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# **EGA position paper on naming of biopharmaceuticals: a contribution to WHO “Review of International Nonproprietary Names (INN) for Biological and Biotechnological Substances”**

## **Context**

Biopharmaceuticals, already worth in excess of US\$40b per year, are the fastest growing medicinal product class both in terms of number and cost. Healthcare systems are wrestling with the challenge of bringing safe, quality access to these expensive and complex medicines to as many patients as possible. The clinical importance of this product family, coupled with cost pressures in healthcare, will drive a biosimilar industry and just as generic drugs have contributed enormously to the affordability of medicines, so too will biosimilars eventually improve patient access to affordable, quality biopharmaceuticals. The WHO’s INN nomenclature system has included biologicals for over 50 years and commercial biopharmaceuticals for over 25 years. These products have passed through several changes of manufacturing process and site each and many have the same INN name as other biopharmaceuticals (for example, there are six different somatropins on the market) without having undergone a comparability exercise. There have never been identification, safety or communications concerns attributed to the nomenclature system itself. The discussion about the INN naming of biopharmaceuticals, and specifically whether biosimilars are a ‘special case’, is therefore not simply an intellectually challenging problem - it is also real, practical and immediate.

## **EGA Recommendations**

1. The existing INN nomenclature system utilised by WHO has displayed some minor inconsistencies, however these generally stem from its inconsistent use by regulators and non-WHO bodies, rather than the nomenclature system itself.
2. No changes are required to the nomenclature system per se, though enhancements based on sound science and logic may be possible. Whatever changes, if any, made to the INN nomenclature system for biologics by the WHO, must be accompanied by more explicit acknowledgement of the potential for two biological products to receive the same INN classification on the basis of an analytical comparability assessment. Radical changes, including allocating INN’s based solely on the manufacturer of a product, are more likely harmful than helpful.
3. Regulators should be acknowledged as the entities with technical competence to assess whether two biological products have sufficient comparability to be afforded the same INN. WHO should assign an INN name in line with current nomenclature rules only if comparability to another product is not asserted or comparability is asserted but a competent regulatory authority, after due enquiry, has found to the contrary..
4. Notwithstanding this, assignment of an INN name, registration of a biological medicinal product and post-authorisation monitoring of the product are distinct and separate processes. A comparability exercise (primarily analytical) will determine eligibility for the same INN name for two biopharmaceuticals. A similar exercise, including therapeutic or clinical comparability, will determine whether a product is entitled to approvals as a biosimilar of another. In practice, unless a biological medicinal product meets the comparability hurdle entitling it to the same INN name as a reference product, it will unlikely be sufficiently comparable to the reference product to entitle it to approval as a biosimilar.



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### Current situation

The INN biologics nomenclature system utilised by the WHO evolved from principles applied to small molecules and therefore has some inconsistencies when applied to biologics.

- The optimal system needs to deal with several complexities
  - Biologics, because of their size and complexity, contain inherent variability from molecule to molecule. Unlike small molecules, in many cases it is virtually impossible to isolate, characterise and purify a single variant at atomic level or to maintain a constant mixture of atomic level variants from batch to batch.
  - At some level this micro-heterogeneity has no impact on the therapeutic and side effect profile of the product. The level at which micro-heterogeneity can influence these parameters can vary from tiny variations in glycosylation or sialisation in some cases (MAbs), through the presence or absence of glycosylation in others (G-CSF), all the way up to changes in amino acid sequence in extreme cases (eg insulin).
  - Determining the level of microheterogeneity that affects therapeutic 'performance' is a complex, technical task, but one that is recognised as scientifically feasible today. Indeed, the possibility of comparability between biopharmaceuticals is the whole basis by which biomanufacturers maintain the same INN through successive (and multiple) manufacturing sites and processes today.
- The nomenclature system in place today has several apparent inconsistencies. These include the fact that glycosylation pattern differences are designated by Greek letter suffixes in the case of EPO, by alpha-numeric strings in the case of IFN's and by pre-fixes in the case of G-CSF's. These differences do not appear to have affected the utility of the nomenclature system.
- More importantly, the application of the nomenclature system by users has been inconsistent, usually as a result of decisions to allocate or use INN's without pausing to consider to whether 'sameness' is demonstrated or even tested:
  - IFN-beta-1a: only one INN name was allocated by WHO. A second product was approved by regulators and the European Commission with a different glycosylation profile without any application to the WHO for a different name.
  - EPO: every EPO from a different manufacturer has so far automatically been designated with a different Greek letter suffix on initial approval. However INN does not change as manufacturing site or location changes, notwithstanding demonstrated evidence in the case of PRCA and EPO/Epex (admittedly in hindsight) that intra-manufacturer product variability can have a greater impact on therapeutic performance.

As the first biosimilars are being approved, the question of comparability is being raised. Due to the sensitivity of the products to changes in manufacturing processes and due to the unpredictability of immunogenicity reactions, originator biotech companies are arguing that the INN system should be modified to require that all biosimilar products, or at least all glycosylated biosimilar products, are identified by a unique INN name or variant. This, it is argued, is necessary to ensure complete traceability of biosimilars (and thereby support pharmacovigilance), to prevent routine prescribing and dispensing practices involving interchanging of reference and biosimilar products (which often could not be routinely interchanged under national laws at the prescribing or dispensing levels if they were assigned distinctive INNs), and because supposedly no two biopharmaceutical products are ever the same. The EGA argues that not only is the use of INN names alone for these first two purposes inappropriate, but also that asserting that every biopharmaceutical is different and should have a different INN would not achieve these purposes, cannot be scientifically supported and would subvert the whole purpose of the INN system.

### INN Nomenclature system for Biologics

INN is a classification system, designed to facilitate the easy naming of active medicinal ingredients (drug substance) in a way independent of source and more simply than the systematic names defined by naming conventions such as IUPAC. This provides the cornerstone then for the use of INN's to facilitate "clear identification, safe prescription and dispensing of medicines to patients, and for the



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communication and exchange of information among health professionals and scientists worldwide” (WHO, Guidance on INN). Note that there is never a suggestion that the INN is sufficient on its own to achieve these objectives

- By implication, a classification system that does not admit the possibility of each class containing more than one element is not a classification system and therefore does not need a global standard/convention.
- Equally, gaining access to the class requires some demonstration of sameness or comparability. This applies even to chemical drugs, though over time and as science has advanced, it has become less explicit for drugs and only the complexity of the exercise has brought this need back to the fore for biologics. Thus, a manufacturer of generic paclitaxel must prove identity to the active ingredient in Taxol® before being entitled to approval with the INN paclitaxel, just as Sandoz were required to prove identity to a somatropin (among other things) before being entitled to approval of a biosimilar somatropin.
- The classification system refers to a specific molecular entity, not to a mixture. Therefore the INN name says nothing, and is not designed to say anything, about purity or other components that may be in a physical sample or drug product. It is usually these impurities that give rise to the safety concerns about biopharmaceuticals of all types.

Changes to the INN naming system are possible, but not necessary. In practice, although the method differs, the more complex the biologic, the greater the level of differentiation of INN names within the class. Adding a further variation that includes a unique qualifier linked to the manufacturer is not logical, is scientifically flawed and is in any case practically very difficult to implement. If any change is made, **the nomenclature system must not evolve in such a way that multiple biologics cannot have the same INN and the EGA urges WHO to reaffirm that medicinal products of any kind, including biologics, should be entitled to the same INN name as another following a relevant and scientifically rigorous comparability exercise.**

To deny the concept of comparability would:

- Destroy the concept of a nomenclature system and would potentially mean inconsistencies of regulator response between FDA and EMEA.
- Totally reverse the basis on which existing originator biological medicinal products retain the same INN when they undergo site transfers or other changes in manufacturing process – a comparability exercise is required to demonstrate sameness.
- Deny the scientific basis on which these comparisons are made, and which are now being applied to demonstrate comparability between products from different manufacturers, a scientific basis already recognised by both EMEA and FDA.
- Require wholesale review of the existing awarded INN names (since those products with the same INN names but no comparability are most vulnerable to the supposed impossibility of comparison) and ongoing amendment of INN names as manufacturers change their sites and processes.
- As a result, create significant confusion in the market place (prescribers, patients and pharmacists) who will never be clear that they are receiving the same medicine from prescription to prescription.

### **Use of the INN nomenclature system by regulatory authorities and the WHO**

INN nomenclature principles must be developed in consultation by appropriately qualified experts in protein function and behaviour.

However, only regulatory authorities have the technical competence to assess comparability. They should be the ones that determine, based on a rigorous comparability program, whether one biologic is sufficiently similar to attract the same INN name. Since at some level, minor degrees of heterogeneity have no impact on the therapeutic activity, this is a useful and established threshold for defining INN sameness. It is the same threshold used to approve changes in manufacturing site today. It is less unlikely that a biosimilar application will be approved on the basis of extrapolation to originator data on the back of limited studies unless it is sufficiently comparable to justify the same INN (but the separation of INN nomenclature and medicinal product registration processes means such a possibility is at least theoretically plausible).



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Companies may file applications for unique INN names for any protein, but this should not automatically be granted. Where WHO is in doubt about sameness, they should refer to regulatory authorities to provide an opinion as to whether a new INN is justified. The same INN should not be awarded in the absence of comparability studies unless there are scientific grounds for believing that the therapeutic effect will none-the-less be the same. This will have been determined at the time the INN nomenclature rules were established for the class. In other words, **the WHO should assign an INN name in line with established nomenclature rules only if:**

- **Comparability to another biological product is NOT asserted; or**
- **Comparability to another biological product IS asserted BUT a competent regulatory authority, after due enquiry, has found to the contrary**

The only scientifically supportable alternative is for the WHO to make the INN determination – but this would require WHO to establish a complete technical infrastructure and effectively require companies to file twice, creating a dual regulatory process, as well as creating an expensive, duplicated technical infrastructure.

### **Consequences of maintaining current INN nomenclature system and reinforcing the comparability principle**

#### On regulatory practice

- Biosimilar approvals will continue to be based on scientific principles of therapeutic comparability.
- There will be no need for retrospective renaming of several existing biologics (with the possible exception of IFN-beta-1a).
- There will be no need to rename biologics when the manufacturing site changes (nor conduct a consideration of whether this is needed).

#### On pharmacovigilance practice

- Pharmacovigilance will not be compromised. An orthogonal set of unique product identifiers (INN, Product Name, MA number, Batch Number, Manufacturer and regional regulator assigned codes) will still be needed for traceability, as is the case today.
- Deficiencies in the ability of the above process to maintain adequate pharmacovigilance will not be addressed by requiring differential INN names – physicians will for example still prescribe “EPO” rather than EPO-alpha as they do today.
- Deficiencies in the ability of the above process to trace biosimilars or biologics are deficiencies in the front line monitoring and adverse event reporting processes and apply to all drugs. They must be fixed by regulatory authorities at national/front line level, not by the WHO via INN policy. To do otherwise is not with the INN scope and purpose.

#### On prescribing and dispensing

- National laws, policies, and clinical practices could be affected by requiring unique INNs for biosimilars.
  - Therapeutic interchange happens independent of INN naming. It is a clinical and/or formulary decision which is transparent, considered by all relevant stakeholders and based on typically annual reviews of formulary policy. Therapeutic interchange happens already today in EPO's.
  - The INN alone is not, and has never been, sufficient to determine prescribing and dispensing. Having the same INN does not prevent local regulatory authorities adopting their own rules in relation to prescribing/dispensing of biosimilars, but having distinctive INNs nonetheless could require changes to national laws.
  - In most cases, biopharmaceuticals are dispensed and administered in specialised care settings. Prescribing decisions in these settings are likely to be based on policy or formulary decisions and served from a central pharmacy – such that INNs are not an issue, except potentially for those existing products which have the same INN but lack comparability data.



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- Indeed, to deny that two products could hold the same INN following a comparability exercise would actually hamper the operation of existing prescribing and dispensing systems since most national laws start with a position that without the same INN there is no possibility of interchangeability. To deny biosimilars, proven to be comparable as well as therapeutically equivalent through clinical trials, the possibility of accessing appropriate prescribing and dispensing mechanisms is under national control and thus beyond the remit of the WHO, tantamount to second guessing the regulatory process, a potential restraint of trade, an undermining of regulatory competence and inconsistent with the whole concept of biosimilars and of INNs.

On clinical practice and communication

- Clinicians and patients will not notice the EGA's recommended policy.
- On the other hand, assigning a unique INN to each manufacturer will create confusion in the minds of patients and medication error potential in the hands of clinicians because
  - A large number of existing medicines may have to be renamed.
  - Marketed medicines may change their name because processes and/or sites have changed.
  - Perceptions of variable quality may be reinforced, irrespective of the fact that all biological medicines will have passed the same high standards of regulatory approval.

### **Conclusion**

There is no pressing need to change the existing INN nomenclature system for biological products.

There is a need to reinforce the concept of comparability in assigning INN names to products, particularly biological products. The WHO should assign an INN name in line with established nomenclature rules only if:

- Comparability to another biological product is NOT asserted; or
- Comparability to another biological product IS asserted BUT a competent regulatory authority, after due enquiry, has found to the contrary

To assign INN names uniquely by manufacturer, no matter how this is achieved, is contrary to sound science, undermining of the whole purpose of INN and detrimental to the regulatory and post-authorisation processes that depend on today's INN system.

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