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Prescrire's contribution to the WHO consultation on List 100 of Proposed INNs

Prescrire is an independent continuing education journal for healthcare professionals. It is wholly funded by its subscribers, it carries no advertising and receives no other financial support whatsoever.
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 clearer and therefore safer 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, namely standardization, differentiation, redundancy, and built-in logical controls. 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 INN, calls for active participation in public consultations on proposed INNs, within a 4-month period of the date of final adoption, in order to review proposed INNs from the perspective of in-use safety (6).
Prescrire is participating in this phase of the survey and has now examined the List 100 of proposed INNs, published on 16 February 2009 (7).

Our analysis of List 100 of Proposed INNs was based on the 2006 list of common stems and its updates, the INN database, and on a database of drugs marketed in France, which provides both brand names and corresponding INNs (8-10).
Prescrire used a two-step Delphi method. First, the participants compiled a list of potentially litigious proposed INNs, along with the relevant reasons. For each of the 32 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 whether a simple comment or a formal objection was more appropriate for each litigious INN, and listed their arguments.

The growing number of monoclonal antibodies is a source of confusion

There are currently 143 monoclonal antibodies with the common stem **-mab** on the WHO list of common stems (9). In addition, there are 14 substances of this type among the 57 proposed INNs on List 100, namely *blinatumomab*, *cixutumumab*, *elotuzumab*, *farletuzumab*, *figitumumab*, *necitumumab*, *oportuzumab monatox*, *panobacumab*, *ramucirumab*, *robatumumab*, *racotumomab*, *siltuximab*, *solanezumab* and *vedolizumab* (7).

This proliferation of INNs with the common stem **-mab** increases the risk of confusion among pharmacological substances based on monoclonal antibodies. Most participants were struck by the very high risk of confusion between *siltuximab* and *cetuximab*. A lesser but still noteworthy risk of confusion between the following pairs was also underlined: *cixutumumab* and *cetuximab*; *cixutumumab* and *siltuximab*; *elotuzumab* and *alemtuzumab*; *panobacumab* and *panitumumab*; *and siltuximab* and *rituximab*.
In terms of potential clinical consequences, the risk of confusion between a cytotoxic drug and an antibiotic (e.g. between *panobacumab* and *panitumumab*) is even more serious than the risk of confusion between two cytotoxic drugs.
If the INNs of monoclonal antibodies are not sufficiently distinctive, caregivers may come to prefer brand names. This would go against the systematic use of INNs, which is supported by *Prescrire*. In practice, guidelines on use of the INN system for drug labeling could be modified to recommend the use of bold type or capital letters for common stems, thus reducing the risk of confusion between INNs.
Ramucirumab is described as an antineoplastic drug, but the substem **-ci(r)-** generally corresponds to cardiovascular drugs (especially**–omab**: *imciromab* and *biciromab*). This exception to the naming rules for monoclonal antibodies is illogical and compromises the clarity of the INN system.

No formal objections

A formal objection was initially envisaged for *siltuximab*. However, as the risk of confusion only seems to involve cytotoxic drugs, which are already subject to strict precautions, the objection was withdrawn.

Other comments

Some proposed INNs generate a theoretical risk of medication errors, for a variety reasons: some carry a risk of confusion with other INNs or common stems; some are difficult to understand; some are incompatible with the indications claimed by the company; and some seem to have a commercial bias.

Risks of confusion with other INNs or common stems. Some proposed INNs carry a risk of confusion with other INNs or with other common stems; these include *adarotene*, *delafloxacin, limiglidole* and *voreloxin*.
Being perceived as a vitamin A derivative, *adarotene* carries a risk of confusion with *tazarotene*, another retinoid, but this risk does not seem to be higher than that between *betacarotene* and *bexarotene*.
In French, the name of the antibiotic *delafloxacin* can be misinterpreted as “*a floxacin*” and carries a risk of confusion with other fluorinated quinolones such as *ciprofloxacin*, *levofloxacin*, *lomefloxacin*, *moxifloxacin*, *norfloxacin*, *ofloxacin* and *pefloxacin*.
“*Limiglidole*” sounds somewhat like “*miglitol*”, another antidiabetic drug. Potentially more serious, *limiglidole* could be confused with *imiquimod*, a cytotoxic drug, on a handwritten prescription. Several proposals were made to make the common stem **–gli(x)-** more visible (e.g. "glilimidol", "glimilidol" or "imiglidol").
Voreloxin, a name that does not evoke a cytotoxic drug, could be confused with INNs ending in "xine", including *venlafaxine*, *gitaloxine* and *quarfloxine*; *voreloxin* is more evocative of an antibiotic, given the similarity with the common stem **–oxacin**.

Poorly comprehensible proposed INNs: foreseeable problems. Participants noted that some INNs might be difficult to understand because their common stems were not sufficiently distinctive, providing no clues as to their properties (*atigliflozin*, *ingenolmebutate* and tiliivapram, for example.
In the case of atigiliflozin, an antidiabetic drug, the proposed common stem **–gliflozin** for phlorizin derivatives is sufficiently distinct from the common stem **-glitazone** but carries a risk of confusion with INNs ending in "zine" (contained in *common stems* such as **-dralazine**, **-izine**, **-rizine** and **-yzine**; and evoking sedative neuroleptic phenothiazines or antihistamines; *mesalazine*, etc.) or with those ending in "sine" (contained in the common stem **-mesine**; and evoking alphablockers such *alfuzosin*).
As it resembles eugenol (a chemical name designating a terpene still used in some topics available in France, such as Alodont° and Pectoderme°), participants considered that *ingenolmebutate* would be difficult to memorize and that the name did not evoke a cytotoxic drug.

Conflicts between a proposed INN and the indications claimed by the company. While other phosphodiesterase IV inhibitors have **-milast** as their common stem (for example *cilomilast*, *roflumilast* and *tetomilast*), the name *tilivapram* is more evocative of another therapeutic class such as analeptics (*doxapram*) or serotonin reuptake inhibitors (*citalopram*, *escitalopram*, etc.).

A proposed INN with a commercial bias? Most requests for INNs are made by the companies concerned and can sometimes be concocted as part of their marketing strategy. Thus, the proposed INN *oportuzumab monatox*, which makes one think of “opportunity”, appears to have commercial overtones.

In summary, after this 4th participation in the WHO consultation on proposed INNs, *Prescrire* recognizes the efforts made by the WHO INN Program but considers that specific information and education will be needed, especially in the case of monoclonal antibodies, if caregivers and patients are to adopt the proposed INNs.

Bruno Toussaint
Chief editor

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