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continuing education
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Prescrire's contribution to the WHO consultation on List 103 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 103 of proposed INNs, which was published in June 2010 (7).

Our critical analysis of the proposed INNs. Our analysis of List 103 of proposed INNs was based on the 2009 list of common stems and its updates, on the INN database, on *Prescrire*'s 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 17 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.

We also examined two INNs, *itarnafloxin* and *turofexorate isopropyl,* that had been proposed in previous lists, then amended in response to objections lodged by *Prescrire* and others.

Formal objections

The risks of mix-ups or misunderstandings we identified for *obenoxazine* and *tasocitinib* appear avoidable. Our formal objections aim to re-examine these two proposed INNs in order to prevent problems for healthcare professionals and patients in the future.

***Obenoxazine*: too similar to other INNs.** Since *obenoxazine* has no informative common stem, the similarity between -oxazine and **-oxacin** creates a very high risk of confusion with *enoxacin*, a quinolone containing the same sequence of vowels. There are already 5 INNs ending in –oxazine (*chlorthenoxazine*, *difencloxazine*, *viloxazine* (no longer marketed in France since 2005), *indeloxazine* and *teniloxazine*). They could be confused with the INNs of quinolones (nalidixic acid derivatives) that have the common stem **-oxacin** but do not end in -floxacin (**a**). And INNs containing “enoxazine” are particularly likely to be confused with INNs containing “enoxacin” (i.e. *enoxacin*, *garenoxacin* and *ozenoxacin*).

As these drugs are used in common conditions, exposure of patients to this risk of confusion is likely to be frequent. The consequences of accidental sedation resulting from such a mix-up should be borne in mind, even if the two types of drug are prescribed in different contexts, antibiotics being often prescribed for a limited period.

***Tasocitinib*: too many risks.** Participants felt that there was a high risk of confusion between *tasocitinib* and the French brand name Tazocilline°, which share three phonetically similar syllables. However, bearing in mind their dissimilar indications and pharmaceutical forms (tyrosine kinase inhibitors tend to be used orally), it may be hoped that most mix-ups will be spotted by patients.

More worrying is the risk of confusion between INNs: the same sequence of vowels present in *tasocitinib* is also found in *dacomitinib* (another proposed INN in List 103), adding the risk of serious adverse effects from mistakenly administering a cytotoxic cancer drug instead of an anti-inflammatory drug.

Amendments to previously proposed INNs

As a result of the objections lodged, the INN programme changed *quarfloxin* (presented as an antineoplastic in List 98) to *itarnafloxin*; and the French term for *turofexorate isopropyl* (presented as a farnesoid X receptor agonist in List 101) was changed from *isopropyl de turofexorate* to *turofexorate d’isopropyle*. These amendments were published in List 103 of proposed INNs (7). The participants examined these INNs with regard to the objections initially raised by *Prescrire* (13,14).

***Itarnafloxin*: the risk remains.** *Itarnafloxin* replaces *quarfloxin* (List 98), a name that strongly suggested that the drug is a quinolone and that could have been confused with *sparfloxacin. Prescrire* considered this to be a critical risk and therefore lodged a formal objection (13).

With *itarnafloxin,* although the risk of confusing the drug with a quinolone appears reduced it still exists, since the INN still contains the syllable -flox-, which is easily identifiable and strongly associated with this class of antibiotics (**a**). As a cancer drug, *itarnafloxin* is likely to be highly toxic, so special precautions will be required to clearly demarcate its use from that of an antibiotic. Such measures may not be sufficient to prevent errors caused by confusion between names.

***Turofexorate isopropyl*: still obscure.** The name *turofexorate isopropyl* (List 101), a farnesoid X receptor agonist that acts through a bile salt mechanism, gives no clues about the drug's properties. *Prescrire* lodged a formal objection because it does not contain a recognisable common stem (14). The new amendment brings the French and Latin names into line with the rules governing INN nomenclature, but does nothing to make the INN more informative.

Other comments

Some proposed INNs generate a theoretical risk of medication errors, for a variety of reasons: some could be confused with other INNs; some are difficult to understand, particularly when they depart from known rules governing the development of INNs; some could be confused with everyday, non-pharmaceutical terms. Hence the following comments.

Risks of confusion with other INNs. Some proposed INNs, such as *anagliptin*, *dacomitinib, ensituximab, itolizumab*, *pegdinetanib* and *verubulin,* could be confused with other INNs or common stems.

Since *pegdinetanib* and *pegaptanib* contain the same common stems **peg-** and **-tanib**, they only differ by one or two syllables. This proposed INN complies with the rules on INN development. With a difference of one syllable, most of the participants who suggested lodging a formal objection considered there was inadequate differentiation between these two INNs. However, the risk of confusion is limited if the drugs' therapeutic indications are different.

Among the INNs that contain the common stem **-bulin**, concern was expressed regarding the risk of confusion between *verubulin* and e*ribulin*, a drug currently in development for breast cancer, due to inadequate differentiation.

Among the INNs containing the common stem **-tinib**, the same sequence of vowels found in *dacomitinib* and *tasocitinib* grounds the formal objection already presented.

Among the INNs that end in **-tuximab**, *ensituximab* was considered to sound too similar to *cetuximab*; the associated risk is moderate however, because in principle they belong to the same therapeutic class. Similarly, *itolizumab* sounds too similar to *eculizumab* and *tocilizumab;* in the latter case, the INNs are virtually identical if the first two syllables are inverted, and such slips of the tongue or pen are easily made. The participants suggested the following alternatives: "italizumab", "patalizumab", "ritolizumab" or "utulizumab".

In addition to the identified risk of confusion between *anagliptin* and *saxagliptin*, it emerged that the beginning of this INN can cause a problem in French when preceded by the definite article (l'*anagliptine*), as it could be understood as "la nagliptine" or be confused with *linagliptin*. This phonetic problem, which only applies to the French language, does not require the other 12 recommended INNs that start in "ana" to be re-examined, but it should be taken into account in the systematic analysis of the risk of errors associated with INNs.

Poorly comprehensible proposed INNs: foreseeable problems. When common stems are insufficiently obvious, the INN does not provide enough clues about the drug's potential use. This is the case for the monoclonal antibodies *roledumab*, *olokizumab* and *samalizumab.*

In the case of *roledumab* and *olokizumab*, the common stem that indicates immunomodulatory activity is not obvious. In the case of *samalizumab,* as an antineoplastic it should have contained the sub-stem -t(u) instead of -l(i)-: the INN should have been "samatuzumab", a suggestion made spontaneously by most of the participants.

Risks of confusion with non-pharmaceutical terms. It was felt that the fact that the prefix veru-, which has already been used for *verucerfont* in List 102, resembles the French word for wart “verrue” and is present in some French brand names, such as Verrulyse°, Verrufilm° and Verrupan°, would not have serious consequences, because the conditions surrounding their prescription are very different.

Common stems in the pipeline. Several of the proposed INNs give the impression that new common stems are imminent, but they are not included in the list of "pre-stems" where future common stems are announced; and no explanations are available in the List 103 of proposed INNs (7,10). The following common stems were identified as being already in use in USAN nomenclature: -glustat (in *eliglustat*) for glucosylceramide synthase inhibitors; -rafenib (in *vemurafenib*) for raf kinase inhibitors; -tibant (in *fasitibant chloride*) for bradykinin B2 receptor antagonists (antiasthmatics); and -toclax (in *navitoclax*) for BCL-2 (B-cell lymphoma 2) inhibitors (15).

This situation highlights how readily some national programmes create common stems and how long it takes for them to be officially recognised by the WHO INN programme. It reflects pressure from the pharmaceutical industry, which increasingly requests the creation of new common stems, to have a new mechanism of action or a new therapeutic approach recognised. The WHO INN programme must therefore demand that drug companies provide data confirming that a new substance does not fall under the scope of an existing common stem.

Dealing with overcrowded groups. The proliferation of INNs for monoclonal antibodies (common stem **-mab**) and tyrosine kinase inhibitors (common stem **-tinib**) increases the risk of confusion among pharmaceutical substances which are used in very different indications. It is probably time to make the INNs of such overcrowded groups easier to decipher and more consistent albeit maintaining enough differentiating common stems.

The number of tyrosine kinase inhibitors is growing: there are 7 on List 103, compared to about 2 each in previous lists. The risk of confusing the anti-inflammatory drug *tasocitinib* with the cancer drug *dacomitinib* highlights the need to expand the common stem **-tinib**, so that tyrosine kinase inhibitors with different properties can be distinguished more clearly.

The 82 proposed INNs in List 103 include a further 12 monoclonal antibodies. The inconsistencies noted in the naming of *roledumab, olokizumab* and *samalizumab* illustrate how difficult it is becoming to devise names for new monoclonal antibodies, despite some relaxation of the rules governing the development of **–mab** INNs (16).

Making potentially confusing INNs easier to decipher. The similarities identified between *obenoxazine* and *ozenoxacin*, *dacomitinib* and *tasocitinib,* and *anagliptin* and *saxagliptin*, suggest that a more thorough evaluation of the risks created by INNs that contain the same sequences of vowels may be necessary.

When INNs have too many common elements, it might be useful to enhance the differences at the point of care by accentuating the parts that differ, for example by capitalising them (‘Tall Man’ lettering) (6,17,18). The risk of confusion between *pegdinetanib* and *pegaptanib* could therefore be mitigated by differentiating the central portion through capitalisation of one or more letter and by careful labelling in the case of injectable forms. For instance, in the case of *gemigliptin,* the second INN to start with “gemi”, *gemifloxacin* being the first, the differences could be enhanced as follows: *gemiGliptin*, *gemiFloxacin*.

This is an avenue worth exploring in the systematic analysis of the risks of confusion between look-alike INNs; then to harmonize.

In short, our analysis of List 103 of proposed INNs shows that progress can still be made to improve the safety of 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

Review prepared and translated by the *Prescrire* Editorial Staff with the participation of healthcare professionals from the *Association Mieux Prescrire*, no conflicts of interest

*a- According to our calculation at the time of preparing this contribution, there were 57 INNs for quinolones ending in the common stem **-oxacin**, 46 of which ended in –floxacin, which is highly characteristic and easily recognisable.*

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