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Response to the WHO public consultation on the draft "Proposal for Assignment of Biological Qualifiers (BQ)"

INN consistency has to be preserved

The WHO draft proposal on biosimilars offers an acceptable solution at global level

Summary:

- **In their joint response to the WHO public consultation, *Health Action International* (HAI), the *International Society of Drug Bulletins* (ISDB) and the *Medicines in Europe Forum* (MiEF) support the assignment of a 'biological qualifier' (BQ) after the International Nonproprietary Name (INN) of glycosylated biosimilars.**
- **The assignment of BQs is an acceptable solution in order to prevent Drug Regulatory Authorities (DRAs) developing parallel and different systems of naming biosimilars, which would endanger medicinal product name consistency at a global level.**
- **The scheme proposed by the WHO will avoid confusion of multiple names for biosimilars. It should however be mandatory, not voluntary, and respected by all Drug Regulatory Agencies worldwide.**

We welcome the World Health Organization (WHO) initiative to consult the public on its proposal to assign a 'biological qualifier' (BQ) (a four letter code) after the International Nonproprietary Names (INNs) of similar biotherapeutic products (biosimilars) when they are glycosylated (**a**) (1).

Why INNs are important. The World Health Organization (WHO) has been assigning INNs for 70 years. INNs make it possible to identify differing medicinal products containing the same drug substance (1,2). INNs constitute an informative and international language shared by health professionals and patients and are crucial for the quality and consistency of healthcare at global level (**b**).

INNs are specific to a given substance regardless of manufacturer or manufacturing process. Moreover, a scientific approach should drive naming, regardless of whether a product is approved as a biosimilar or as a new drug. In other words, if an application is for the same substance, it should get the same INN. The role of INNs is not to enable users to identify the method used to manufacture biotechnology-derived medicinal products (2,3).

INN consistency is crucial at global level. To avoid losing market share when originator biotherapeutic products are copied, originator companies attempt to prevent their substitution for a cheaper biosimilar, in particular by pharmacists, in any of the many countries where generic substitution is permitted (2). Generic substitution is an important component of universal access to medicines, and should not be confused by multiple product names for similar products.

Originator companies have argued that each biosimilar should be assigned a different INN in order to make it possible to trace the origin of adverse effects, which could differ between the originator biotherapeutic product and its biosimilars (3-5). Several drug regulatory agencies, including Australia's Therapeutic Goods Administration (TGA) and the US Food and Drug Administration (FDA), have succumbed to industry pressure by starting to modify the existing INNs of biosimilars, independently of the WHO INN programme and of national drug nomenclature committees (1,2).

There is no justification for giving a biosimilar product a different INN from the originator product unless a difference in efficacy or adverse effects has been demonstrated. In the vast majority of cases, the efficacy and adverse effect profiles of these products will be similar (**c**) (6). It would serve no useful purpose, but could potentially confuse professionals and patients (1,6). Moreover, for traceability, using an INN together with brand names (or National Drug Codes) and batch numbers would be sufficient (6).

WHO's proposal: adding a "biological qualifier" (BQ) code after the INN. The WHO could have encouraged Health authorities to train health professionals and patients to use INN plus trademarks (or National Drug Codes) and batch numbers when spontaneously reporting to pharmacovigilance databases suspected adverse reactions with a biological or a biosimilar. The WHO proposes instead a voluntary scheme to be adopted by regulatory authorities.

The proposed scheme will offer regulatory authorities the option to oblige a manufacturer to apply to the INN Secretariat to obtain a "biological qualifier" (BQ). This BQ would be added after the INN of glycosylated biosimilars (1). A BQ is defined as '*an alphabetic code assigned at random to a biological active substance manufactured at a specified site'* that is NOT part of the INN (**d**). Such an application for a BQ would be made by the manufacturer at the time of submission of a marketing application if the regulatory authority requires the manufacturer to do so (1).

According to WHO's proposal, the scheme would be applicable prospectively, but also retrospectively, in order to correct a few inconsistencies that already exist (e.g. naming of epoetins including a Greek letter within the INN) (1,7). It will also allow for the establishment of a database of BQs. This database would be publicly available ('*except for details of the manufacturing site(s) and any other commercially sensitive information*'), making it possible for health authorities, health professionals and patients to identify possible issues associated with patients' responses to different products containing substances with the same INN (1).

"Biological qualifiers" added to an INN: an acceptable solution, to be made mandatory. WHO's proposal for a biological qualifier for glycosylated biosimilars is a sensible compromise at a global level. However, it should be mandatorily adopted by all regulatory authorities worldwide and not only voluntary. In fact, for the scheme to be successful and to guarantee global INN consistency, DRAs must where necessary have to oblige manufacturers to apply to the INN department of the WHO for a BQ. In line with countries' commitment to protect the integrity of INNs, individual regulatory authorities must refuse to modify an INN by themselves (8).

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Notes:

a- Glycosylation refers to the enzymatic process that attaches glycans to proteins. The glycan structures are dependent of the manufacturing process (nature of the production cell, conditions of cellular culture, etc.), which can lead to slight structural differences between a reference biological and its biosimilar.

b- Thanks to INNs, healthcare professionals and patients are better informed about the true nature of medicines and are better able to spot drugs to be avoided, for example because of a risk of interactions, of dose accumulation, of contraindications or of allergies.

c- For example, a possible causal relationship was suggested between the method of production of the various epoetins and rare adverse effects (erythroblastopenia), but the same adverse effects were later reported with all of the epoetins on the market (refs 9,10,11).

d- We welcome the proposal that the BQ comprising 4 letters should include only consonants, not vowels, to avoid confusion with common stems in suffix position or with meaningful words (ref. 1).

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References:

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Signatory organisations

Health Action International (HAI) is a non-profit, independent, global network of over 200 consumer and non-governmental organisations, healthcare providers, academics and individuals in more than 70 countries that strive to improve access to essential medicines and the rational use of medicines. More info: http://haiglobal.org. Contact: bobbi@haiglobal.org.

The International Society of Drug Bulletins (ISDB), founded in 1986, is a worldwide network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of the pharmaceutical industry. Currently ISDB has about 80 members representing 41 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org.

The Medicines in Europe Forum (MiEF) was launched in March 2002 and reaches 12 European Member States. It includes more than 70 member organisations representing the four key players on the health field, i.e. patient groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is testament to the importance of European medicines policy. More info: english.prescrire.org. Contact: pierrechirac@aol.com