60th Consultation on International Nonproprietary Names for Pharmaceutical Substances
Geneva, 13-15 April 2015

Executive Summary

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
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EXECUTIVE SUMMARY

INTRODUCTIONS

The meeting was opened and participants welcomed by Dr Lembit Rägo, Head, Regulation of Medicines and other Health Technologies (RHT). Dr Rägo expressed his gratitude for the dedication of the INN Experts. There are controversial topics to be addressed such as the Biological Qualifier and the forthcoming BQ meeting in June will be crucial. Good progress is being made with the cell therapy scheme and there is close to a record number of INN applications to address at this meeting. The INN Programme responds well to these varying needs and Dr Rägo wished the Experts success with their deliberations.

The Chair, Prof. Derek Calam, formally welcomed all to the 60th Consultation, noting the presence of new INN experts and advisors. To his surprise, the number of applications continues to increase, due mainly to an increase in requests for INN for biological substances, which now represent >40% of the more than 200 applications received over this and the previous meeting. The bulk of the Experts’ work is conducted pre-meeting and he was especially grateful for the time and effort spent by them and in a timely manner. He also thanked those involved in ad hoc working parties dealing with complex biological issues, especially the working group on the Biological Qualifier which has performed a huge amount of work. He welcomed the appointment of Dr Patience Holland as the Vice-chair of the INN Expert Group, as a precaution for when the Chair is unavailable.

NOMENCLATURE of INNs

During the Consultation, a total of 143 INN requests were discussed, including:

- 103 new INN requests, including 45 for biological substances
- 37 outstanding requests
- 3 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 119 new names were selected, which are planned to be published in List 114 of Proposed INNs, while 16 requests were deferred for future discussion. Five requests were rejected by the INN Expert Group, as the substances did not conform to the criteria for INN selection. Three amendments are planned to be published in List 113 of p.INN. Two new stems/substems have been selected and 7 suffixes have been promoted to the pre-stem list.

REPORTS of AD HOC WORKING GROUPS

Biological Qualifier

A detailed re-assessment of the responses to the draft proposal showed that two third were in favour, mainly comprising industry and patient groups, but that a significant minority disagreed, comprising funding organisations, pharmacists and personal submissions, whilst a sizeable portion was in partial agreement/disagreement. Government agency responses varied with Australia, Canada and Japan in favour, Argentina, Brazil, Colombia and South
Korea against the proposal and despite the European Medicines Agency being partially in agreement, most constituent EU member states were against. Opposition was largely based on the issue of biosimilars, viz., that there would be a deleterious effect on the uptake of biosimilars.

Based upon respondents’ comments and feedback from the Regulatory Forum held on March 30, 2015, the proposal had been modified to remove all reference to biosimilars emphasising that the BQ would apply to all biological medicines, to assign the BQ to the Marketing Authorisation Holder (MAH) rather than to the manufacturing site, to expand on the explanation of the use and value of the BQ, and to clarify confidentiality and the inclusion of international data. Despite the removal of reference to biosimilars in the proposal, some regulators still held that it would affect their uptake.

Other issues discussed at the Forum included the form of the code, the use of a checksum, regional and chronological differences, the manner of application of a BQ, and the use of Greek letters for glycosylated proteins.

A random four letter code remained the preferred format. A potential alternative was a code based upon 2-3 letters for the MAH plus random 2-3 digits; but given that a 2-3 letter code would be unlikely to cover the high number of MAHs, this format was rejected, especially by regulatory authorities. The idea of a 5th letter checksum had a lukewarm reception as this would exacerbate an already non-memorable 4 letter code, and that it can only be used with appropriate software. However this will be further explored.

The need for a process to capture differences between jurisdictions and a change in the MAH have been addressed in the new draft proposal and agreed with regulatory agencies. The BQ would be applied to a product throughout its lifecycle unless comparability following a process change was not upheld. Regulators felt that it was the BQ applicants’ responsibility to report changes affecting the BQ back to the INN Secretariat. With regard to Greek letter second words, these should stay in place until such time as the BQ is widely accepted, at which time the scheme could be reviewed.

With an improved discussion on the value and use of the BQ, and clarity on access to BQ data, the modified proposal should be considerably more acceptable although some no doubt will remain entrenched against it.

**In discussion,** it was re-iterated that stakeholders want to move the BQ away from the manufacturing site to the MAH, although manufacturing site data should still be captured within the BQ database. It was also re-emphasised that the BQ would be for the drug substance and would not be part of the INN; it would only be used in conjunction with it and participants of the Regulatory Forum had agreed with this. It was further clarified that although the fine details of applying for a BQ remain to be elaborated, the assignment of a BQ would be to an MAH and initially could well be for a single manufacturing site in a single jurisdiction. If that same substance is then manufactured by the same company at a separate site using a comparable process (with assessment of comparability being the responsibility of regulators) then the same BQ would apply; that BQ will also get applied to the same manufacturer’s compound as it gets registered in different countries even although the licence holder itself may differ. Where two manufacturing sites are making the same drug substance under the auspices of the same company, but the processes are assessed by regulators not to be comparable, then the drug substances would need distinct BQ.

The value of the BQ was becoming clearer to Expert Group members. It was recognised that with the BQ being for international usage, this would give national regulators a global and valuable view of a particular drug substance. As such it will only work if regulators accept it.
and if major changes are reported back to INN for a new BQ. It could also have great relevance to Pharmacovigilance.

It was noted that comments from stakeholders reflect their different positions on the use of a BQ. Some saw its value in identification of licenced materials, some had an emphasis on prescription and avoidance of interchangeability, whilst others saw its importance in pharmacovigilance. What was becoming clear was that when the BQ is in place, regulators who sign up to it would use it actively, whilst those who do not sign up but have access to the database, would use it passively.

The BQ could also have added value in addressing counterfeit medicines. Many jurisdictions are developing systems to detect and prevent counterfeit/falsified medicines. In the EU it is the 2D barcode system and in a few years’ time all packaging will bear a 2D code containing all background information on the medicine; the BQ could easily be incorporated into the code. Its use within that code would be up to national regulators, but nonetheless its presence could put another barrier in the path of counterfeiters.

Whilst there was general antipathy towards the use of a checksum, one Expert argued in favour explaining from experience that in cataloguing 1500 chemicals, the use of a simple algorithm for checking CAS numbers found many simple errors and so was an invaluable tool.

In closing the discussion, the Chair noted that the response by stakeholders to the draft proposal had shown not only considerable support for WHO to continue to develop a scheme but that a majority were in favour of it. Different aspects of the proposal have been summarised by the ad hoc working group and some issues arising from stakeholders’ feedback had been addressed; but details remain to be developed, e.g. who makes the application, assignment to applicant rather than the manufacturing site, the content of and access to the database, the form of the code (with a current consensus on a 4 letter code), and arguments for building in a check mechanism. These would all have to be addressed by the ad hoc group. Finally, assignment of Greek letters might become redundant and this can be reviewed in some years’ time.

The INN Expert Group agreed that the ad hoc working group should continue to develop the scheme taking into account comments received. The framework of the scheme has to be on a solid foundation and present a clear idea of what it is for and how it operates, and the finer details need to be addressed. In June (2015), an open Stakeholder Forum will be held for further discussion of the scheme after which the ad hoc group will refine the draft proposal for presentation to the INN Expert Group at the 61st Consultation in October 2015. The October version could be close to final with possible adoption before the end of 2015, although it could take another year of deliberation. The Chair proffered his thanks to the ad hoc group for their contributions.

**Cell Therapy**

There had been a formal request for a cell therapy (CT) nomenclature scheme and to date one INN for CT has been assigned with several INN requests pending. Several CTs have been approved globally and so there is merit in exploring an INN scheme for them. An ad hoc INN working group had recently been set up to examine the details of the current scheme, but given the scepticism of most group members about the scheme, the value of retaining or abandoning the scheme was assessed.

The working group felt that an INN would reflect more the manufacturing process than the cells, which are complex mixtures, and a description of them cannot be encompassed solely by the name. However, INN could aid knowledge of CT dissemination, facilitate cross
border trade and assist in pharmacovigilance, and it was concluded that there remained value in developing a scheme.

The current scheme provides for long, complex and unpronounceable names, potentially containing 10-12 syllables. Some names may have similar infixes but the CTs may have different therapeutic actions. The scheme appears rigid and not suited to rapid evolution. An important issue is that the INN scheme differs from the USA and South Korea, and a distinct INN scheme would likely be confusing. Four options were suggested: (i) devise a more flexible simpler scheme with shorter names and a descriptive part; (ii) adopt the USAN scheme but omit the terminal -T, -L, -X letters; (iii) maintain the current scheme and find common ground with USAN; (iv) no INN for CTs.

The US FDA representative clarified that CBER, which controls CT products, developed the naming scheme adopted by USAN but to which USAN does not contribute. Thus any discussion on aligning the USAN name with an INN should be with CBER and not USAN. Indeed it was noted by WHO that CBER staff had been involved in discussions of an INN scheme versus the CBER/USAN scheme and tentatively there will be a meeting between WHO, CBER and USAN in the near future on this.

The Chair noted that dialogue with USAN and CBER would be important and that input from the ECBS also would be useful. The ad hoc working group should further develop a concrete proposal for discussion with the USA side. The USAN representative was agreeable to consider any new scheme and to suggest modifications.

The Chair concluded that of the four options, options one and two provided the best solution, i.e. a more flexible shorter name with appropriate information in the description, or simply take on board the USAN scheme. He emphasised the need for effective dialogue with USAN and CBER, and suggested to the ad hoc working group to find common ground with the USAN scheme and return with a new set of proposals. Any INN already created will, of course, not be changed. Pending requests for CT INN could be deferred for a further 6 months and perhaps USAN could similarly defer new requests for a short period.

**mAbs**

The INN mAbs working group, USAN and the US FDA discussed the definition of ‘humanized’ (-zu-) and ‘chimeric’ (-xi-) mAbs at a WebEx conference in February, 2015. The meeting was productive and full agreement was reached on the use of the amino acid sequence of the heavy and light chains rather than taking into account the method of antibody engineering to define ‘humanized’ and ‘chimeric’. Amino acid analysis should be performed by applicants using IMGT/DomainGapAlign. This tool is publicly available and runs against the IMGT reference directory of the *Homo sapiens* germline genes and alleles (global reference used by NCBI and HGNC, and approved by WHO/IUIS). Results are standardized and therefore identical whether performed by the applicant, USAN or INN.

The Chair congratulated the group on the successful outcome and agreed with a comment from the floor that this decision should be published, once agreed by the INN Expert Group and by USAN, as it is different from past approaches.

**Conjugated Substances**

The conjugates working group highlighted three issues, two for biological and one for chemical substances.

(i) *Pegylated biologicals*: these comprise a large group with many high profile products and two different naming approaches are used. One is a two word scheme, with the first word for the biological and the second word for the ‘peg’ moiety. The other involves one word with a
peg- prefix, although occasionally a fantasy prefix is added resulting in a -peg- infix. There is no real problem with this situation, but it is not clear to applicants why there are distinct schemes and if one approach confers something specific over the alternative, which usually it does not. The recommendation of the group is that the system for assigning pegylated compounds with a one word or two word name should be explained, possibly in the Bioreview, or perhaps the INN should simply adopt a single scheme for all future applications.

(ii) **Conjugated compounds containing two active substances**: these also comprise a large group with some high profile products and with numbers likely to increase. Normally they have a targeting molecule and an effector moiety, with the latter often being a toxin, and are given two word names. Issues relate to transcription errors with omission of the second word being the most common. Often this does not create a problem but where the targeting moiety exists as a standalone substance, transcribing errors can affect patient safety, as in the case of **trastuzumab emtansine** where one regulatory agency modified the INN with an ado- prefix to distinguish the conjugated antibody from the standalone antibody. Thus there are real clinical and naming issues which need to be addressed.

(iii) **Conjugated small molecules**: these are given two word names. A general problem is that they look like names of pharmaceutical salts for which the second component in the name is usually pharmacologically irrelevant. Hence there is an inherent risk of underestimating the importance of the second word for these two-word INN, since the second part can be important, and this needs resolution.

It was highlighted in discussion that users do not know if a conjugated small molecule is an ester or a salt, or constitutes a modified INN (INNM), which are not published in the INN List. Conjugated small molecule INN are published even if it is not known if the substance is a salt or an ester.

For pegylated compounds, there appeared to be merit in assigning a one word name, with alternative fantasy prefixes to denote differing pegylation of the same active substance. The INN Expert Group was requested to bear this in mind with future applications and the Secretariat was requested to work with the working group as to how to publicise the thoughts of the INN Expert Group on this issue. Publicising the issue could be made via Q&A’s on the website.

It was not clear that any decisions could be made immediately on the issue of conjugated biologicals with two active substances and it was proposed that interested members meet to address this issue. Other non-INN groups are also working on this with the involvement of one of the INN Experts.

**Greek Letters**

The use of sequential Greek letters in the INN as a second word to distinguish glycoproteins with the same amino acid sequence but different glycosylation features has been in place for more than 20 years. The working group concluded that where an applicant states that there is a difference in glycosylation, the INN Expert Group should accept that at face value and assign a new Greek letter as the INN Expert Group do not have the time or the expertise to challenge such statements. Where an applicant states that glycosylation is identical to a substance with a previously assigned Greek letter, the request should be rejected as the Committee again does not have the remit not the expertise to do so. Where a regulatory authority determines that glycosylation is comparable, then the original assigned Greek letter name can be applied as it already exists. The nature of the cell line does not impinge on the
above ruling. This rule should be published, say on the WHO website, so that applicants are aware of it.

In discussion, concern was expressed about applying this rule to mAbs, that they do not need the Greek letter, and that a different approach should be sought to describe mAb glycosylation. To date, mAbs have been assigned INN without Greek letters. The Chair highlighted that the Greek letter scheme was developed for heavily glycosylated proteins. The working group has clarified the situation for glycoproteins but this does not preclude that a different approach may have to be taken for mAbs. However, in the assignment of the Greek letter beta to a new mAb INN application, where an INN had previously been assigned to the amino acid sequence, one Expert wished to put on record that this experts were strongly against the assignment of any Greek letter to mAbs, adding that it would be sufficient to describe any differences in glycosylation in the Definition. It was decided that the Secretariat would write to the applicant in question to request assistance in defining the mAb and to help in writing the description.

Pegylation

Polyethylene glycol (PEG) chains begin with a methyl group, followed by the polymer part, then a chemical linker to attach it to a protein or nucleic acid. The key part of the formula is the number (n) of repeat units of the polymer, where ‘n’ can range from c. 20 to c. 880, with a corresponding molecular weight of <1,000 to 20,000 Daltons. For any given pegylated INN, this can represent a considerable change in unit mass and have a significant effect on PK. In previously published INN for pegylated compounds, descriptions of the PEG moiety vary considerably.

The working group advised that the pegylation size should not be part of the INN, that the value ‘n’ can never be defined precisely and should be preceded by circa, and that substances which differ only in the mass of the pegylation should not have distinct INN. In contrast, there is still discussion on whether when the linker changes, a new INN should be assigned or not. A major issue identified by the group is that information on the pegylation moiety needs to be provided in the Definition in a harmonised format, which needs to be developed, for example, as to whether information should provide the molecular weight or the number of units.

COLLABORATORS’ UPDATES

British Approved Names (BAN)

The British Pharmacopoeia Commission Expert Advisory Group met in February 2015 to finalise the content of Supplement No 4 to the British Approved Names 2012; Supplement No 4 should be published in August 2015.

International Council for Commonality in Blood Bank Automation (ICCBBA)

The ICCBBA was formed in 1995 as an international non-profit standards organisation whose purpose is the management of ISBT 128 (Information Standard for Blood and Transplant 128), an international information standard for medical products of human origin (MPHO). The use of ISBT 128 will enhance patient safety and ICCBBA’s vision is the global adoption ISBT 128 for all MPHOs.

Problems arising from the lack of unique blood unit identification and no common product descriptors or electronic coding information in units dispatched from various countries to a war zone, highlighted the need for an international standard. Such issues were not unique to
the war zone situation and a similar lack of standard terminology existed even amongst Wales, England, Scotland and Ireland, and so it was difficult to move products around even within the UK. Work began in 1989 in devising an international coding and labeling system for blood with the first version of ISBT 128 being released in 1994. It was extended to cover cell therapy and human tissues in 2000 and currently also includes coding for organs, milk and tissue engineering/advanced therapies. ISBT 128 is used by licensed facilities in 77 countries, is endorsed by 21 scientific and professional societies, and is used in labelling of more than 50 million products.

WHO resolution WHA63.22 recommending standard coding for human tissues and organs was an important milestone and saw the establishment of a WHO/ICCBBA joint work programme. In 2014, ICCBBA became an NGO in official relations with the WHO. A WHO initiative for MPHO highlights three strategies for global governance, including a prohibition on making the human body and its parts a source of financial gain, global use of ISBT 128 for all MPHO, and global collaboration on vigilance and surveillance of MPHO.

Key elements of ISBT 128 include a unique donation identification number, standard terminology, international product codes, and standard bar coding of information, originally linear but moving to 2D coding for product labels. Generic terminology is based on a high level class name and a wide range of flexible attribute values, and allows for variable levels of detail in the product description. Technical advisory groups cover a variety of product categories and work with a variety of professional societies in publishing internationally agreed standards for terminology and labelling.

ICCBBA is aware of the WHO proposal for assigning INN to cell therapy products and expressed a desire to work with INN to develop the optimal solution for coding and labelling of them. ISBT 128 is already used by over 600 cell therapy products. As many of these are approaching licensure it is opportune to discuss how ISBT 128 and INN can work together, for example an ISBT 128 product description code can be provided for each cell therapy INN, or a generic ISBT 128 product description code can be used alongside the specific INN name.

The Chair agreed on the value and desire for INN to work with ISBT 128 and to consider the ways the two bodies can work together, to examine to what extent the specific nomenclature systems of the two organisations can be meshed together. Each INN application is assigned a 5 digit sequential reference number and so every INN published has behind it this unique 5 digit numerical code and this might provide a link between INN and ISBT 128. It was agreed a small working group between the two organisations could be useful and the INN Secretariat was requested to take this forward.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

The mission of the PMDA includes the preparation of draft Japanese Accepted Names (JAN) and the Japanese Pharmacopoeia (JP) as it is the Secretariat for both activities. The JAN expert committee has 17 members of varying disciplines and usually meets four times per year although recently a fifth meeting had been held due to an increase in JAN submissions. In 2014, approximately 60 JAN were submitted and published.

United States Pharmacopoeia (USP)

The USP operates on a five year cycle with each cycle initiated with a major convention during which the membership of expert committees is changed. The current cycle began in 2015 and already the next Convention, ‘Insight 2020’, is being planned with 2020 being the bicentennial of the USP. A new chief scientific officer, Dr Japp Venema, has been appointed; Dr Venema has a background in biologics. On the technical side, the schedule of publication has been changed to align with the calendar year, so that printing time is now in January, with the first 2015 edition on its this way.

United States Approved Names (USAN)

The 2015 Winter USAN Council meeting took place on January 8-9, 2015 in Manalapan, Florida where names for 35 drug substances were reviewed and discussed.

Four new infixes to be used with existing stems were approved at this meeting (-sudil, -gr(o)mab, -dustat, -dostat). One new stem was approved and added to USAN’s stem list (-vancin). Two stems were revised (-ibat revised to -ixibat and -siranib revised to -siran). Nine stem definitions were revised to harmonize with INN definitions. Thirty INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 60th INN Consultation.

The 2015 summer meeting of the USAN Council is scheduled to occur July 16-17 at USP Headquarters in Rockville, Maryland.

Through to March 2015, USAN staff processed, researched and made recommendations for 46 new USAN applications and forwarded this information to the USAN Council in 2015. Also through March 2015, 17 USAN and 10 modified USAN were adopted during 2015 and revenue was realized for an additional 2 negotiations.

United States Food and Drug Administration (FDA)

The FDA representative informed the meeting that the FDA Commissioner had resigned after six years in office; an interim commissioner had been appointed until a new one is found. The FDA is working on the development of guidance for biologics, including related biologicals and biosimilars, including nomenclature guidance; however, the document will have to be approved high up at the level of HHS to cover legal, economic and insurance issues. Hopefully it will be available soon for public consumption.

WHO Collaborating Centre for Drug Statistics Methodology, Norway

In 2014, the Centre assigned 99 new Anatomical Therapeutic Chemical (ATC) codes of which 41 were for drug combinations; the large number of combination products was partly due to Turkey adopting the ATC coding system and they had many to assign. At the spring telephone meeting, the expert group assigned 30-40 new codes. Complicated issues can be difficult to discuss over the phone and so are better dealt with at the face-to-face autumn meeting. Items on the working agenda include an option to reclassify Hep C drugs into a therapeutic group and sub-dividing blood glucose lowering drugs into smaller groups as the group is getting large. The Centre expressed interested in the new BQ proposal and how it compares to ATC coding.

World Customs Organisation (WCO)

The WCO promotes the facilitation of international trade, revenue collection and the protection of society, public health and safety. Its activities relating to INN include the Harmonized System classification of INN which is important for national customs tariffs. In 2015, 200 new products have been examined and classified and so far WCO has classified
more than 4,000 INN. Classification of new INN sometimes requires additional chemical, structural and pharmacological information, and WCO will usually approach WHO for this. The WCO has requested a WHO INN staff member to attend meetings as an expert and this occurred for their January 2015 meeting. The WCO is highly appreciative of the support given by and the cooperation of the WHO/INN and would like this to continue.

IDMIS UPDATE

The Chair expressed his gratitude for the successful WebEx meeting that the Secretariat had recently organised; this had involved a considerable amount of work on the WHO’s part with participants joining from all around the world. With the set-up involving visuals of participants onscreen and full video shots of speakers, it had made chairing the meeting so much easier.

With another INN WebEx meeting pending, the IDMIS manager reiterated the procedure for joining the meeting online with the option of phone or computer for audio, with phone giving the better quality of audio. If need be, participants can ‘chat’ with the IDMIS manager online.

CLOSE of MEETING

The Chair thanked all participants and the Secretariat for the work done before and during the meeting. There were a number of issues to be taken forward before the October Consultation and all will be busy over the summer.

NEXT MEETING

The 61st INN Consultation will take place at WHO Headquarters, Geneva, 13-16 October, 2015.
Participants were welcomed to the Open Session by the Chair, Prof. Derek Calam, who added that the INN Expert Group recognised the value of face-to-face discussion with INN applicants who have issues and also that the Open Session had expanded to include comments on general INN policies. Despite the meeting title, in reality it was a closed session with at least some information being commercially confidential; until approved and published, the proceedings were to be kept confidential and not for public dissemination.

Dr Raffaella Balocco-Mattavelli, Group Lead, INN Programme, highlighted that the agenda contained several presentations on the proposed Biological Qualifier (BQ) and informed the meeting that following publication of the BQ proposal the previous August, more than 100 comments covering more than 300 pages were received. Since then, the BQ Working Group had compiled and analysed the comments, which were summarised at a recent Regulatory Forum attended by regulators from developed and developing countries. Overall, comments indicated that a good majority were either in partial or full agreement. The process would continue and comments would be shared with stakeholders at an open Front Page meeting on 16 June (2015).

**PRESENTATIONS on BQ PROPOSAL**

**GPhA (Generic Pharmaceutical Association)**

GPhA believes that the existing WHO INN nomenclature rules, focusing on the drug substance, are adequate and that many products successfully share INN. Clinicians cannot be expected to remember both brand name and INN, and patient safety is best assured when clinicians know which biologics share active ingredients by having shared INN. INN have never identified the final product, with other identifiers being used for product recognition such as the brand name, company name, and lot numbers. Even packaging design features distinguish products. It has been argued that distinct BQ are needed for safety. Drugs must be identified by healthcare professionals for accurate prescription and the INN helps identify the active ingredient regardless of language. Furthermore, biological products are typically dispensed in a controlled manner often inside a hospital or clinic with detailed dispensing records available for each patient.

For years innovative biologics undergo post approval changes to improve and change product profile with no change in INN or brand name. Similarly if comparability is established between a reference product and a biosimilar no new INN is required, nor should a new BQ be proposed.

The twenty or so biosimilars now approved in Europe are subject to robust monitoring with the most important identifiers being brand name and batch number. Since late 2008 more than 99% of the post-marketing reports received by Hospira regarding Retacrit were successfully identified as Hospira’s product without the need for INN differentiation. Also, systems are in place to query additional product identifiers should the INN alone be conveyed in a report, whilst barcoding and serialisation approaches being introduced will further enhance tracking.
The USA market place is now opening up to biosimilars with the first one, Sandoz’s Zarxio being approved in March 2015 with the temporary name filgrastim-sndz. The FDA is still drafting nomenclature guidance but GPhA and others still advocate that a unique INN is not necessary to distinguish biosimilar products and that the same INN should be used.

Recently the Australian Therapeutic Goods Administration announced that it is reconsidering its position in biosimilar naming and that in the interim, biosimilars will use the ABN without a specific biosimilar identifier. GPhA supports this stance. The GPhA recommends to keep the same INN for innovative and follow-on biologics. If the INN Committee need to establish a BQ, it needs to be voluntary, be used consistently, be applied to all biologics and be applied retrospectively. A BQ, if used, should not be required for prescribing and should not include a manufacturing site designation. If a modifier is to be used, the clearest format for a BQ is the MAH’s name. There needs to be improved guidance from the INN Committee on how to use a BQ to avoid unintended consequences that could lead to unequal adoption, impact patient access and potentially impact patient safety.

**European Generic medicines Association (EGA)/European Biosimilars Group**

The EGA is grateful to the INN Programme for the efforts being shown to avoid a proliferation of naming schemes for biologics and for listening patiently to diverse opinions. The EGA considers that any identification scheme should be simple, with the simplest scheme making use of a unique product tradename or brand name, or a combination of the INN and the company name. The greater the number of elements that needs to be reported, the higher the likelihood that something will go awry. There are already a lot of identifiers; the EU has a new 2D barcode arising from the Falsified Medicines Directive, the USA has its National Drug Code, and there is the lot number. Is there really a lack of identifiers? There is a need for good systems, but they must be simple for everyone, systems that can be followed through so that if anything is missing it can be followed up. Beyond good systems existing today, there is a need for good discipline, good training, and an obligation for healthcare providers to report. No system can ever compensate for the failure of healthcare providers to maintain complete and accurate records.

EMA pharmacovigilance data currently show good follow-up with a high level of reporting brand names (90%) although there is a problem in reporting lot numbers (22%). AE reporting data from Sandoz on marketed products covering many millions of patient days show 94%-98% identification with robust brand name and sometimes INN being reported. This shows the current system to be working well. Biologics form a small subpart of drugs and a system introducing a new BQ for a specific class of products could increase the risk of errors in prescribing, dispensing and reporting. A random element for the BQ is especially challenging; a name with a meaning would be easier to remember whereas a random sequence of consonants will be much harder to remember resulting in a high likelihood of it being misspelled or even not recorded at all.

Whatever happens, what gets implemented should not do more harm than good. Listening to stakeholders is good but any new identifier must be tested systematically with all key stakeholders by an independent institution, comparing it with the current system (trade name or INN + company), assessing safety risks and added value. Unless it is clear what the need is and whether or not the proposed change effectively and safely addresses this need, no change should be introduced. In context, the current system introduced over 20 years ago by WHO Resolution WHA16.19 to encourage the use of the company name alongside the INN for multisource products introduced after patent expiry has worked well in many countries. So what is the need for change now? Is a new identifier really simpler than the company name? There is a lack of background information on what is trying to be achieved and the
EGA continues to support the current system (trade name or INN + company name) as the risks and complexities of a new identifier outweigh the benefits.

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

The IFPMA sees the BQ to be a unique tool linking pharmacovigilance (PV) to biological drug substances. Globally there are many ways to define products robustly but only the EU has legislation addressing PV for biologicals and unfortunately the effectiveness of PV varies from country to country. The BQ may provide this global link. So the IFPMA welcomes the BQ and is supportive of WHO’s efforts to develop this coding system. From the IFPMA’s point-of-view, the BQ should be assigned to all biological drug substances, both proactively and retrospectively, and should be used alongside the INN in all circumstances when the INN is used. A random 3 or 4 letter (excluding vowels) code should be used. The BQ should be linked to the parent company or entity responsible for licensure globally and it should be independent of the regulatory pathway; it should not be linked to the manufacturing site or regulatory jurisdiction. Linking the BQ to the entity legally accountable for the DS and the DP within different regions would avoid confusion, proliferation of BQs, and assign clear responsibilities for tracking and PV.

With regard to the form of the code, the IFPMA would prefer fewer letters to aid memorability. A 3 letter code would provide 8,000 codes and should satisfy current and future demand. The IFPMA considers the code to be an INN qualifier and not a standalone identifier. It was also stressed that the code should not be linked to the manufacturing site, adding that the manufacturer’s quality system and regulatory compliance assures manufacturing and product consistency between alternative sites.

The IFPMA vision is that there would be universal active use of the BQ. However, cognizant of the fact that some regulatory authorities may not adopt the BQ and use it passively, where this happens, it will be important that the licence holder is not required to have different labels and that the BQ can be part of labelling and product information in jurisdictions not actively using the BQ.

Finally, during implementation, a phased roll-out should be considered, perhaps with some regulatory agencies taking the lead combined with physician, patient and pharmacist surveys. Feedback could be used to improve implementation and it is incumbent on WHO to recommend global implementation. Whatever mechanisms are adopted should facilitate and not delay implementation. In summary IFPMA continues to support a BQ and supports ongoing dialogue. The ideal BQ should be a unique global identifier used in conjunction with INN especially as a tool for PV. All regulatory authorities should implement the BQ for all biologics, both proactively and retrospectively.

Alliance for Safe Biologic Medicines (ASBM)

Since its inception in 2010, the ASBM has conducted several physicians’ surveys on biologics naming and presented the data to health ministries, at conferences and in a scientific publication. The Alliance fully understands the benefits of biosimilars but clear product identification is absolutely essential to ensure clear communication, clear prescribing and dispensing at all points, accurate tracking, and transparent accountability.

In surveys conducted in Canada, the EU and the USA, the vast majority of physicians consider a biosimilar with the same INN as the reference product to be structurally identical to the reference product, whilst significant numbers report the INN only in adverse event reports. In the Canadian survey, there was overwhelming support for distinct INN for every biologic and biosimilar.
The US FDA has recently registered its first biosimilar using a suffix linked to the company on the INN as a temporary means of identification. Since it is absolutely essential that patients know what they are receiving and that physicians know what they are prescribing, there are advantages of linking the suffix to the company.

Pharmacists increasingly have to balance efficacy, safety and cost, and need to be able to distinguish one biosimilar from another in prescribing, dispensing and PV, since they are not identical. Pharmacists need a good distinguishable name and occasionally industry has been asked in the past to change a name because of similarity. At a recent technical workshop, two thirds of the pharmacists present had not heard of or could not define a biosimilar. About half thought that they had identical structures to reference products, whilst 41% believed that a biosimilar with the same INN as its reference product could be safety switched between them with no added risk. In conclusion, from a patient perspective, it is important to use the correct vocabulary, and the ASBM encourages all regulators to adopt the WHO’s BQ proposal.

Comments from the Chair

The Chair and the Expert Group were reassured to hear the broad support for the BQ approach. Regulators are also broadly in favour and have similar questions and concerns on the details. If the scheme is adopted there is strong support for retrospective application; however it is becoming apparent that there would be major legal problems in some jurisdictions in applying the scheme retrospectively. This may not preclude limited retrospective implementation and once the scheme is established there may be ways found to broaden retrospective application such as when substantial manufacturing changes are made to an authorised product or DS. Ultimately, the Expert Group may still recommend retrospective application and it would be up to regulatory agencies whether or not to adopt.

The Chair also noted that it was clear that details matter. The INN Group was asked to and, in 2014, produced a draft BQ scheme that produced a far greater response than imagined. From these responses, and responses from the Regulatory Forum, a new draft has been developed, but until the framework has been sufficiently developed, there is no point in the fine detail. One presentation at this meeting suggested a 3 letter code might suffice. In the EU there are more than 40K MAH codes issued mostly for small molecules, but with an increasing number of biological drugs being developed and the need to establish a system that will last 10-20 years, 8,000 BQ codes using a 3 letter format is unlikely to be enough, and a 4 letter code is the best compromise. However, 4 letters or consonants will not be memorable and may give rise to transcription errors, and so a built-in safety feature which would check that the code is correct and not mis-transcribed, is a possibility. This is the type of fine detail being looked at.

The Chair expressed his thanks for the valuable contributions and comments made on the BQ scheme by stakeholders.

PRESENTATIONS on INN APPLICATIONS

Gilead.

The company petitioned the INN Experts for the name andecalizumab for their mAb GS-5745 as this would reflect its claimed humanised rather than chimeric origin. GS-5745 has been developed for treating inflammatory disease and was humanised using modern technology to develop a safe product with reduced immunogenicity whilst preserving its physical properties and high potency. A chimeric designation could misinform healthcare
users and could work against the company in bringing forward a safe mAb with a unique mode of action.

The parental antibody was chimeric and was humanised by removal of mouse framework regions. Composite multi-germline analysis indicates GS-5745 is more human than mouse. Defining what is human, what is non-human and what is humanised is problematic. The IMGT CDR definitions are limited and non-IMGT CDR residues and Fw residues are also important as there are numerous antigen contact regions even beyond the Kabat CDR definition. Using Z-score analysis, both GS-5745 heavy and light chain humanisation has resulted in a clear shift away from mouse and into the distribution of human sequences. Such analyses shows GS-5745 to be more human than mouse and more humanised than being mouse or chimeric. The company felt that the INN definitions of chimeric and humanised were slightly out of date as the current humanised definition does not allow for the use of non-human germline Fw residues. Fw changes are almost always required to reconstitute comparable antigen binding (to that of a non-human parent) and GS-5745 consistently fits in with several licensed mAbs designated humanised.

**Jazz Pharmaceuticals**

The name *dexamfetanol carbamate* proposed by the INN Experts for compound JZP-110 has been rejected by the company as it is too suggestive of dextroamphetamine with JZP-110 having a different chemical structure, different mechanism of action and different behavioural effects. Furthermore, it has a *dex-* prefix but is not dextrorotatory, has an *–amfeta-* body but is not phenethylamine, and is not an alcohol or phenol and so the *–ol* suffix is not appropriate. In terms of pharmacology, JZP-110 is an uptake inhibitor of dopamine transporters, and unlike amphetamines it does not promote the release of monoamines, does not produce rebound insomnia, and in a rodent model did not have the abuse liability of traditional stimulants.

JZP-110 does not fit into an established stem class, and as a phenylalanine derivative, a *–lanine* suffix would be appropriate. In contrast, *–fensine*, *–faxine* and *–bamate* stems would not be appropriate for reasons provided. The name *dexamfetanol carbamate* could also be clinically problematic due to confusion with amphetamine effects, medication errors due to the misuse of the *–ol* suffix, and potentially serious errors due to phonetic similarity to fentanyl. Such problems would be circumvented with a *–lanine* stem. In conclusion, the proposed name *dexamfetanol carbamate* is inaccurate and clinically problematic; a *–lanine* suffix would avoid these problems and place JZP-110 alongside a structurally and pharmacologically similar molecule – *afalanine*. The company respectfully requested a reconsideration of the names originally submitted and provision of a *–lanine* stem.

**CLOSE OF MEETING**

Following this final presentation, the Chair drew the Open Session to conclusion, thanked all presenters for coming to the meeting for a very short time, and on behalf of all experts noted that the presentations are helpful for our general discussions and for individual applications where there is dialogue ongoing between INN an applicants.