagulant isolated from medicinal leeches. Hirudin analogues are non-glycosylated polypeptides produced by recombinant biotechnology. The stem *-irudin* will be used for hirudin compounds, a random prefix will allow to differentiate for different amino acid sequences.

hirudin analogues : *-irudin*

Hormone release stimulating peptides

The common stem selected for hormone release stimulating peptides is *-relin*. INNs for hormone-release inhibiting peptides should include the stem *-relix*.

hormone-release stimulating peptides : *-relin*

growth hormone release stimulating peptides :	*-morelin*
thyrotropin releasing hormone analogues:	*-tirelin*

hormone-release inhibiting peptides : *-relix*

Interleukins

The first general stem selected for interleukins was *-leukin*, which was derived from the name *interleukin* assigned by the *International Union of Biochemistry* (IUB) - *International Union of Pure and Applied Chemistry* (IUPAC) - *Joint Commission on Biochemical Nomenclature* (JCBN). Randomly assigned prefixes should distinguish between the different compounds.

Based on the needs for naming further interleukins, the following stem system was accepted for recombinant interleukins :

interleukin	*INN stem*
Il-1	*-nakin*
Il-2	*-leukin*
Il-3	*-plestim*
Il-6	*-exakin*
IL-8	*-octakin*
IL-11	*-elvekin*
receptor antagonist:	*-kinra*
Il-1	*-nakinra*

It was agreed to publish the INNs for glycosylated interleukins with *alfa, beta*, etc, in accordance with the general policy for naming glycosylated proteins.

Pituitary hormones

The name selected by the IUPAC-IUB have, to date, been chosen for compounds with identical amino acid sequence as the naturally occurring human hormone. Addition of a Greek letter as second name will allow to differentiate for different glycosylation pattern for compounds produced by biotechnology.

The following scheme is at present in use :

pituitary hormones : *-tropin*
follicle stimulating hormones : *(-)follitropin*
luteinizing hormones : *(-)lutropin*

Monoclonal antibodies

The following scheme for common stems has been developed for naming monoclonal antibodies:

I.	*General stem:*		*-mab*
II.	*Sub-stems for source of product:*		
		human	*-u-*
		rat	*-a-*
		hamster	*-e-*
		primate	*-i-*
		mouse	*-o-*
		chimeras	*-xi-*
		humanized	*-zu-*

The distinction between chimeric and humanized antibodies is as follows:

A chimeric antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable region of both heavy and light chains linked to heavy and light constant regions of human origin.

A humanized antibody has heavy (H) and light (L) chain variable (V) regions, consisting of the amino acids comprising the complementarity-determining region (CDR) segments (and possibly frameword residues)

from foreign antibodies inserted appropriately among variable regions framework segments of human-derived amino acid residues, linked to H and L constant regions of human origin.

III. *Sub-stems for disease or target group:*

bacterial	*-ba(c)-*
cardiovascular	*-ci(r)-*
immunomodulator	*-li(m)-*
infectious lesions	*-le(s)-*
viral	*-vi(r)-*
tumors:	
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.

IV. *Second word:*

If the product is radiolabelled or conjugated to another chemical, such as a toxin, dentification 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.

If the monoclonal antibody is used as a carrier for a radioisotope, the latter will be listed first in the INN, e.g. technetium (^{99m}Tc) pintumomab.

ANNEX 5

WHA46.19 Nonproprietary names for pharmaceutical substances

The Forty-sixth World Health Assembly,

Recalling resolution WHA31.32 on the importance of using nonproprietary names in establishing national drug formularies;

Noting the fundamental contribution of the WHO programme on international nonproprietary names (INN) to effective communication in medicine, and the challenge inherent in maintaining the nomenclature as new substances are introduced into clinical use;

Acknowledging with satisfaction the increasing contribution of generic products to national drug markets in both developed and developing countries;

Noting the current trend to market products with the same active ingredient as, and intended to be clinically interchangeable with, a product currently on the market (multisource products) under trade-marks or brandnames derived from stems or other descriptors for international nonproprietary names nomenclature;

Recognizing that such use, particularly in respect of single-ingredient prescription drugs, may compromise the safety of patients by creating confusion in prescribing and dispensing medicines and by interfering with the orderly development of the nomenclature for international nonproprietary names;

Aware of the concern expressed by the International Conference of Drug Regulatory Authorities at its last meeting about the increasing use of pharmaceutical brandnames that are very similar to or derived from international nonproprietary names;

Noting the recommendation made by the WHO Expert Committee on the Use of Essential Drugs, in its fifth report,[1] on the need to discourage, as a matter of urgency, the use of trade-marks that are derived from international nonproprietary names,

1. REQUESTS Member States:

(1) to enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic names) used in the labelling and advertising of pharmaceutical products are always displayed prominently;
(2) to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than on trade-marks, to promote and market multisource products introduced after patent expiration;

(3) 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 established INN stems as trade-marks;

2. CALLS ON the Director-General to intensify his consultations with governments and representatives of the pharmaceutical industry on ways of reducing to a minimum the problems arising from drug nomenclatures that may create confusion and jeopardize the safety of patients.

Twelfth plenary meeting, 12 May 1993
A46/VR/12

[1] *WHO Technical Report Series*, No. 825, 1992.

ANNEX 6

Procedure for the selection of international nonproprietary names for pharmaceutical substances

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefore.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the "*General principles for guidance in devising International Nonproprietary Names*". The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

A. Such notice shall be given by publication in the *Chronicle of the World Health Organization*[1] and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

(i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

B. Such notice shall:

(i) set forth the name under consideration;
(ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;
(iii) identify the substance for which a name is being considered;
(iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;
(v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent theacquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization.*[1]

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization.*[2]

A. Such objection shall:

(i) identify the person objecting;
(ii) state his interest in the name;
(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

[1] The title of this publication was changed to *WHO Chronicle* in January 1959. From 1987 onwards lists of INNs are published in *WHO Drug Information*.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or tra de-name.

ANNEX 7

Applications for INNs through national authorities (addresses)

a) National Nomenclature Commissions:

France: **DCF** - Dénominations Communes Françaises

Agence du Médicament
Direction des Laboratoires et des Contrôles
Unité Pharmacopée
145-147 boulevard Anatole France
F-93285 Saint-Denis Cedex
France

Italy: **DCIt** Commission - Denominazione Communi Italiane

Director-General
Pharmaceutical Division
Ministero della Sanità
Viale della Civiltà Romana 7
I-00144 Roma
Italy

Japan: **JAN** - Japanese Accepted Names

Japanese Ministry of Health and Welfare
New Drugs Division
Pharmaceuticals Affairs Bureau
1-2-2, Kasumigaseki, Chiyoda-ku
Tokyo 100
Japan

United Kingdom: **BAN** - British Approved Names

The Secretary
British Pharmacopoeia Commission
Market Towers
1 Nine Elms Lane
London SW8 5NQ
United Kingdom

USA: **USAN** - United States Adopted Names

The Secretary
United States Adopted Names Council
American Medical Association
515 North State Street
Chicago, Illinois 60610
USA

b) Other national nomenclature authorities:

Belgium:

L'Inspecteur en chef-Directeur
Ministère de la Santé Publique et de l'Environnement
Inspection générale de la Pharmacie
Cité administrative de l'Etat
Quartier Vésale 333
B-1010 Bruxelles
Belgium

China:

The Deputy Chief
Drug Standard Division II
The Chinese Pharmacopoeia Commission
Ministry of Health
Temple of Heaven
Beijing 100050
People's Republic of China

Hungary:

Director-General
National Institute of Pharmacy
P.O. Box 450
1372 Budapest 5
Hungary

ANNEX 8

WORLD HEALTH ORGANIZATION **ORGANISATION MONDIALE DE LA SANTE**	**Request for an international nonproprietary name (INN)** **Demande de dénomination commune internationale (DCI)**

Authority or manufacturer:
Autorité ou fabricant:

Name of applicant / *nom du demandeur:*
Name of responsible officer / *nom du responsable:*
Address / *adresse:*

Telephone No/*No. de téléphone:* Fax No./*No. de fax*

We hereby request the World Health Organization to establish a free and unrestricted INN for the pharmaceutical substance described below.
L'OMS est priée de bien vouloir établir une DCI à usage libre pour la substance pharmaceutique en question.

For completion by WHO/
A remplir par l'OMS

No:
Date:
Copies forwarded:

Date:

Acknowledged:

SUGGESTED NAMES (in order of preference): 1.....
DENOMINATIONS PROPOSÉES
(par ordre de préférence) 2.....

3.....

CHEMICAL NAME OR DESCRIPTION (INCLUDING STEREOCHEMICAL INFORMATION):
NOM OU DESCRIPTION CHIMIQUE (Y COMPRIS DE L'INFORMATION SUR LA STÉRÉOCHIMIE)

GRAPHIC FORMULA:
FORMULE GRAPHIQUE

MOLECULAR FORMULA:
FORMULE BRUTE

CHEMICAL ABSTRACTS SERVICE (CAS) REGISTRY NUMBER:
NUMÉRO DU REGISTRE CAS

TRADE NAME (known or contemplated):
NOM COMMERCIAL (connu ou envisagé)

ANY OTHER NAME OR CODE:
AUTRE NOM OU CODE

PRINCIPAL THERAPEUTIC USES AND POSOLOGY; PHARMACOLOGICAL ACTION:
UTILITÉ THÉRAPEUTIQUE ET POSOLOGIE; ACTION PHARMACOLOGIQUE

For completion by WHO/
A remplir par l'OMS

WHO 5233* PHA (9/97) - 1000

PTO/TSVP

1. The process of selecting an INN should be initiated during that period of investigation when the compound is undergoing clinical study in human subjects. Please indicate the date when clinical trials began:
La procédure de sélection d'une DCI débute pendant la période d'investigation au cours de laquelle la substance fait l'objet d'études cliniques sur des sujets humains. Veuillez indiquer à quelle date ont débuté les essais cliniques:

2. This proposal is made on the understanding that insofar as is known, none of the suggested names is either registered or pending registration.
En présentant cette proposition, le signataire déclare qu'à sa connaissance aucune des dénominations suggérées n'a été déposée ou n'est sur le point de l'être.

3. The Undersigned confirms that the Chemical Abstracts Service (CAS) number is correct and permission is granted to WHO to publish it in the INN publications.
Le soussigné confirme que le numéro dans le registre du CAS est correcte et que l'OMS est autorisée à le publier dans les publications relatives aux DCIs.

ADDITIONAL COMMENTS:
REMARQUES

Date ..... *Signature* .....