PROTECTION OF INN ENSURING PATIENTS' SAFETY AND INTELLECTUAL PROPERTY

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International Nonproprietary Names (INN) are used to identify and define pharmaceutical substances. They are globally recognized and are also referred to as the generic names. INN play a crucial role in facilitating communication between health care professionals, scientists, regulators, and users around the world. The use of the INN has many positive implications regarding the prescribing, dispensing, sale, transportation, pharmacovigilance and patient access to medicines [(1)].

The INN Programme was initiated in 1950 by a World Health Assembly (WHA) resolution WHA3.11. The first list of INN was published in 1953. Since then, more than 12,000 recommended INN have been published. Every year, about 500 new names are selected for new chemical/ biological entities for use as medicines. INN should be distinctive in sound and spelling and should not be liable to confusion with other names of medicines. As suggested by their name, INN are public property and can be used without restriction, to identify pharmaceutical substances. INN are used in medicines regulations and are written into national medicines legislation in most countries across the globe [(1, 2)].

INN and trademarks

The Agreement on Trade-Related Aspects of Intellectual Property Rights as Amended on 23 January 2017, refers to trademarks as "Any sign, or any combination of signs, capable of distinguishing the goods or services of one undertaking from those of other undertakings, shall be capable of constituting a trademark. Such signs, in particular words including personal names, letters, numerals, figurative elements, and combinations of colours as well as any combination of such signs, shall be eligible for registration as trademarks. Where signs are not inherently capable of distinguishing the relevant goods or services, Members may make registrability depend on distinctiveness acquired through use. Members may require, as a condition of registration, that signs be visually perceptible" (https://www.wipo.int/wipolex/en/text/500864) [(3)].

Although they represent opposite concepts, INN and trademarks share some common features, as both are aiming to define and distinguish one single product or substance from others. While INN allow for proper identification of a medicinal substance, brand or trade names are linked to specific products owned by a single commercial entity. INN are selected by the World Health Organization's (WHO) Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations serving the INN Expert Group. The selection process follows a strict procedure and is carried out in close collaboration with national drug nomenclature bodies. To protect the rights of trademark owners and to ensure a name is safe for use as a medicine, a four-month review period follows the publication of new INN (which are referred to as Proposed INN). During this period, any interested person can submit an objection to a name. A name will not be published as an official INN (which are referred to as Recommended INN) whilst an objection is maintained [(4)].

Another important component of the INN system is the use of stems: medicines that work in the same way contain a common stem, demonstrating the relationships amongst them (in the chemical structure and/ or pharmacological action). For example, the INN stem -*sartan* is used to identify antihypertensive angiotensin II receptor antagonists, such as the widely used *candesartan*, *irbesartan*, *losartan*, *telmisartan*, *valsartan* and others [(5)].

Appropriation of INN infringes the fundamental programme of the INN system. Conflicts between INN and trademarks are mainly due to:

- Similarity between a trademark and an INN (the INN and the trademark are identical or very close)
- Registration of trademarks that contain INN stems

Since both INN and trademarks should be distinctive, the similarity between them should be reviewed both when INN are selected and when trademarks are registered. High degree of similarity with trademarks is jeopardizing the INN system, as it may prevent the safe use of an INN by parties that have to use the INN when it is in the legislation of the region they are marketing a product in. The creation of INN-like trademarks and trademarks containing INN stems, is exhausting the possibility to create new INN and may lead to confusion for patients and healthcare professionals regarding the composition of a medicine. Furthermore, it may lead to medication errors, as the trademark may suggest the medicinal product contains a pharmaceutical substance that is different from the actual one or contains a new substance for an indication whereas it is the same as other products on the market (the later can also lead to unintentional overdosing).

These concerns ultimately led to the adoption of the WHA46.19 resolution in May 1993. In which, the WHO Member States agreed to the WHA request to:

- "enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic name used in the labeling 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 trademarks, 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." [6].

It is thus recommended to avoid trademarks that are derived from INN and from the incorporation of INN stems in trademarks. In this context, it is important to highlight that WHO is encouraging the use of the manufacturer's name in conjunction to the INN for the naming and labelling of multisource (generic) products. Nonetheless, those names cannot be registered as trademarks [6].

For example, if a medicine containing the pharmaceutical substance *adalimumab* is produced by an imaginary manufacturer called GoodPharma, the drug product can be marketed as adalimumab GoodPharma; this is considered a generic name used for regulatory purposes and should not be permitted as a trademark. Should the company wish to generate an INN-like trademark e.g. GoodPharmalimab®, it contravenes the WHA Resolution 46.19 and it should not be permitted.

Recommended for regulatory purposes	Not permitted for trademarks
adalimumab	GoodPharmalimab
adalimumab GoodPharma	adalimumab GoodPharma®

Pharmaceutical substances can be marketed using the INN, alone or in addition to the manufacturer's name. Nonetheless, the registration of INN as trademarks, as well as the creation of INN-like names, is discouraged

To ensure the appropriate use of INN, WHO has requested national bodies such as drug regulatory authorities, Intellectual Property/patent authorities should avoid granting proprietary rights that infringe INN. Once a new list of proposed or recommended INN is published, WHO circulates it to all its Member States through a Note Verbale. When a trademark registration that is identical or very similar to an existing INN is identified, the WHO INN Secretariat requests the relevant national authorities to reject the application or to revoke its registration after it has

already been granted. A similar request is issued when WHO identifies the registration of trademarks that contain INN stems.

Trademark registration for pharmaceutical substances

Unfortunately, globally accepted definitions of what is 'similar to' an INN or what 'conflicts with' an INN do not exist. In 2008, during the 19th session of WIPO Standing Committee on the Law of Trademarks, Industrial Designs and Geographical Indications (SCT), a discussion was held on the approaches to the examination of trademark applications against recommended INN. It was noted that INN were interpreted in a divergent manner, especially regarding whether offices should refuse registration as trademarks to those signs that are identical or similar to recommended INN or should refuse registration only to those signs which are identical to recommended INN [7].

Trademarks for medicines usually undergo a dual review process before they can be used with a specific medicinal product: (1) by the intellectual property register in the region(s) where the medicine is to be used and (2) by the medicinal regulatory body in the region(s) where the medicine is to be used. While the trademark register is considering the different aspects of intellectual property, the role of the drug regulatory authority is to evaluate the safety aspects of the invented name.

According to the European Medicines Agency (EMA) draft for update of the guideline on the acceptability of names for human medicinal products processed through the centralized procedure, invented names should be distinct enough from other names of medicinal products. A similarity of 50% and over to an INN in writing and speech and the inclusion of the INN stems are to be considered. The characteristics of the specific substance, such as the indication, the patients' population, the clinical setting, route of administration and more should be considered, in light of the potential harm to patient in case of a mix-up [8, 9].

The United States Food and Drug administration (US FDA) is applying similar principles. The US FDA is using a computational method, the Phonetic and Orthographic Computer Analysis (POCA), to determine similarity between two drug names. The US FDA refers to a threshold of 70% or higher as to high similarity. While the EMA is addressing concerns regarding confusion between invented names and INN, as well as the inclusion of INN stems, the US FDA recommends avoiding the use of United States adopted names (USAN) stems in the product's name [10]. While this is useful in the case of a closed market, global trade and free movement of passengers between states raise the need for a global rather than a local approach.

Intellectual Property (IP) Australia would accept a trademark application that is same as or similar to an INN when the trademark is made for a product that contains the substance the INN is referring to. When an INN stem is used in a meaningful way with respect to the specific drug product, IP Australia could also accept the requested trademark [11]. For example, the trademark Roximycin was registered, based on the INN *roxithromycin* and the INN stem -*mycin* (defined for antibiotics, produced by Streptomyces strains). Adimab is registered as a Nice class 5 trademark in various WHO member states, although it is derived from adalimumab and contains the stem -*mab* (used for monoclonal antibodies). This is not in line with the WHA resolution 46.19 and contributed to exhaustion of the INN system [12].

As a result of the dual review/registration process of names, many trademarks registered as Nice class 5 are never used for a marketed medicinal product. An analysis made by the European Medicines Agency revealed that from 423 names submitted for approval in 2022, only 248 could be accepted (about 58.6%). Most of the refusals to names were due to similarity with other invented names (538 out of 738 non-endorsed objections, 72.8%) and similarity with INN (74 out of 738 non-endorsed objections, 10.0%). The inclusion of INN stems in a name is a justification to refuse the name and was accepted as a reason for refusing a minor proportion of cases (2 out of 738 non-endorsed objections, 0.02%) [13]; however, it should be noted that it is rare that an INN stem is included in names submitted through this route as the practice is specifically discouraged in the EMA naming guidance [8].

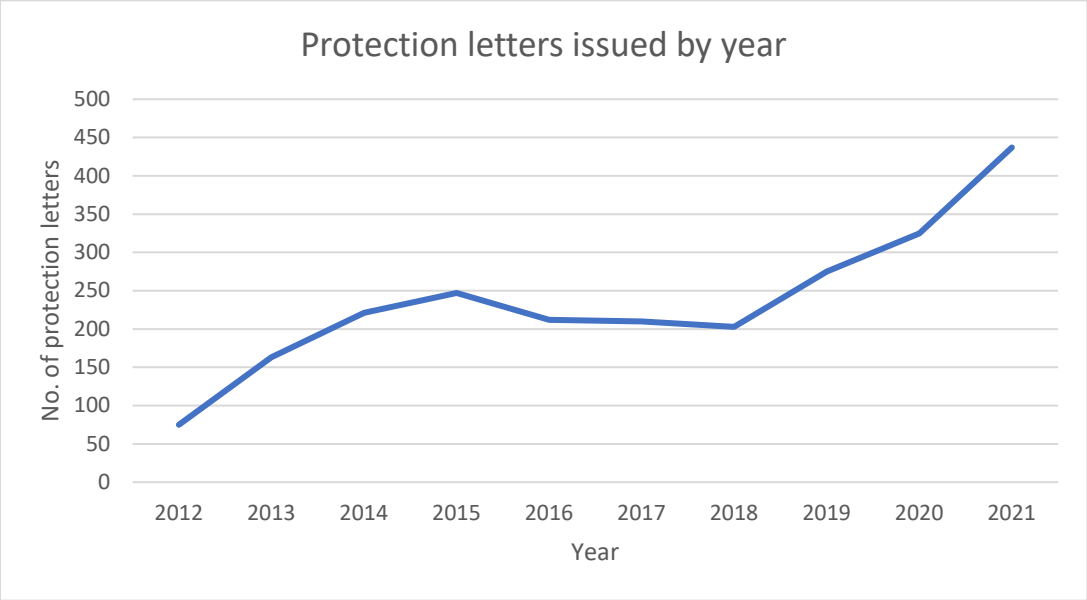
Protection of INN

Since the establishment of the INN Programme, the INN secretariat issued thousands of protection letters, requesting the regulatory authorities in the WHO Member States to act on the registration of trademarks that are too close to INN. In the period between 2012-2021, a total of 2,374 protection letters were issued. An increase in the no. of protection letters issued each year is demonstrated in the trendline. India is the Member State for which the largest number of protection letters were issued. It is followed by Nigeria, Viet Nam, Pakistan, and Peru.

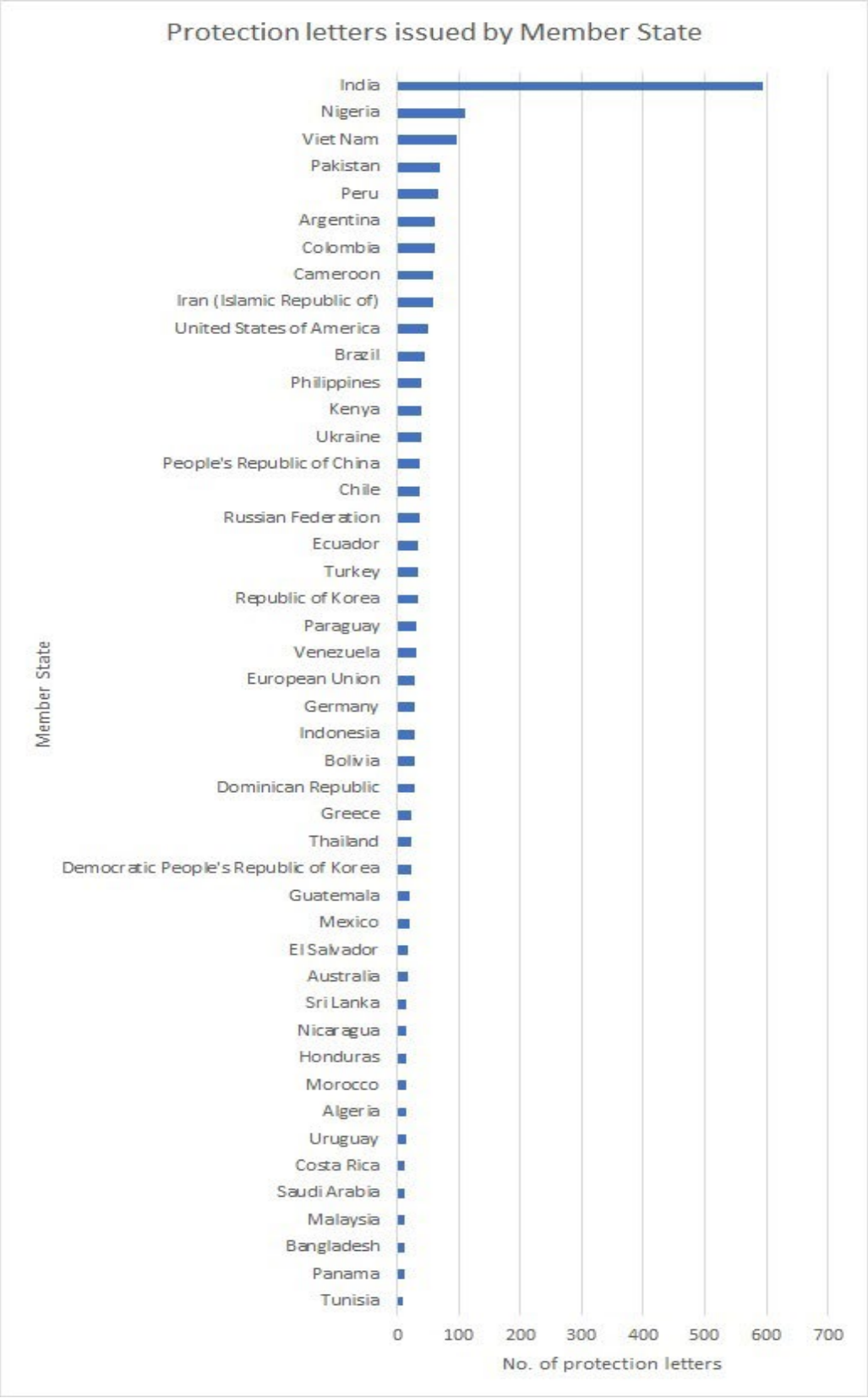
1,113 letters (46.88%) were based on a similarity of the registered trademark to a recommended INN, while 1,789 (75.38%) were addressing INN stems in trademarks (the ratios are cumulated to more than 100%, as some trademark registrations are using both the INN and the stem).
The angiotensin II receptor antagonist *telmisartan* is the INN for which the largest number of protection letters were issued, 81. Another angiotensin II receptor antagonist, *valsartan*, is rated fifth in terms of protection letters issued. *zoledronic acid, capecitabine,* and *ciclosporin* are rated second, third and fourth with 78, 55, and 53 letters respectively.

Accordingly, when looking into the INN stems used in trademarks, -*sartan* is the most abused stem, with 345 protection letters issued; the stem -*mab*, used for monoclonal antibodies, is second with 235 letters; -*mycin* (for antibiotics, produced by Streptomyces strains) has 167 letters, -*ac* (anti-inflammatory agents, ibufenac derivatives) has 165 letters; and *gli* (antihyperglycaemics) has 124 letters.

The protection of the two-letters stems as -*ac* is of special challenge, as those short stems are less distinct. The stems -*aj*- (used for antiarrhythmics, ajmaline derivatives), and -*aI* (for aldehydes), -*ox* (antacids, aluminium derivatives) are barely used in new INN. Nonetheless, they are still protected although in some cases, they could be used in a trademark without a risk. For example, when -*ac* is appearing as a part of a word such as 'cardiac', 'hypochondriac', or 'aphrodisiac'. Therefore, some Member States do not object to using them in trademarks [10].



Only for no. of protection letters ≥ 10



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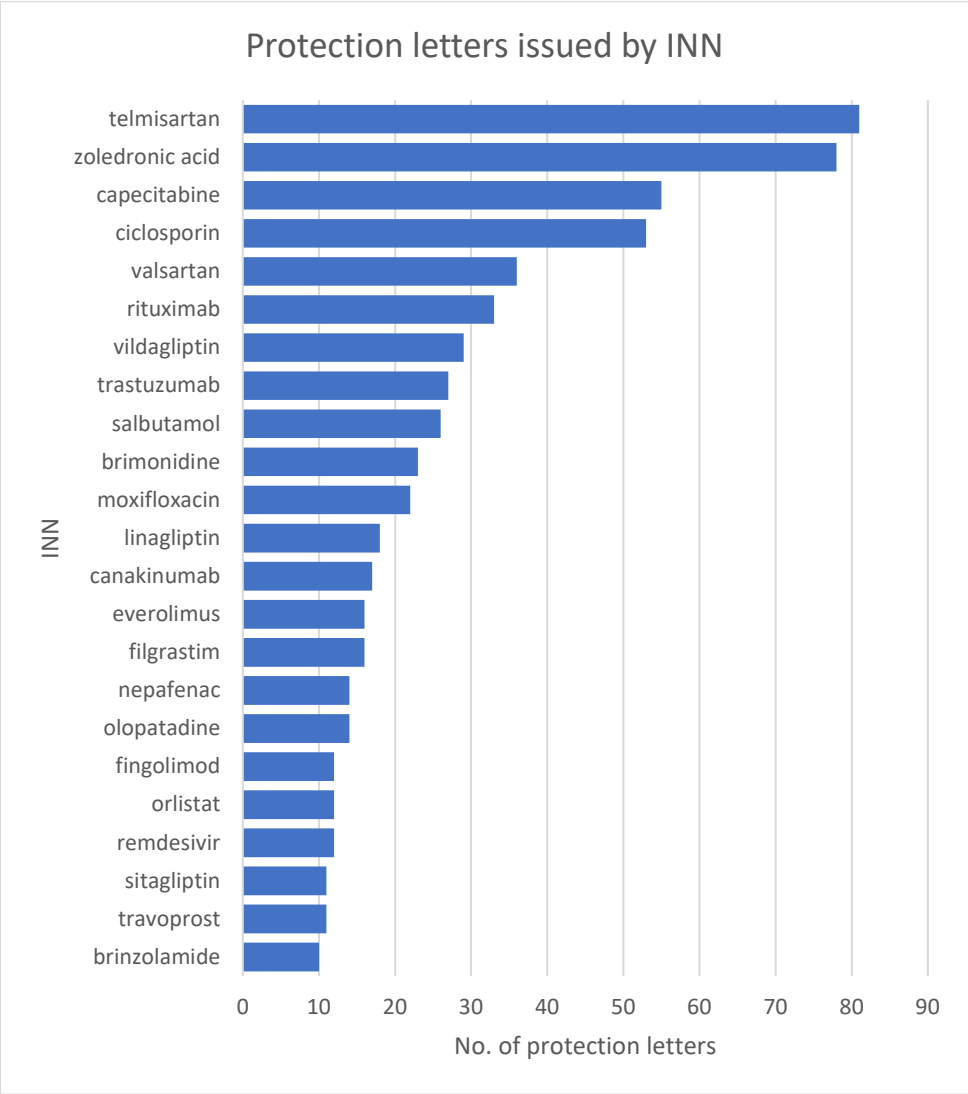

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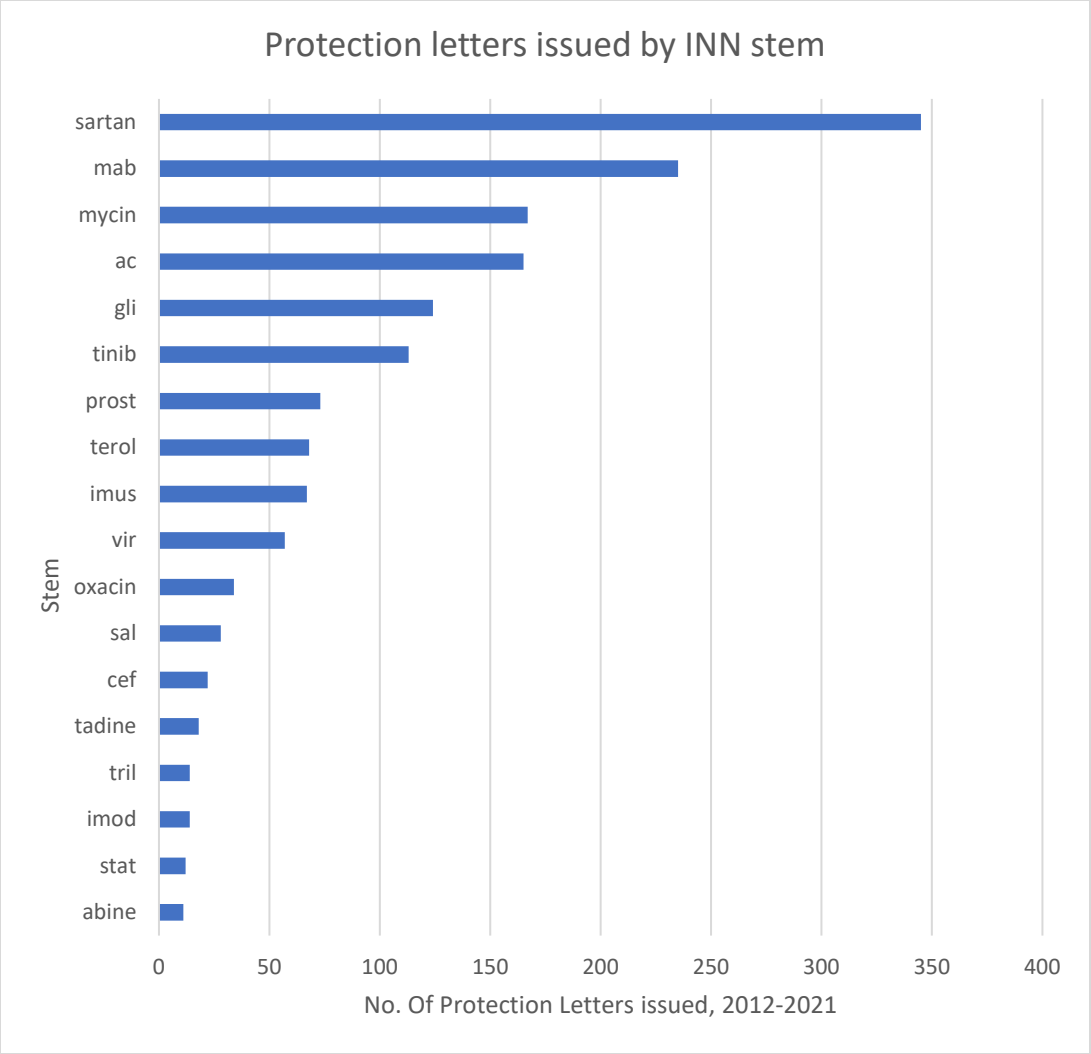

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Considerations for assessing the similarity between INN and trademarks

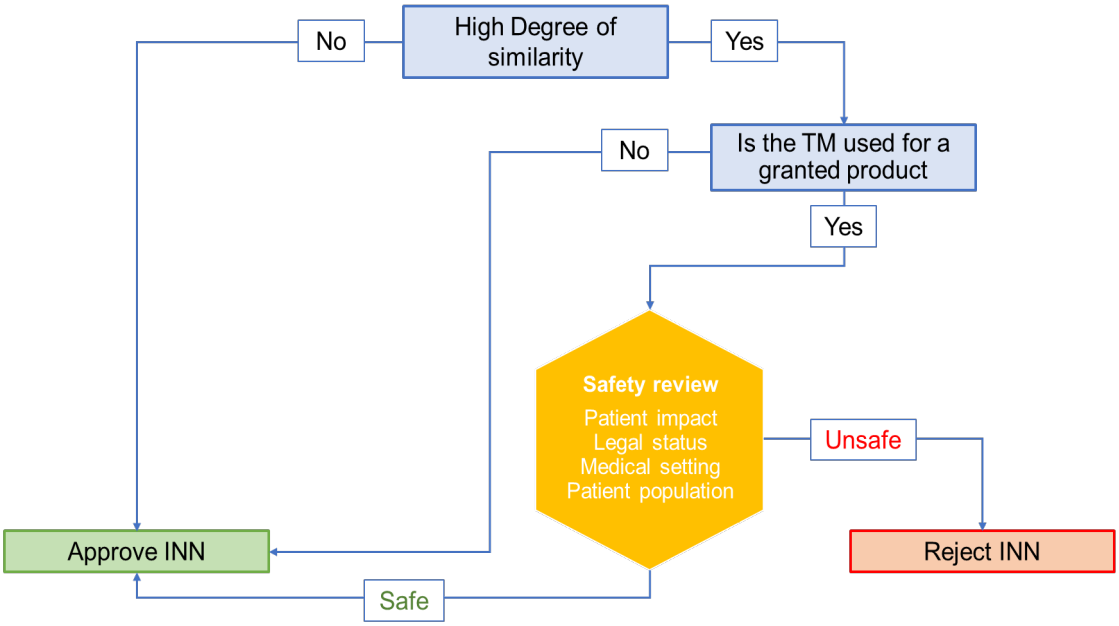
Currently, more than four million trademarks belonging to Nice class 5 are registered in the World Intellectual Property Organization's (WIPO) website, alongside the >12,000 Recommended INN [12]. As the numbers of INN and trademarks are growing, the selection of INN is becoming more complex.

In 2021, the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations adopted a new scheme for the assessment of conflicts between INN and trademarks. Patient-safety is the guiding principle, but other considerations exist. According to the new scheme, when a conflict between INN and a TM is discussed, the INN Experts Group is looking into the following aspects:

- Phonetic and orthographic similarities and their degree of similarity
- The inclusion of the trademark in a granted marketing authorization
- The medical settings in which the medical substance is prescribed and used, its legal status (prescription, non-prescription, special settings), the patient populations that are likely to be the users of the suggested INN and the trademark, the likelihood of a mix-up and its impact on the patients.

According to the above-mentioned criteria, a decision is taken if the names could co-exist. During the discussions conducted by the INN Experts Group, it was noticed that the perception of phonetic and orthographic similarities was much dependent on the accent, culture and background of the reader/reviewer.

Naming similarity is considered subjective with varying rationale for why an individual may find name pairs similar (or not). Because of this it was agreed that objective reasoning needed to be in place when reviewing names flagged as potentially conflicting with the existing names of medicines. Below is a flow diagram that can be used for assessing the level of risk in name pairs for medicines. It should be noted that when the names are very similar (ie 1-2 key letter differences) the new name would likely be refused regardless of the likelihood of mix-up; this is due to the administration of medicines, stock control etc. The decision point regarding the trademark being used for a granted product is an important one; given the huge number of Nice Class 5 trademarks and the knowledge that a high percentage of them will never be used, it was decided that only trademarks for granted products could be considered for protection, the future risk would then be controlled by the regulatory body when completing their name reviews (although not ideal, this was the only practical approach available as too many INN were being refused for these conflicts when the trademark only existed in databases and not for products).



A decision tree used to facilitate the discussion on similarities between INN and trademarks.

Summary

INN and trademarks are important for the identification, sale, and supply of medicines. Despite the challenges, both systems co-exist, allowing for both the free use of INN and the protection of intellectual property. The INN Programme is striving to protect INN to facilitate access to medicines, reduce medication errors and enhance patients' safety, and is happy to collaborate with regulatory authorities, trademark offices and the industry to improve the naming of pharmaceutical substances.

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