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59th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 14-16 October 2014

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)
World Health Organization, Geneva

59th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 14-16 October, 2014

EXECUTIVE SUMMARY

INTRODUCTIONS

Participants were welcomed to the 59th INN Consultation by Dr Kees de Joncheere, Director of Essential Medicines and Health Products (EMP). Dr de Joncheere explained that for the first time, three normative expert committees - the INN Expert Committee, the Expert Committee on Biological Standardisation (ECBS) and the Expert Committee on Pharmaceutical Preparations (ECPP) - are meeting concurrently. This will provide opportunities for cross working and also to promote the normative work of these committees when the chairs meet together with Dr Chan, the WHO DG.

At the 2014 World Health Assembly items that impact on EMP included discussion on access to medicines, falsified medicines, antimicrobial medicines, and the adoption of resolutions on strengthening regulatory systems and access to biotherapeutics, an important issue for many countries, including emerging and middle income countries. At the recent ICDRA meeting, which WHO convenes every two years, there was a pre-meeting on biotherapeutics with one issue being nomenclature.

The 59th INN Consultation has a busy agenda with a record 108 new requests, along with discussions on a new scheme for CTPs, the draft biological qualifier, conjugated mAbs and vaccine definition. Dr de Joncheere thanked participants for their presence and the hard work performed between Consultations.

The Chair, Prof. Derek Calam, added his welcome to participants. The importance of the INN is being recognized within WHO by the arranging of a meeting of various chairs including himself with the DG, at which he will bring the achievements and challenges of the Group to her attention. A key part of the work of the Group takes place between meetings and the Chair and indeed the Secretariat is very grateful to the Experts for their contributions. The Stakeholders meeting continues to be useful and interesting and the Chair noted the increasing extent of policy presentations in addition to presentations by specific INN applicants.

The Manager of the INN Programme, Dr Raffaella Balocco-Mattavelli expressed her gratitude to the Chair, to the experts and the observers for their contributions, and also for the tremendous support provided by staff of the INN Programme. Two new members of the Group, from China and from Italy, were welcomed.

NOMENCLATURE of INNs

During the Consultation, a total of 144 INN requests were discussed, including:

- 108 new INN requests, including 51 for biological substances
- 35 outstanding requests
- 1 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 121 new names were selected, which are planned to be published in List 113 of Proposed INNs, while 14 requests were deferred for future discussion. Seven requests were rejected by the INN experts, as the substances did not

conform to the criteria for INN selection. Two requests are the INNM of already existing INN. One amendment is planned to be published in List 112 of pINN. Four new stems/sub-stems have been selected and 5 suffixes have been promoted to the pre-stem list.

REVIEW OF BIOLOGICAL QUALIFIER

Following the 58th Consultation held in April 2014, the draft Biological Qualifier document was further modified based upon extensive internal comment after which it was placed on the WHO website with a request for comment from external parties. Over 100 comments were submitted from a mix of organisations, institutes, individuals and companies. In addition, Dr Balocco-Mattavelli has reached out to stakeholders whilst travelling to discuss and receive comments. The BQ scheme was also presented at the ICDRA conference in August in Brazil with good discussion with industry and academics although some developing country participants felt that the standards being created by the INN Programme were too high and prevented developing countries getting appropriate medicines.

Of the 100 plus comments there was a spread of opinion from 'strongly agree' to 'strongly disagree' although two-thirds of respondents provided some level of agreement. An analysis of comments by type of respondent, showed that regulators and 'institutions' were least in favour of the BQ, whilst industry, academic and collaborating centre respondents were most in favour. 'Other' respondents (patient groups, pricing associations, user groups), which provided almost half of the comments received, were about two-thirds in favour. Pharmacist associations were generally not in favour, especially those in the USA. A sub-group of the INN Experts will be formed to assess all comments in detail, many of which were very constructive, and to devise a way forward prior to the next Consultation.

The Chair noted that comments generally divided into three groups, those that disagree, not seeing a particular use of the BQ, those comments that were neutral and not sure about the value of a BQ but not particularly against it, and those in favour, and the Chair was especially struck by the force of comments from patients and users groups (in favour of the scheme).

The FDA representative added that whilst there were no comments from the FDA, the BQ draft is being discussed and once comments are cleared they will be submitted to the WHO. The USP is in strong agreement with the scheme.

It was also noted that many of those providing negative comments generally did not appear to understand the scheme, and there seemed to be a communication issue. A particular area of confusion was the role of the BQ, whether it is for prescribing or pharmacovigilance or other purposes. But with it being voluntary, as is the INN itself, it would be up to the user to decide how a BQ would be best used within a particular jurisdiction. There are countries that potentially do not need the BQ.

The Chair, in closing the discussion, noted that the 2D bar codes being developed globally to help in the identification of medicinal products, especially to help combat counterfeit and falsified medicines, can contain a huge amount of information and the four letters of a BQ would comprise merely a half line of the 2D code. With the level of support for a BQ being at least half of the respondents it seems that the Group could develop a potentially useable BQ.

CELL THERAPY ISSUES

The most recent version of the draft nomenclature scheme for cell therapy products was presented and discussed. The scope has been expanded to include autologous cells in

addition to allogeneic and xenogeneic cells. The structure of stems and substems is relatively unchanged with the basic stem *-cel* to represent all cell therapy products preceded by a substem *-ato/lo/xo-* for the type of cell (autologous, allogeneic, xenogeneic, resp.). Stem cells are to be identified with the additional substem *-tem-* plus a further indicator of the origin of the stem cell. Taking on-board a comment from the FDA, the additional infix *-def(i)-* will be used to indicate a cell that has differentiated from a stem cell; in such cases the origin of the stem cell will not be indicated although the substem *-tem-* will be retained. Infixes to indicate manipulation or modification of the cells have now been defined. Infixes for specific cell types and primary tumour types are designated. Where a tumour type infix is used, the use of the infix *-tu-* may be redundant.

Genetically modified cells will continue with a two word name, the first word indicating the nature of the modifying gene, as in gene therapy product nomenclature, and the second word indicating the cell type. Any vector used in genetic modification will not be indicated within the name.

The USAN scheme will maintain the infix *-tu-*, and uses only one word for genetically modified cells which incorporates an infix for the genetic modification. Indicating the type of a differentiated stem cell in the USAN scheme is desirable although this has not been fully resolved.

It was noted that in the EU, a descriptive common name is currently applied for cell therapy products. These names tend to be long but have the advantage of being more informative than the names resulting from the proposed INN scheme. In the absence of an adopted INN scheme some companies may insist on applying the USAN also in the EU and this is not an ideal situation as it may cause confusion.

The TGA, Australia, representative noted that some of his colleagues welcome the inclusion of autologous cells since if they are not included there is little point in having a cell therapy nomenclature scheme. In contrast, other colleagues prefer a more descriptive system such as the ISBT (International Society of Blood Transfusion) 128 standard technical specification.

The Chair, in remarking that autologous cells concern a commercially based process and not a specific product, proposed that the Group is not yet ready to name CT products and that any current applications for a CT INN get deferred, unless it is more appropriate to name them under the gene therapy scheme. The Chair further proposed that the Secretariat consider how to move forward whether by consultation or meeting of interested parties, to discuss the matter further and provide guidance for the Group in developing a scheme for very complex cellular entitles, and whether autologous cells, which are unique batches of material from single patients, should indeed be included.

BIOREVIEW

Vaccine policies

Several peptide vaccines and one recombinant vaccine have been given INN. Also, an oncolytic virus and several viral-based gene therapy products have been given INN. In light of the increasingly defined structure and varied nature of vaccines, and increasing applications for INN for vaccines or vaccine-like products, it is necessary to revise Bioreview Item 3.10 General Policies for vaccines, which was last updated in 1998, and Item 4.23 Peptide vaccines/recombinant vaccines. The description of recombinant vaccines in Item 4.23 especially needs revising or replacing.

Several definitions of a vaccine exist in various documents and it should not be the role of the INN Group to further define a vaccine; nonetheless, the Bioreview Items highlighted above require consideration. It was proposed that a small group redraft these Items and table amendments at the next Consultation. The Chair would also seek advice from the ECBS to obtain its perspective on how the INN Group should handle INN for vaccines.

Conjugated substances

At the previous Consultation, it was suggested that when an INN is requested for a conjugated mAb where no pre-existing INN exists for the naked mAb, that an independent application is also made for an INN for the naked mAb. This suggestion has been published as a rule and is currently being followed. This however raises the question as to whether such a rule should be applied to all conjugated substances, bearing in mind that decisions on INNM are made without necessarily having an INN for the unmodified substance.

The Chair requested that comments are obtained from the INN Biologicals Experts and that the expansion of the rule for obtaining an INN for a non-conjugated entity alongside that for a conjugated substance is distributed for consultation and whether it is justified or not.

PUBLICATION ISSUES

Health Canada has received comments from stakeholders about the risk of dispensing errors between *trastuzumab* and *trastuzumab emtansine*. Canadian cancer facilities were aware of errors reported during trials of *trastuzumab emtansine* and that the US FDA had modified the INN to *ado-trastuzumab emtansine* for the US market. HC uses the INN *trastuzumab emtansine* and makes no judgment on the *ado-* prefix. By time the conjugated mAb was marketed in Canada, HC had issued a communication to alert about the potential for confusion and recommended the use of the brand name. However, following this, two near misses were reported. HC would like to see a standard set of tools or strategies developed to mitigate the risk or error. So far, only fragmented risk mitigation strategies, i.e. some software modified to include the generic name, have been put in place and sometimes the brand name has been added to the end of the INN. The two INN remain in close proximity in software although one facility has added the brand name to the software. HC is also aware of *ado-trastuzumab* being used by itself in paperwork, without the *emtansine*, and this could further generate problems. Regardless of risk mitigation strategies adopted, there will always be a risk of error without a name change. However, until there is a proper introduction of risk mitigation strategies, HC will not be moving towards a name change.

The INN Programme has received a letter from HC forwarding concerns expressed by the Canadian Association of Provincial Cancer Agencies (CAPCA). Whilst recourses available to the INN Committee are limited, the Chair remarked that the INN Committee should not distance itself from the issue. Is there a fault in the policy of two word names or simply with this particular one, noting that two word INN have existed for a long time? Alternatively, can the order of the names be reversed or substituted with a one-word name? However, it was noted that there are several conjugates with *emtansine*, with many more in the pipeline, and any attempt to place *emtansine* first is likely to lead to other problems such as administering the wrong mAb. Many of the issues with this two word name occur in its usage, i.e. are human errors, and not INN errors, and so to some extent are out of INN control. The issue of an alert is also a possible course of action.

Ultimately, HC wants to see greater use of risk mitigation strategies first before taking any further action. INN composed of two words are not a basic problem for healthcare systems; most are used without problems and errors can and do occur with one word names also.

Changing a recommended INN can only take place after a formal government request to change in light of a serious public health issue and must have the approval of all 194 WHO Member States.

COLLABORATORS UPDATES

British Approved Names (BAN)

Supplement 3 to BAN 2012 was published in August 2014.

Chinese Pharmacopoeia Commission

The Chinese Pharmacopoeia Commission seeks more contact and cooperation with the WHO INN programme in order to increase harmonisation not only in biological nomenclature but also with biological standards. The Commission has a specific division for biological standards and drug names, and has been working on names in the biological area in recent years. A national guideline for Similar Biotherapeutic Products will be out for public comment soon.

Post-meeting note: the guideline was released by the CFDA on 28 Feb 2015; the Chinese version is available at: http://www.sfda.gov.cn/WS01/CL0051/115102.html.

International Union of Biochemistry and Molecular Biology (IUBMB)

Recent changes include the addition of 102 new enzymes, 3 new sub-subclasses, 26 modified entries, 4 transferred entries and 4 deleted entries.

International Union of Pure and Applied Chemistry (IUPAC)

Work continues on identifying errors and inconsistencies in the new Blue Book. Details are available from http://www.chem.qmul.ac.uk/iupac/bibliog/BBerrors.html.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

The preparation of Japanese Accepted Names (JAN) takes place in consultation with the JAN Expert Committee. Normally the Committee meets four times per year, but for 2015 there will be five meetings to deal with an increasing number of submissions. In the first half of 2015 there were 20 applications for JAN and the Japanese Pharmacopoeia (JP) was updated accordingly. The 2nd Supplement of the 16th edition of the JP has been published and an English version is now available online. The JP 17th edition is due to be published in spring 2016.

Therapeutic Goods Administration (TGA), Australia

The Biological Qualifier continues to be discussed at the TGA. The policy of the TGA is wherever possible to adopt INN for Australian Approved Names (AAN) and Australian Biological Names (ABN). Under the auspices of a labelling and packaging review, the TGA is rationalising AAN retrospectively to conform to INN. Finally, there is no further information available at this time on whether there will be a merger of Australian and New Zealand regulatory authorities.

United States Approved Names (USAN)

The 2014 Summer USAN Council meeting took place July 10-11 in Chicago at AMA headquarters, where names for 27 drug substances were proposed and approved. Five new stems were approved at this meeting (*-apt, -fadine, -forant, -manid* and *-siran*). Two sub-stems were approved (*-becestat* and *–metnib*). Forty INN applications for proposed USAN

were prepared and forwarded to the INN Programme to be discussed at the 59th INN Consultation.

Dr Gail Karet of USAN spoke on the topic "Generic Naming in the United States" at the 89th Conference of the Pharmaceutical Trade Marks Group on October 8, 2014 in Chicago.

The 2015 winter meeting of the USAN Council meeting is scheduled to occur January 8-9 in Palm Beach, Florida. Through October 2014, USAN staff processed, researched and made recommendations for 123 new USAN applications and forwarded this information to the USAN Council. Also by October 2014, 72 USAN, 29 modified USAN and 2 revised USAN were adopted during 2014. Revenue was also realized for an additional 10 negotiations.

United States Food and Drug Administration (FDA)

FDA is currently considering the appropriate naming convention for biosimilar and interchangeable products licensed under the pathway established by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) enacted as part of the Patient Protection and Affordable Care Act. FDA has opened several dockets for public comments on issues related to the proposed biosimilar products and interchangeable products, including issues related to naming. FDA is carefully reviewing and considering the comments submitted to these public dockets and the views of stakeholders, including comments and views that relate to the WHO INN proposal for a biological qualifier. FDA will take into account all comments received, as well as other relevant considerations, in finalizing the existing biosimilar guidance documents and developing future policies regarding biosimilar products and interchangeable products, including policies regarding naming. Because FDA's process regarding the development of policies regarding the naming of biosimilar products and interchangeable products is ongoing, it is premature for FDA to comment on any proposals.

United States Pharmacopoeia (USP)

The USP is not part of the federal government and, like other bodies, is awaiting the FDA statement on SBP's. It participates in discussion of SBP's in the USA and presents its position at meetings and conferences. The USP will not directly use the proposed Biological Qualifier but basically supports the concept.

The 2015 USP Convention is a membership meeting held once every five years to bring together Delegates from USP Convention Member Organizations to discuss and provide guidance on issues relating to USP's future. It will take place in Washington DC in April. At the meeting, Delegates will elect USP's Council of Experts, USP's Officers and Trustees, adopt resolutions that advance the mission and vision of USP, and confirm USP's structure and operational framework as they review and vote upon amendments to USP's bylaws.

UPDATE on IDMIS

There have been no new features added to the electronic IDMIS system, although Experts were reminded on the more important features of entering comments on applications both pre and post meeting. Experts were also reminded about the function for checking new requests for inadvertent stem inclusion and of the link to the WIPO Madrid International Trademark database. A link from the main page to the shared system will be inserted.

FEEDBACK FROM THE CHAIR

The Chair of the INN Committee along with the Chairs from the ECBS and ECPP met with the WHO DG for the first time. The INN Chair outlined the work of the INN Group, the

number of names being requested, issues with biological qualifiers and the need for the INN to collaborate with the ECBS on vaccine and cell therapy issues. With regard to the work of the INN Group, the DG commented that Médecins Sans Frontières, which has criticised WHO for having too high standards, were in fact in favour of the BQ scheme. The meeting with the DG was a milestone for the Group and shows recognition of its work.

CLOSE of MEETING

The Chair thanked participants for their contributions both before and during the Consultation, and also Prof. Malan for temporarily taking over the Chair whilst he (Prof. Calam) briefly attended a separate meeting.

NEXT MEETING

The 60th INN Consultation will take place on April 13-15, 2015 at WHO headquarters in Geneva.

OPEN SESSION for INN STAKEHOLDERS

59th Consultation on International Nonproprietary Names (INN) for

Pharmaceutical Substances

Geneva, 14th October 2014

The stakeholders meeting accompanying the 59th INN Consultation was opened by **Dr Lembit Rägo**, Head of Regulation of Medicines and Health Technologies. The open sessions are excellent venues for hearing the views of stakeholders and it is useful that in addition to individual companies presenting on a particular INN or substance, that associations are also present to share their views on important topics. The WHO cannot promise that views expressed will necessarily be taken fully on-board as it has to balance the input to achieve the right result. The stakeholders were welcomed to the meeting and with a very busy schedule, Dr Rägo handed over to the Chair to guide participants through what will be a very intensive meeting.

The Chair, **Prof. Derek Calam**, similarly welcomed all present, highlighting that these meetings exceed expectations. The agenda has broadened from clarification on individual applications into policy issues, and this one especially will discuss the vexed question of biological qualifiers (BQs). Since the previous meeting in April 2014, comments have been received on the draft BQ proposal. They have not yet been discussed but will be at the following INN plenary meeting and comments today will also be taken on-board after which the INN Group will attempt to proceed with the BQ.

The Chair emphasised that although the meeting is called an open session with stakeholders, commercially confidential matters or policy issues will be aired. Questions and comments from the INN experts are not to be construed as INN policy and all proceedings should be kept within the room and the people present. In the past some pre-released reports were wrong and misleading, so it is best not to comment on proceedings until the meeting report is finalised.

Dr Raffaella Balocco-Mattavelli, INN Programme Manager similarly welcomed all present, companies, associations and the INN experts.

BQ RELATED PRESENTATIONS

Generic Pharmaceutical Association (GPhA)

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Biosimilars can provide significant savings to patients in regulated markets and WHO naming guidance for biologics is important for fair competition.

INN naming has been simple and intuitive and this should not be changed. The brand name is what distinguishes final formulated products with the same active ingredient whereas the INN has to represent the active ingredient and be non-proprietary. This current system works for biosimilars, for example Neupogen® and Nivestim® have unique brand names, unique packaging, unique lot numbers, and the same INN (filgrastim) for the common active ingredient. It is not clear why the addition of a BQ would provide any additional value.

Safety is enhanced by globalisation of non-proprietary names, which need to be kept simple. The proposed BQ will not necessarily increase safety as products are tracked with batch

numbers and not a drug substance related BQ. A four letter code will be difficult to remember whilst application to the manufacturing site will cause confusion as some drug substances are manufactured at multiple sites. Even slight modification of the INN can have unintended consequences such as the lack of reimbursement or of tendering for biosimilars when the INN Greek letter suffix differs from that of the reference product. In summary, the proposed BQ scheme should be voluntary, should apply to all biologics and be applied retrospectively, and should not have a manufacturing site designation. But if a modifier is to be used, the clearest format would be the Marketing Authorisation Holder's (MAH's) name.

European Generic Medicines Association (EGA)

The EU naming system provides for unique product names in addition to and separate from the active substance name (the INN), and is a good model that could be adopted worldwide. The system has worked well for identity and prescription.

The proposed BQ should only be used where needed; where traceability works well, for example in the EU, introducing another component would only lead to confusion. The EGA welcomes some key principles of the BQ proposal, especially that it will be separate from the INN, that it would be applicable to all biologics and not just biosimilars, that it should be applied retroactively, be voluntary for regulatory agencies, and be administered by the INN Secretariat. However, the EGA does not support linking the BQ to the manufacturing site. This would divorce the product from the MAH which is legally responsible. It would not work for contract manufacturing or where different combinations of manufacturing sites are used for different countries.

The proposed four letter code will not be easy to remember and if used for prescription it could easily result in errors. Alternative options for a code should be researched and systematically tested with stakeholders and in workshops in order to develop a BQ that is easy to remember and difficult to mix up. The company name itself should be a consideration. Different BQ options should be generated and thoroughly user tested to facilitate the final decision.

With regard the forthcoming EU directive on counterfeit and false medicines, the EGA representative did not think that the proposed BQ would be incorporated into the EU 2D barcode as all important features such as a "product code", a serial number, the batch number and the expiry date will be incorporated and there did not seem to be added value in including the BQ.

The EGA looks forward to contributing further to the discussion on BQs.

IFPMA

The IFPMA strongly supports the efforts of the WHO in their development of a BQ and its application to all biologics. Reporting requirements for adverse drug reactions vary amongst regulatory regions and the BQ, in conjunction with INN, will provide a unique global link for pharmacovigilance activities. The IFPMA has concerns however regarding the current proposal to link the BQ to a specific manufacturing site. It feels that this will add confusion and complexity, potentially creating multiple BQ's for the same active ingredient from the same company. The BQ needs to be linked to the MAH, i.e. the parent company or entity legally responsible globally for the product. The IFPMA recognises that the BQ will not be part of the INN and so consideration should be given to displaying it on packaging in a

different font style, size and/or colour. The 4-letter code is acceptable but a shorter code might facilitate adoption by regulatory agencies and be more memorable for users.

Retrospective implementation of a BQ needs to be done carefully and further details on this should be provided. The proposed BQ-related database needs careful consideration to ensure protection of sensitive information and needs to be kept up-to-date. Indeed, linking the BQ to the MAH consolidates the responsibility for updates. WHO should consider developing educational workshops for drug regulatory authorities (DRAs) to support the implementation of the BQ. As the BQ will be voluntary, the WHO also needs to explore with DRAs who are not adopting the BQ how a global BQs may nevertheless be utilised within their jurisdictions.

The IFPMA looks forward to continued support of the WHO and the BQ proposal and welcomes further discussions, especially on the details of a BQ workshop.

In discussion, an INN Expert commented that these first three presentations were unanimous in that the BQ should not include the manufacturing site and requested further clarification.

It was explained that different manufacturing sites can supply different regions with the same drug substance from the same company. With each site having a unique BQ, there would be confusion if switching occurred due to shortage of supply in one region, or where a specific combination of drug substance is used in one region and another in a separate region. Furthermore, if a specific region restricted prescribing to a specific BQ, this would amount to restricted prescription practices.

In addition, parent companies can license out drug substance manufacture to contract manufacturers. If a BQ is linked to a particular site, this could convey sensitive information. Also, during the life cycle of a drug the manufacturing site may change, creating long term ramifications of assigning a BQ to a specific site. From a safety perspective and transparency, the lot number is valuable and a site specific BQ is not required, especially as quality defects tend to be at the drug product level and not drug substance.

The opinion of industry associations was that the marketing authorisation holder (MAH) should be assigned the BQ for a particular drug substance as it is the MAH which is legally responsible. Lot numbers are very important although do not get used consistently, which is why the legal entity is important. However, it was noted also that if the MAH is assigned the BQ, there could be three different BQs for the same drug substance if three different MAH's source their drug substance from the same manufacturing facility.

Alliance for Safe Biologic Medicines (ASBM)

The ASBM representative provided the views of a practicing physician. What patients receive, how medications are used, and is the treatment effective or not, are all extremely important factors, and at the crux of this is the identification of each product. It is critical to know who is getting what and a BQ will be important in distinguishing medicines. It is also critical that medicines can be tracked and traced and information about which particular biosimilar is used is recorded, as one may be superior and knowing that is important. Data from the ASBM European Prescribers Survey of biologics and biosimilars revealed considerable misunderstanding amongst prescribers. It showed for example that where biosimilars are used, less than a third of prescribers use both the brand name and the INN, and less than quarter use the INN only, so a unique identifier will be important.

A system that works globally will enhance patient safety and the speaker was fully supportive of the BQ proposal; it will help improve safety, decrease inadvertent substitutions and improve accountability. The scheme is possible and practical but should be linked to the

MAH and not the manufacturing site; the site is not responsible for the medicine. There is a need to have a global system universally accepted and whilst this scheme is to be voluntary, a single system is needed and the ASBM is fully supportive of the proposal.

INN RELATED PRESENTATIONS

Amgen

Amgen petitioned the INN Group for clarification of nomenclature for mAbs described in a 2008 WHO INN document (INN Working Doc. 08.242).

Amgen supports the direction of the BQ programme, but as it will be submitting regulatory applications for biosimilar mAbs within the next 1-2 years, it requested clarification on how they will be identified, not just in the EU but in other regions where DRAs do not encourage use of brand names for prescription records. The INN Working Doc. 08.242 for mAbs notes that 'if future INN applications are received for mAbs with the same sequence as an existing mAb, but different glycosylation, the INN for the later application could be the existing INN but with a terminal beta added'. But what constitutes a difference in glycosylation – a statistically significant quantitative difference or a biological function difference? Amgen pointed out that sufficient and specific quantitative differences can exist between mAbs to justify a distinguishable Greek letter suffix.

Two cases studies were presented for illustration of existing Greek letter issues. In the first case, the glycan profiles of three mAbs, two commercially licensed with the same INN and a candidate biosimilar from Amgen, were compared. Analysis of afucosylation and of hybrid structures showed statistically significant structural differences between the three mAbs. These differences are not inconsequential as for example one mAb exhibited statistically significant reduced ADCC activity compared with the other two. In the second case, multiple versions of epoetin alfa, originator products and biosimilars, show clear differences in sialylation and lactosamine extension outside of normal lot-to-lot variability, and such differences can impact potency.

In conclusion, whilst the relevance of differences between biosimilar and reference products is a regulatory determination outside of the scope of the INN system, clarification is requested on the WHO INN Greek letter policy for subsequent mAbs that have glycosylation differences. Amgen will be applying for regulatory approval for candidate biosimilar mAbs in a year or so and needs to know what INN to apply for.

In discussion, it was commented that while it is important to define structures precisely and accurately, this cannot be easily achieved for glycosylation, not only because of heterogeneity but also the different methodologies being used by different laboratories and the lack of report standardization. Also, glycosylation of erythropoietin cannot be compared readily with that of mAbs because in stark contrast to erythropoietin, mAbs usually have only one glycosylation site on their heavy chain (with glycans representing only 1% of the mAb molecular weight versus >40% in erythropoietin) and there have been no regulatory issues related to glycosylation microheterogeneity to date. Structural glycosylation features provided by the applicant are reported in the INN definition.

Regarding use of Greek letters for glycoproteins, much depends on information presented at the time of application. At the onset of the use of Greek letters, very little information on glycosylation was presented to the INN committee but when there was a clear difference in glycosylation profile, a different Greek letter was assigned. The INN committee has not

always been consistent in assigning Greek letters and the debate on how different is different lingers on.

In summing up, the Chair, pointed out that the INN Group name substances based upon structure and do not and cannot judge clinical implications. The INN Group can only respond to applications received and if there is no application, it cannot comment. The Group fully accepts that the public policy is not as clear as it might be and may need revision. At each Consultation, there is a session on the review of biologicals nomenclature and the issue highlighted by Amgen is one such item; such situations are constantly being assessed.

Seattle Genetics

Seattle Genetics lobbied the INN Group to reconsider the designation of 'chimeric' to their anti-CD33 mAb SGN-CD33A when the company considers it to be 'humanised'. The current INN guidance for mAb nomenclature and chimeric versus humanised definitions was emphasised, noting that the goal of both mAb types is to achieve a 'human' antibody in function. Medical practioners recognise the role of stems in identifying groups of substances having similar pharmacologic activity and are influenced by whether a mAb is humanised or is chimeric. Seattle Generics strongly considers its SGN-CD33A mAb to be clearly humanised. The construction of the heavy chain involved grafting Kabat-defined CDRs onto human frameworks and specific framework residues were mutated back to the murine sequence to preserve antigen binding. Over 30 constructs were made and tested to identify the maximally humanized sequence that retained specific, high affinity binding of CD33.

Following an INN submission, the company was informed that the variable domain is closer to mouse than human and according to current nomenclature was designated chimeric rather than humanised. The mAb shows only a marginally higher identity to murine rather than human germline sequences and the company pointed out that the ratio of human to murine identity is not always >1.0 for 'humanised' mAbs, and similar to many mAbs already designated 'humanised', the human/murine ratio of SGN-CD33A is only slightly less than 1.0. The pre-humanised/chimeric version of SGN-CD33A has a much lower human/murine ratio, in line with many mAbs with a chimeric substem, and the large increase in ratio to the humanised version shows the extent of humanisation. In fact, at least eight mAbs already designated by INN as humanised have a slightly higher identity to murine versus human compared to SGN-CD33A.

An online questionnaire shows that physicians do have greater concern of using chimeric over humanised mAbs and with SGN-CD33A being similar to other humanised mAbs, it is important that SGN-CD33A sits alongside other mAbs named humanised by INN.

In discussion, it was underlined that the humanised versus chimeric assignment to an antibody chain is based on the resulting amino acid sequence, and not on the methodology per se, which allows protocols other than grafting to be used. Thus, the variable domain of a humanized chain has a V region amino acid sequence which, analysed as a whole, is closer to human than to other species, whereas the variable domain of a chimeric chain has a V region amino acid sequence which, analysed as a whole, is closer to non-human species than to human. In the past, the assignment was based on information given by the applicants, which led to discrepancies. In recent years the INN assignment has been progressively standardized. The tool for assessing mAb V region amino acid sequence comparison is publicly available online.

Creabilis

Creabilis's CT327 is a tyrosine kinase inhibitor for topical application against psoriasis. Its submitted INNs were discarded in favour of a name with a *-staur-* infix and a *peg-* prefix. The Company has declined this name (*pegastaurtinib*) and request a reconsideration of their previously submitted names, the first of which was *cantratinib*, for the following reasons. The presence of the *-staur-* substem is inappropriate because CT327 is not a staurosporine but a K252a derivative, deriving from a different bacterium, *Nocardiopsis sp.* (and not *Streptomyces staurosporeus*) and so is structurally and pharmacologically different. The addition of PEG to the K252a scaffold also dramatically changes the selectivity of CT327 to kinase inhibition. So maintaining the *-staur-* infix will be misleading to physicians since all other *-staur-* named drugs are used for the systemic treatment of oncological conditions.

The *peg-* prefix is also misleading as the PEG moiety of CT327 has a tenfold lower molecular weight than is usual in pegylated drugs. In CT327, a topically applied drug, the amphiphilic property of the low molecular weight PEG moiety is used to enhance kidney secretion of any drug absorbed systemically and provide an optimal safety profile, rather than to enhance systemic half-life as for most pegylated drugs. Consequently, Creabilis would like the INN to reconsider the name and revert to the original name(s) proposed by the company. Creabilis is a small biotech company looking to sell its product to a larger company, so an INN that properly reflects the function of the molecule is important for a future sale of the product.

Curevac

CureVac is a spin-out company from Tübingen University, developing mRNA based vaccines and therapies. The use of RNA as a drug may seem counterintuitive since RNA is considered unstable; however CureVac have developed a way of stabilising it, involving an RNase-free environment and a formulation that includes lyophilisation. RNA has the advantage over DNA of a lower half-life and an inability to integrate into the cellular genome, aspects that are very relevant if is used as a vaccine. Also, nucleic acid vaccines can be readily constructed to encode any (protein) antigen.

The mode of action of CureVac's RNAactive® vaccines involves the uptake of the mRNA by antigen presenting cells, expression and presentation of the vaccine antigen followed by the activation of the adaptive immune system to give a balanced B and T cell response. The drug substance for CureVac's INN application is a prophylactic rabies vaccine comprising an 1800 nucleotide RNA molecule encoding the rabies virus glycoprotein. A phase I study is ongoing following pre-clinical studies that demonstrated complete protection of mice from a lethal rabies challenge. Excellent stability of the mRNA vaccine has been demonstrated even after 6 months at 40°C and gives the vaccine an advantage in hot climates and in regions with a poor transport and storage infrastructure. The rabies vaccine is not a one-off success and a similar construct encoding the F protein of RSV has shown good neutralisation and protection from RSV in cotton rats. Indeed, CureVac won the Europeans Commission's 2014 Vaccine Prize for a leap forward in vaccine technology.

CureVac argued that their first-in-class mRNA vaccine fulfils the WHO requirements for an INN application and suggested the new stem *-maran*, for an mRNA drug substance, taking into account the existence of the pre-stem *-siran* for siRNA. In addition, a substem *v(i)* for viral and *ra(b)* for rabies were suggested, resulting in a submitted first choice INN of *bravimaran*.

Apeiron Biologics

An anti-neuroblastoma mAb, ch14.18, is undergoing development in both the USA (by United Therapeutics) and in the EU (by Apeiron). The mAb is for an ultra-orphan population with most patients being between 1-5 years of age. The USA product is manufactured in the SP2/0 mouse cell line, while the EU product is manufactured in Chinese hamster ovary (CHO) cells. The amino acid sequence of either product is supposed to be identical although the USA one is reported to have 50 sulphur atoms while the EU has 48; this is being investigated and may be a counting error.

Due to the alternative cell production systems, there are glycosylation differences between the two products. The USA product contains Gal1-alpha 3Gal 1-(3)4GlcNAc- epitopes, which may be immunogenic, while the EU product does not. There are also biological differences between the two products, observed both *in vitro* and in the clinic. These biological differences could impact on the safety of the products.

Apeiron is concerned that given the differences in biological and clinical activity and the resulting different treatment regimes, that the two products are not interchangeable. If they received the same INN due to having the same amino acid sequence, there is a threat of mix-ups and a threat to the health of the children. Consequently Apeiron is requesting an INN distinct from that of the USA product and suggested a variety of alternative names in its INN application.

CLOSE OF MEETING

Following this final presentation the Chair thanked all stakeholders for their contributions; they have all been extremely helpful and have highlighted additional issues for the INN committee to think about.