Support of INN's Original Purpose

The United States Food and Drug Administration (U.S. FDA) continues to support the original purposes, premises, and uses of the INN and believes the system has provided many positive elements to the world’s public health, especially in facilitating the exchange of scientific data and reports on various products same active ingredient(s).

The USA recognizes the INN system as a cataloging system whereby many products worldwide may share the same internationally recognized nonproprietary name based on drug substance. In this manner, the INN system provides a clear mechanism to health care professionals worldwide for identifying medicines and communicating unambiguously about them based on pharmacological class.

The U.S. FDA’s concerns in today’s discussion are (a) that the INN not be used in ways that could jeopardize the health of patients, and (b) that we not unnecessarily institute changes that could jeopardize the public health benefits of the present INN system.

Specifically, INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist.

Pharmacologic Interchangeability

“Interchangeability” is a term used for purposes of this discussion to designate the situation where scientific data convincingly demonstrates that two products with very similar molecular compositions or active ingredient(s) can be safely substituted for one another and have the same biologic response and not create adverse health outcomes, e.g., generation of a pathologic immune response.

With small molecular products, there is a long history to support the use of various scientific approaches to establishing “bioequivalence” between products with the same active ingredient(s) produced by different manufacturers. We know now that these “bioequivalent” products can indeed be expected to behave in a pharmacologically interchangeable manner when used in patient care.
With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.

Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response.

When scientific data establishing pharmacologic interchangeability do not exist, especially with more complicated protein molecules with potential critical immunologic safety issues, it is important that patients and physicians be aware that protein products with similar molecular composition may indeed not be interchangeable.

U.S. FDA believes that the only way to establish pharmacologic interchangeability is through scientific data, and nomenclature should not be used as a way to imply such when there are not credible supporting data.

**Situation in the United States of America**

*Product Dispensing*

To date, the USA does not use non-proprietary names as a vehicle for communicating pharmacologic interchangeability. There are examples in both small molecule products and more complex proteins of products having the same non-proprietary name and not being scientific data establishing the interchangeability of the products. For example, multiple innovator products containing interferon β-1a, insulin, or somatropin share the same non-proprietary name and there are not scientific data that support the pharmacologic interchangeability of these products.

In the USA there are recognized mechanisms in place other than non-proprietary names for assigning pharmacologic interchangeability: e.g., equivalence ratings in the Orange Book; specific labeling regarding pharmacologic interchangeability.

In addition, in the USA, there are drug dispensing systematic “checks” to help assure appropriate dispensing of products based on whether or not there are scientific data establishing interchangeability. However, this might not be true in other countries.

Because of the many alternative mechanisms in the U.S. for preventing inappropriate substitution, at this time the U.S. FDA does not consider the proposed change to the INN policy for naming biosimilars to be necessary to prevent inappropriate substitution in the United States. Appropriate prescribing and dispensing practices in the U.S. encompass more than just conveyance of a drug name from prescriber to pharmacist. Regulations concerning drug substitution by pharmacists vary from state to state in the United States. However, there is always a mechanism by which the prescriber can authorize that the brand or innovator product be dispensed. As an additional safeguard, many states utilize a state drug formulary that includes listings of drugs with the “same” active ingredient(s) considered to be pharmacologically interchangeable. Even if two biosimilars would have the same nonproprietary name, they would
only be included on a list of interchangeable products, if there were scientific data to justify such. Thus, a common INN in itself does not imply or warrant inclusion on a state’s list of interchangeable drugs. The FDA recognizes that the authorized prescribing information represents the most important means of communicating information about an authorized product to prescribers and pharmacists. The authorized prescribing information should distinguish a product from others considered to be biosimilar if indeed there is not data to substantiate pharmacologic interchangeability. In addition, the role of continuing professional education about interchangeability risks with biosimilars should be further emphasized.

The issue of interchangeability is not an issue of nomenclature but a scientific question that needs to be decided on its own merit. The question of nomenclature is more relevant to concerns about pharmacovigilance and the prevention of inappropriate substitution. However the FDA believes that these issues transcend a naming convention. It would be the U.S. FDA’s preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing."

**Pharmacovigilance:**

In the USA, the non-proprietary name may serve as a useful tool in pharmacovigilance as it may be one means of product identification, but it should not be relied upon as the sole means of product identification. Pharmacovigilance is the dual responsibility of the manufacturer and the U.S. FDA. In order to practice the most robust pharmacovigilance, all involved should employ all the various tools available for product identification, including lot numbers, NDC codes or other such national coding systems, etc.

As such, the USA does not see any reason to change present INN practices for pharmacovigilance purposes when there are other identification systems in place to allow product identification beyond the level of the non-proprietary name.

**U.S. FDA Concerns Regarding INNs and Complex Proteins**

If the outcome of assigning the same INN to two products with highly similar ingredient(s) created the implication that the two products were pharmacologically interchangeable AND there were NO scientific data to support that finding, then the U.S. FDA would have serious concerns...
about such an outcome, especially with more complicated proteins. As of today, FDA has not determined how interchangeability can be established for complex proteins.

If the outcome of assigning different names or names with unique identifiers to two products with highly similar active ingredient(s) created the implication that two products were not interchangeable when indeed there were scientific data establishing such, the U.S. FDA would have serious concerns.

It is beyond the role of the INN Expert Committee to make product interchangeability determinations. This would place an unrealistic burden of responsibility with accompanying liability on the INN Expert Committee. The INN should not be used as a determinant of interchangeability. It would be bad public health policy to allow, just because they share the same INN, the substitution of products with a shared INN in patient care when there are no scientific data to demonstrate pharmacologic interchangeability.

Likewise, it would be bad public health policy to disallow, solely because they have different INNs, the substitution of products with different INNs which indeed have scientific data that demonstrate pharmacologic interchangeability.

Each national regulatory authority should oversee the evaluation of interchangeability based on bioequivalence and/or other validated scientific data and not link such decisions to INNs.

**Conclusions**

This discussion among national regulatory authorities and the WHO should be a first discussion on this issue to fact find and to determine how changes to the INN system would impact both positively and adversely, the regulatory systems and public health of WHO member states.

- The FDA is concerned that some countries may be using the INN as an indicator of interchangeability. Although this is not the case in the U.S., the U.S. FDA considers this apparent inappropriate use of the INN to be a public health concern.
- The U.S. FDA encourages the WHO to further investigate the worldwide prevalence of using the INN as a determinant of interchangeability (note: the BCG study sponsored by Amgen investigated 6 EU countries and use of the INN in prescribing was encouraged in most of these 6 countries, but not required).
- The U.S. FDA suggests that the WHO/INN Expert Committee clarify and re-iterate the intent of the INN with participating countries.

It would be the U.S. FDA’s preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at
a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing.”

At this time, the U.S. FDA acknowledges that biosimilars have not been demonstrated to be interchangeable through any scientific process. The world community may ultimately decide that INN policy for this class of products should be treated differently than that for small molecule drugs. A different naming scheme for these products might involve utilizing a different level of granularity, which may be more detailed or less detailed depending upon the utility in the INN system. Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment.

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