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Prescrire's contribution to the WHO consultation on List 102 of proposed INNs

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As an active member of the Medicines in Europe Forum and the International Society of Drug Bulletins (ISDB), *Prescrire* has long been advocating the routine use, by both healthcare professionals and patients, of international nonproprietary names (INNs), which are more informative, safer and clearer than brand names (1-4).

Making INNs safer. The principles underlying the creation of INNs are the same that apply to the prevention of medication errors: standardisation, differentiation, and facilitation of logic and redundancy checks. INNs make pharmaceutical substances easier to identify and are less frequently confused than brand names (5).

However, even with the INN system there is a residual risk of confusion, partly owing to the sheer number of INNs now in circulation. A report from the Council of Europe, which recommends the use of INNs, calls for active participation in public consultations on proposed INNs, in order to identify any risk of confusion during their clinical use (6). The editorial staff of *Prescrire* and members of the not-for-profit organisation *Association Mieux Prescrire* are participating in this phase of the consultation and have examined List 102 of proposed INNs, published in January 2010 (7).

Our critical analysis of the proposed INNs. Our analysis of List 102 of proposed INNs was based on the 2009 list of common stems and its updates, on the INN database, on *Prescrire* own data search, and on a database of drugs marketed in France, which enables searches on both brand names and INNs (8-12).

Prescrire used a two-step Delphi method. First, the participants compiled a list of potentially contentious INNs, along with the reasons for their doubts. For each of the 27 proposed INNs selected for further scrutiny in this first step, the participants assessed the risk of confusion and/or misunderstanding, along with the potential clinical consequences of such errors. Finally they decided for each contentious INN whether a simple comment or a formal objection was more appropriate, and listed their arguments.

Formal objections

Objections were deemed necessary for several reasons for a number of proposed INNs from List 102: for not respecting existing common stems, for the absence of a common stem, resulting in an INN that gives no clues about the drug's supposed properties, and

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when the consequences of confusing the INN with other INNs, common stems or in some cases what we presume to be pre-stems, could be serious.

Absence of common stems or potential confusion: too risky for patients. Existing common stems need to be applied if INNs are to be informative and safe. The following proposed INNs lack common stems: *lasmiditan, mapracorat, pridopidine, latrepirdine*. No reasons are given to justify this departure from the usual conventions for developing INNs.

Lasmiditan is the second antimigraine serotonin receptor agonist not to include the common stem **–triptan**; the first was *alniditan* (not yet marketed). Failure to apply this familiar common stem means that the drug's therapeutic activity cannot be identified through its INN. There is also a risk of confusion with the common stem **-pitant** (*aprepitant*, *fosaprepitant*), which is used to identify antiemetics that are substance P receptor antagonists.

As the proposed INN *mapracorat* lacks an identifiable common stem, it gives no indication as to the drug's anti-inflammatory properties. An informative common stem would help healthcare professionals prevent the multiple risks associated with NSAIDs, which are mainly cardiovascular and gastrointestinal adverse effects and additional risks when prescribed to pregnant women.

The proposed INN *pridopidine* could create confusion with several drugs, due to resemblance to other INNs and common stems. Examples include the INN *ticlopidine*, exposing patients to the risk of bleeding, and the common stem **–dipine**, with a risk that it will be mistaken for a *nifedipine* derivative such as *amlodipine*, *felodipine*, *isradipine*, *lacidipine*, *lercanidipine*, *nicardipine* and *nitrendipine,* which are calcium-channel blockers. In short, there are too many opportunities for medication errors with this proposed INN.

Latrepirdine is actually an old antihistaminic that used to be called *dimebolin.* Its potential anticholinesterase properties have been evaluated in Alzheimer's disease (development stopped during Phase III studies), and are currently being evaluated Huntington's disease. As with the previous proposed INN, *latrepirdine* was felt to sound too similar to *ticlopidine* and many participants said that it brought to mind the common stem **–dipine.** The suffix "-pirdine" is currently used in USAN nomenclature to designate cognition enhancers, but it has not yet been approved by WHO as either a stem or a "pre-stem" (10). This consultation provides a timely opportunity to draw the INN Programme's attention to the risks of confusion associated with this potential common stem, particularly for patients with neurological disorders.

In summary, the proposed INNs mentioned above are poorly designed because they wrong-foot those healthcare professionals who make the effort to memorise common stems.

Confusion between INNs. *Tivozanib* sounds very similar to *diloxanide*, an oral antiparasitic drug that has been granted temporary authorisation in France. The risk and impact of confusing these two INNs (in both sound and spelling) were considered significant: mistaking an oral antineoplastic for an antiparasitic drug would have serious consequences.

The potential clinical consequences of the mix-ups or misunderstandings associated with these INNs were deemed sufficiently serious to justify these formal objections. They should prompt the INN programme to re-examine the various inconsistencies identified to prevent potential problems for healthcare professionals and patients in the future.

Other comments

Some proposed INNs generate a theoretical risk of medication errors, for a variety of reasons: some are difficult to understand; some do not correlate with the indications claimed by the pharmaceutical company; they could be confused with other INNs; and some could be confused with French brand names. Hence the following comments.

Poorly comprehensible proposed INNs: foreseeable problems. As with most of the objections set out in this letter, common stems were either insufficiently obvious or missing in the proposed INNs *carotegrast, omecamtiv mecarbil* and *sotatercept*. The proposed INN therefore provided no clues as to the drug's potential use.

Certain common stems that were adopted seemed counterintuitive. The proposed INN *carotegrast* does not indicate the fact that the drug is an anti-inflammatory - in fact **-ast** is usually used for antiallergics and other drugs such as phosphodiesterase inhibitors. The common stem **-cept** refers to receptors. As a result, it is found in the INN of drugs with very different pharmacological properties, used in a variety of therapeutic fields. It is therefore confusing to find it combined with an undefined substem, to form **–tercept** in the proposed INN *sotatercept*. It may be time to clarify the common stems used for receptors.

Omecamtiv mecarbil gives no clues about the activity of the drug; *mecarbil* refers to a particular radical that has not yet been listed by the INN programme and the two words together form a complicated INN that contains no common stem and is difficult to remember. Perhaps a common stem could be adopted to express positive inotropic effect, **-dan** being the only stem currently used for *pimobendan* derivatives.

Common stems in the pipeline? Several of the proposed INNs give the impression that new common stems are about to be adopted: for example **–cerfont** in *emicerfont* and *verucerfont*; **-glurant** in *dipraglurant* and *raseglurant*; **–sertib** in *barasertib* and *volasertib*. However they are not included in the list of "pre-stems" and no explanations have been provided with the list of proposed INNs (10).

Risks of confusion with other INNs. Some proposed INNs such as *afatinib*, *dinaciclib and intedanib* could be confused with other INNs or common stems.

Within INNs including the common stem **-tinib**, *afatinib* could be confused with *lapatinib and dasatinib,* as well as with *avasimibe,* which has the common stem **–imibe** (although neither *avasimibe* nor *pactimibe* are currently marketed in France).

Dinaciclib has the common stem **–ciclib**, which has been preselected to refer to cyclin-dependent kinase inhibitors. Several participants felt that this common stem could be confused with **–cycline** by people unaware of the existence of these two similar-sounding common stems.

A lower risk of confusion between *intedanib* and *indapamide* (Fludex°) was identified.

Risks of confusion with non-pharmaceutical terms. The prefix "emi" in *emicerfont* is reminiscent of "hemi" meaning half in French, which could result in a dosing error if the INN "cerfont" existed. Some INNs already start with "emi" (*emiglitate*, *emitefur*, *emideltide*, *emivirine*), but none of them have yet been marketed in France. We would therefore like to alert the INN programme against using the prefix "emi" with terms that resemble other INNs.

Condoliase reminded several participants of a number of everyday words, including condolences, condyloma and condom, preventing easy identification of the common stem. Indeed, several participants mistook "-liase" for a common stem and thought it might mean "liaison", which in French means binding, a misunderstanding that was reinforced up by the prefix "con-". In fact the common stem is **–ase,** meaning enzyme.

Risk of confusion with French brand names. Similarities were noted between a few of the proposed INNs from List 102 and various drug brand names used in France: *lasmiditan and selexipag.*

We have lodged a formal objection (see above) about *lasmiditan,* but in addition it was felt to sound too similar to Lamisil°, a brand name that itself is already often confused with Lamictal°.

Several participants considered the risk of confusion between *selexipag* and the brand name Selexid° to be more serious. An aggravating circumstance in the absence of an identifiable common stem is that "selexi" implies that the drug is selective, which could provide a promotional advantage to the company concerned.

Helping healthcare professionals deal with the growing number of monoclonal antibodies. The proliferation of INNs with the common stem **–mab** increases the risk of confusion among pharmaceutical substances based on monoclonal antibodies which are used in very different indications. According to our calculation, there are currently 197 INNs for monoclonal antibodies with the common stem **–mab** (9). They accounted for nearly a quarter of List 100 of proposed INNs (14 out of 57) and 12 out of 75 in List 101 (13, 14).

The 58 proposed INNs in list 102 include a further 9 monoclonal antibodies: *benralizumab*, *dalotuzumab*, *glembatumumab*, *mavrilimumab*, *moxetumomab pasudotox*, *secukinumab*, *suvizumab*, *tralokinumab* and *yttrium (^{90}Y) clivatuzumab tetraxetan*.

Prescrire takes advantage of every opportunity to help its subscribers be on guard against this risk of error. So articles about *catumaxomab* and *ofatumumab* gave us a chance to re-examine the latest revision of the nomenclature used to create monoclonal antibody INNs (15,16).

INN training programmes are needed. Healthcare professionals would be better educated if the INNs were part of the academic training and continuing education (17). The WHO INN unit should emulate WHO programs addressing patient safety and develop training tools that promote the use of INNs (18).

In short, the main problems we identified with proposed INNs from List 102 relate to whether they will be properly understood by healthcare professionals. The proposed INNs that do not use existing common stems or lack a common stem deserve our objections; such situations should be explained if the INN Programme is to remain consistent and useful to healthcare professionals. Progress can still be made to improve the safety of INNs.

After this sixth participation in a WHO consultation, *Prescrire* recognises the efforts made by the WHO INN Programme but considers that specific information and education will be needed, especially in the case of monoclonal antibodies, if healthcare professionals and patients are to adopt the proposed INNs. Prescribers and users can only think in terms of INNs when these names are devised in a rigorous and consistent way.

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Chief editor

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