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55th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 16-18 October 2012

Executive Summary

Programme on International Nonproprietary Names (INN)

Quality Assurance and Safety: Medicines (QSM)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

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EXECUTIVE SUMMARY

INTRODUCTION

The Chair of the INN Expert Group, Prof. Derek Calam, greeted participants and invited Mr Kees de Joncheere, the new director of EMP, to open the meeting. Prior to his current position, Mr Joncheere, with a background in pharmacy and business, had been the WHO representative in Ukraine and had also spent time working for WHO in Central and South America and within the EU. He had not previously been involved with the INN Programme but from his pharmaceutical work is fully aware of the importance of INN and the work of the INN Expert Committee. He was very appreciative of and grateful for the hard work performed by the experts and wished them a fruitful and productive meeting.

The INN Programme Manager, Dr Raffaella Balocco-Mattavelli also welcomed the participants and pointed out the new arrangements whereby experts would no longer work from hard copies of applications, instead papers would only be available electronically on tablets supplied to each participant for the duration of the meeting.

The Chair expressed his gratitude to the secretariat and INN members for all the work performed prior to the meeting. A special meeting on 'Cell Therapy Products and Proposal for Biosimilars' was held on Monday 15th October, the day before this plenary session, and was attended by the INN biological advisers and external cell therapy experts. It was chaired by Dr Kevin Grant who will provide a summary to this session.

NOMENCLATURE of INNs

During the Consultation, a total of 112 INNs were discussed, including:

- 83 new INN requests, including 30 for biological substances
- 25 outstanding requests
- 4 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 102 new names were selected, which are planned to be published in List 109 of Proposed INNs, while 7 requests were deferred for future discussion. Three requests were rejected by the INN experts, as the substances did not conform to the criteria for INN selection. One amendment is planned to be published in List 109. One new stem have been selected and 8 suffixes have been promoted to the pre-stem list.

PROPOSAL for INN for BIOSIMILARS

An opinion on the naming of Similar Biotherapeutic Products (SBPs) was provided to the INN Experts (this opinion was also presented to the special meeting on Cell Therapy Products and Proposal for Biosimilars held the day before the plenary meeting).

An SBP is a copy version of a registered biotherapeutic product for which there has been some kind of comparability study between the SBP and the registered product, with a specific focus on quality aspects. The companies manufacturing SBPs would like to have them treated as generics, whilst the innovator companies (those first to develop and market a particular biotherapeutic) do not. SBPs are variously termed:

- similar biological medicinal products (EU/TGA)

- "biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product" (US FDA),
- follow-on biologics (PMDA, Japan),
- subsequent entry biologics (Health Canada),
- and, popularly, biosimilars.

Compared to a small chemical entity, biotherapeutic proteins are large and complex, with four levels of structure (primary, secondary, tertiary and quaternary). The complexity of their structure is often further augmented by glycosylation and other molecular modifications, whose variability can impact on bio-activity. For example, a preparation of erythropoietin (EPO) could theoretically contain ~250,000 variant protein molecules due to partial C-terminal truncation and huge variability within the three N-linked and two O-linked glycans. Lack of terminal sialic acid residues on glycans decreases circulatory half-life and thus bioactivity, whilst the removal of further sugar moieties can reduce bioactivity 1000-fold. The micro-heterogeneity of EPO is determined not by its gene but by the cell in which it is expressed and the cell culture conditions, and EPOs expressed in different cell lines or even after distinct transfection events in the same cell line will consist of a different spectrum of micro-variants with a corresponding impact on bio-activity. Thus the product of any gene, especially a glycosylated product, expressed in alternative environments may be comparable, but there is no guarantee that they will have identical bio-activity and differences in immunogenicity and circulatory half-life cannot be ruled out.

The current INN policy for biosimilars follows two different approaches, one for those that are glycosylated and one for those that are not. Non-glycosylated biosimilars are considered to have highly similar post-translational modifications and receive the same INN, whilst those that are glycosylated are considered comparable but distinct; they get the same INN name but are further qualified by a Greek letter suffix. Within a decade, SBPs will outnumber their original innovator reference products and if the current policy is maintained, two major problems are likely to emerge: first, that Greek letters will become exhausted, and second, that the use of identical non-proprietary SBP names in prescribing may lead to inadvertent switching from one SBP to another.

There are already several different naming policies for SBPs amongst individual regulatory authorities and in some cases, alternative interpretation of INN policy has led different authorities to assign different non-proprietary names for the same product. If prescribers rely on regulatory authority names, this will lack global consistency and could lead to different SBPs having the same name in different countries.

Four approaches are suggested on how to deal with this situation:

- continue with the *status quo*
- treat all SBPs as unique products and provide them with a unique INN
- create a biosimilar 'identifier' to be used for all SBPs (and not just glycosylated ones), e.g. use the original INN and add a fantasy code suffix.
- encourage regulatory authorities to provide an 'identifier' under the guidance of WHO.

The first two are not viable for reasons given above and additionally the second approach is unlikely to be acceptable to the pharmaceutical industry. The last two approaches fulfil the need for a unique identifier of a biosimilar and it would be preferable for the WHO to perform this (i.e. the third option); if regulatory authorities are involved (fourth option), there is no guarantee that a name will be accepted and adopted globally. The naming of SBPs needs to be addressed globally and soon while the number of registered SBPs remains relatively small and with the INN programme being the best forum to achieve this.

Following this presentation, various views were offered by participants.

Overall, it was agreed that there is a lack of a global system. However, it was pointed out that the INN system was not created to show that *glycoprotein alfa* and *glycoprotein beta* are not interchangeable, but flags that they might have differences, and the Greek letter system has by no means been exhausted, even for EPOs, for which there have been no further applications despite many EPOs biosimilars being produced around the world. But it can be appreciated that there is a need for

further elaboration and the proposals tabled are not radically different from the current system. If the third option is adopted and a biosimilar identifier is assigned then it is up to regulators to use it or not, for example *filgrastim* is used for all filgrastim biosimilars in the EU but other jurisdictions use modifications of this. Perhaps the INN Programme indeed needs to publish an addendum, expanding the current naming policy.

A further complication with biosimilars is that the INN Programme cannot force a company to apply for an INN, and if it chooses not to, it can still use an INN based on comparability studies. So in these circumstances perhaps the INN Programme should indeed work with regulators to ensure the correct INN is applied.

It was also highlighted that it is not the role of the INN Group to discuss whether a substance is a biosimilar or not, that is a regulatory matter; but it is the role of the INN, where a glycoprotein biosimilar is involved, to provide the same INN or not.

During discussion, support emerged for believing that the use of Greek letters is not sustainable and that the use of an SBP identifier is attractive, with one possibility being to add the brand name after the INN as is done by some regulators. Some felt however that scientific principles should drive the name, for example, if the application is for the same compound then it gets the same INN, regardless of whether or not it is (or will be registered as) a biosimilar, e.g. the current approach with *filgrastim*; to change this on account of controversy over biosimilars is wrong. In addition, it should be kept in mind that a product may be authorised via different regulatory routes (e.g. biosimilar versus stand-alone application) in different regions.

The Chair agreed that the present situation is not satisfactory and that action is required. He suggested that the Group request the Secretariat investigate ways in which the present system might be improved and to consider guidance or recommendations for regulatory authorities in dealing with issues that biosimilars raise after they are placed on the market. This was agreed.

GUIDELINE on CREATION of INNMS and for COMPOSITE and RELATED SUBSTANCES

INNM (International Nonproprietary Names Modified) are two word names created for individual members of a group of closely related substances where one member of the group, the active moiety, is given an INN and further members of the group are referred to as INNMs; these include substances such as salts, esters and hydrates. A similar approach is increasingly being used for composite substances such as enantiomers, carrier molecules of various types, substances containing polyethyleneglycol (PEG) and substances containing radioactive elements.

A revised version of 'Guidelines on creation of Modified International Nonproprietary Names (INNMs) and INNs for composite and related substances' (INN Working Doc. 10.278. Rev. 3) was tabled as a working document for the INN Group only. The guidance was first drafted in 2005, modified in 2011, and this current version takes into account the INNs being given to various substances using the INNM approach plus a request from the European Pharmacopoeia for an explanation on the creation of modified names in Latin. Although the Group works in English, INN are published in six UN languages plus Latin, with the Latin name being presented first followed by the other languages in alphabetical order. Latin, once used widely in medical nomenclature, has been retained to help those still using it for pharmacopoeia products, for regulatory reasons or to have a common designation. However, there are linguistic problems of transposition of English into Latin since English nouns have no declension, and for INN normal practice has been to treat the Latin version as a noun of second declension and neutral gender. The draft also confirms that the creation of many INNM occurs outside of the INN programme by pharmacopoeia commissions, regulatory bodies and pharmaceutical companies.

The Chair expressed his gratitude for the huge amount of work that had gone into this draft. However, the representative from IUPAC felt that the document needs to be further updated as the terminology used for naming chemical compounds is not in line with current IUPAC terminology. Also, allowing the use of alternative names for salts should be removed as INNM, like INN, must be

internationally unique. Finally, it is only the INN Group that should devise an INNM name, and the pharmaceutical industry should not be guided into proposing them. IUPAC would be pleased to help to revise the draft taking into account current IUPAC terminology.

The Chair thanked IUPAC for these comments. It was intended that INNM nomenclature follows chemical nomenclature, but it appears that the INN have failed to fully understand developments running in parallel on chemical nomenclature by IUPAC. This needs to be corrected and are grateful for IUPAC's offer to help modify this document.

A final thought from the Chair was that this and earlier versions give explanations for use of INN and INNMs in English and Latin. Many INN documents provide names in English only, despite INN being officially provided in five other languages (and Latin). Consideration should be given to names appearing in this document in English only.

CELL THERAPY INN

On the day prior to this plenary session, there was a special meeting of INN and other biological experts to discuss the provision of INN for cell therapy medicinal products. Dr Kevin Grant, Chair of this special meeting, summarised the proceedings. There were a variety of presentations accompanied by lively discussion, with presentations summarising the regulatory situations and associated naming strategies for cell therapies in China, the EU, USA, Japan, Germany and Australia. There was a special focus on the USAN naming convention which is providing names for all cell therapy types, including autologous cells, however it was felt that naming autologous cells was more about naming a process rather than a product. All participants had the opinion that there are some cell therapies (e.g. allogeneic) that will probably need an INN because they can be banked and given to a number of people. There was no progress in how to name, although participants concluded that the EU/Spanish approach, being descriptive, resulted in names that were too long for a container, whilst the USAN convention, although providing a shorter name, has features that go against basic INN rules. Despite this, the USAN approach could be a starting point, e.g. the infixes, without reinventing the wheel. Finally, a decision was made that many cell therapy products are associated with a matrix and that such matrices should not be part of a cell therapy naming scheme.

The Chair of the INN Committee opened discussion within the plenary session, summarising the types of cell therapies that could be included in a naming scheme. Autologous cells are removed from an individual, modified, and returned to that individual; allogeneic cells are removed from an individual, expanded, banked, and used to treat a number of patients; xenogeneic cells, e.g. porcine pancreas islets cells for diabetics, are similarly banked and used for multiple patients. Autologous cells tend to be developed by universities or SME's which are unlikely to pay for an INN for only one patient, but where cells can be more commercially viable, i.e. allogeneic and xenogeneic cells, these are of interest to the INN Group.

The INN Programme Manager has received many enquiries on INN for cell therapies and in light of the advice from the cell therapy meeting to consider assigning cell therapy INN, should the INN Committee now consider applications and how should the Group move forward on this? Participants of the cell therapy meeting have offered their advice on assessing existing systems and which parts are essential, desirable or not needed.

A strong desire was expressed for the INN Committee to proceed in the direction of a naming scheme; both developers and regulators are requesting it and they should be informed that INN Programme is considering this. Whilst the Group should move cautiously, there is also a need for urgency in order to protect any new stem for cell therapies. The INN needs to avoid the situation that occurred with interferons, where a *–feron* stem could not be created as it was already used as a trademark.

Ultimately, there was a clear consensus from the INN Experts that the INN Secretariat should look into a scheme for cell therapies, and sooner rather than later. As was heard at the cell therapy special meeting, there are several pre-existing schemes and a small group should look into all of these in order to help develop a proposal for an INN scheme. Interested parties beyond this Committee should

be informed that INN will consider applications for cell therapies but how these are assessed will have to await a review of the situation but bearing in mind that some say speed is of the essence.

UPDATES from COLLABORATORS

British Approved Names (BAN)
The current edition of the British Approved Names is 2012, and the first supplement was published in August 2012.

Food and Drug Administration (FDA), USA
With regard to the names adopted by the FDA for two biologics, i.e., *ziv-aflibercept* and *tbo-filgrastim*, where prefixes have been added to the INN, these compounds are stand-alone biologics, were reviewed on their own merits and did not refer to another approved biologic. To date the FDA has never approved a biosimilar application, having no legal process to do so. A further point to note is that a Biologics Licence Application (BLA) gets considered by CBER which does not require an established name, whereas a New Drug Application (NDA) for a recombinant biotherapeutic, which gets considered by CDER, must have a USAN. This will be clarified further when more policy is defined by the FDA.

With regard to conflicts, protests and objections, currently the FDA consults USAN ballots that correspond to proposed or recommended INNs and submits these to DMEPA (Division of Medication Error Prevention and Analysis) for evaluation of potential conflicts with other existing USAN names. If DMEPA finds a serious conflict between a rINN or pINN and another USAN, a protest/objection will be noted to USAN Council, with a recommendation that the name be changed and/or not adopted as a USAN. Following this the USAN Council can submit the objection to the INN Expert Committee. The FDA representative has given talks to the DMEPA about INN and the INN/USAN relationship, and tries to act as bridge between them and USAN. There will be further consultation with them to try to resolve comments and protests (on USAN) before they reach INN status. Also, in the future, for any name associated with an NDA, the FDA will try to cooperate more with INN.

The Chair added that the concern of the INN Programme is not that the FDA has *tbo-filgrastim* and *ziv-aflibercept* but is about the approach taken so far by the FDA in modifying the INN itself.

International Union of Pure and Applied Chemistry (IUPAC)
Revision of Nomenclature of Organic Chemistry, or the 'Blue Book', is reaching its final stage (final checking of cross-references and for any errors that may have inadvertently appeared) and will then be sent to the publisher. It is not yet known if it will be available only as hard copy or also online and its cost, but usually the publisher, the Royal Society of Chemistry, has control for the first year and thereafter IUPAC is at liberty to decide whether to place a copy on the web.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)
The Division of Pharmacopoeia and Standards for Drugs within the PMDA is responsible for preparing drafts of Japanese Accepted Names (JAN) and of the Japanese Pharmacopoeia (JP). The sixteen member JAN Expert Committee is chaired by Dr Haruhiro Okuda and considers applications four times per year. The Committee receives about fifty JAN applications per year of which 10-25% are for biological medicines. There are two types of application; those already assigned an INN and those without. For the latter, the selected JAN will go forward as an INN proposal and if it is not accepted as an INN, the JAN will be changed to reflect the adopted INN. The JAN follows the same INN rules on stems. The JP is revised periodically and the 16th Supplement came into effect in September 2012. An English version is currently being prepared and will be available on the JP website in several months' time.

United States Approved Names (USAN)
The 2012 summer USAN Council meeting took place on July 12-13 in Washington DC at the American Pharmacists Association (APhA) headquarters. Names for 27 drug substances were

proposed, 6 new stems and 2 revised stem definitions were approved and posted on the USAN website whilst 1 designation for radicals and anions was approved and posted. For this 55th INN Consultation, USAN submitted 45 proposals for discussion.

Planning for the winter USAN meeting has begun and is scheduled for January 17-18, 2013 in Miami Beach, Florida; at this meeting the new USAN Council representative from the APhA will be welcomed. Through to October 2012, USAN staff processed, researched and made recommendations for 93 new USAN applications and forwarded the information to the USAN Council. Also through to October, 87 USAN, 32 modified USAN and 7 revised USAN were adopted during the year whilst revenue was realised for an additional 14 negotiations.

United States Pharmacopoeia (USP)

The USP representative had concern and surprise that the FDA had created prefixes onto INNs (see above, *ziv-aflibercept* and *tbo-filgrastim*). The USP has a legal role for monographs for published names and has discussed this with the FDA; it is currently with the FDA for re-consideration and their decision will be published in the Code of Federal Regulations.

Previously it had been mentioned that the 'salt' policy approved by USP was coming into effect in May 2013. This policy states that drug names should not include counter ions, and should be based upon the active moiety where the active moiety is non-covalently bonded, e.g. salts. Esters, including those designed to be labile after administration, are excluded. The Committee also decided not to use prefixes such as di- or tri- (for example as in di-hydrochloride).

World Intellectual Property Organisation (WIPO)

The WIPO representative expressed the gratitude of WIPO to Dr Raffaella Balocco-Mattavelli (INN Program Manager) and Mr Antonio Romeo (INN IT specialist) for their attendance at the WIPO Standing Committee on industrial design. The presentation on INN made by Dr Balocco-Mattavelli is available on the WIPO website and has received favourable comments. The WIPO representative also requested that the stem book is included within the INN data hub; it is realised that this might be problematic but it would greatly facilitate trademark offices. WIPO has a high interest in INN and was interested as to whether WHO publishes lists of rejected INN. Finally, patents are of interest to WIPO and would appreciate Dr Balocco-Mattavelli briefing the Standing Committee on this topic. Both WIPO and the INN Programme appreciate this close interaction between the two organisations.

PUBLICATION ISSUES

The updated 'Bioreview' [International Nonproprietary Names (INN) for biological and biotechnological substances (a review)] contains two main changes: the 'General policies for gene therapy products' was revised to include new infixes identifying the expressed gene and an additional vector, whilst the rat/mouse category for the origin of monoclonal antibodies was changed to rat-mouse. The addendum to the 'Stem' book (WHO/EMP/QSM/2011.3) was similarly updated with the new gene therapy infixes.

The approach to stem creation has evolved over the years, being based initially on chemical groups, then therapeutic groups, and in more recent times on the target receptor. This has tended to occur on a case-by-case basis when new substances appear not always with systematic approach, with some exceptions, like, for example, in the case of inhibitors (–ib) for which a summary INN document exists .Furthermore, in recent drug development, new substances are being designed to hit multiple targets and this has created a challenge in using the target as the basis of a stem and there could be value in having guidance from INN on this.

The Secretariat agreed to the Chair's suggestion that they take this onboard and with assistance from others produce a short report for the next meeting, commenting on whether it is premature or not and how to proceed.

UPDATE on IDMIS SYSTEM

Further refinements have been made to IDMIS, the INN electronic submission, tracking and assessment system, to improve the ability of experts to perform their advisory work including the establishment of personal folders.

CLOSE

In his closing remarks the Chair commented that the use of tablets and electronic paperwork had been spectacularly successfully, and may even have helped speed up the process; so the Group is very grateful for the IT support provided. The Chair was also grateful for the huge amount of work performed by the INN Experts, the Observers and the Secretariat, all of which helps the role of the Chair.

NEXT MEETING

The 56th INN Consultation will be held in Geneva on 15th-17th April, 2013

OPEN SESSION for STAKEHOLDERS

55th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 16 October 2012

Stakeholders' open sessions began a few years ago in conjunction with INN Consultations to give applicants the opportunity to explain their applications and to address general INN issues of concern. Prof. Derek Calam, Chair of the INN Expert Group, opened the meeting and welcomed the participants. The INN Programme Manager, Dr Raffaella Balocco-Mattavelli similarly welcomed the stakeholders on behalf of the Director of the Department of Essential Medicines Pharmaceutical Policies. Decisions on individual INN applications are not made during these meetings but data provided is valuable to the INN experts for future deliberation. Six companies/organisations attended this Open Session.

Celltrion

Celltrion's CT-P13 drug was approved in 2012 by the Korean FDA and is under consideration by the EU's EMA with approval anticipated in 2013. It is being assessed as a biosimilar against Remicade (*infliximab*) as the reference product and the company is seeking the identical INN, *infliximab*, with no further qualifier such as a Greek letter suffix. This request is supported by the provision of further comparability data including glycan and oligosaccharide profiling, DNA sequence comparison, protein sequencing, disulphide bond analysis and antibody array analysis. Protein sequencing was performed on both CT-P13 and Remicade using liquid chromatography/mass spectrometry using multiple enzymes to achieve 100% coverage, including the constant region, with separately submitted raw data of MS spectra. The argument for the same INN was also based upon observed batch-to-batch variation data for Rituxan versus Rituximab and precedent for Eprex/Binocrit versus Epoetin alpha, where in both cases the same INN was given (respectively).

European Generic medicines Association (EGA)

The EGA acknowledges that whilst assignment of an INN to a new biosimilar is the responsibility of the WHO, decisions concerning the extent of its similarity to an existing product and approval of that biosimilar are regulatory decisions. In the current debate on biosimilar INNs, accurate nomenclature, pharmacovigilance, patient access, interchangeability and a consistent INN approach are all important factors. Biotherapeutic glycoproteins are not single species but mixtures of micro-variants due to glyco-heterogeneity, and whilst differences in batches can be identified in this respect, the assigned INN remains the same for different batches. It is a concern of EGA that non-comparable products get marketed (in some jurisdictions) using the same INN, whilst products that are indeed comparable get distinct INNs.

Biosimilars are designed to meet the highest standard of similarity to the reference product as defined by ICH, FDA and EMA guidelines and it is the EGA's opinion that if a regulator confirms adequate similarity, then the same INN (as the reference product) should be assigned. Assignment of a distinct INN for a biosimilar would impinge on the market for biosimilars, on competition and price, and ultimately on patient access. A different INN may also confuse practitioners and patients, and impinge on interchangeability. Whilst pharmacovigilance is important, it has to be borne in mind that the INN alone is not sufficient and that other data such as the origin of the product and its batch number are needed.

In conclusion, the INN is a good system and should be maintained; it must stay science based and be consistent. Assignment of a distinct INN to a biosimilar would be unequal treatment *vis-a-vis* manufacturing changes in original products whilst assignment of a distinct INN to all biosimilars would lose the non-proprietary nature of the INN and endanger the INN system.

Ferring Pharmaceuticals

Ferring Pharmaceuticals is developing FE 999049, a recombinant follicle-stimulating hormone (rFSH) expressed in human-derived PER.C6 cells and which has been provided with the INN *follitropin delta*. With its more human like glycans FE 999049 confers higher clinical potency and requires a unique dosing regimen that would make substitution potentially unsafe. Consequently the company seek an alternative name containing a distinctive prefix despite FE 999049 having the same amino acid sequence as other rFSH, i.e. follitropin alfa and beta which are expressed in CHO cells. In support of this, analytical studies show that FE 999049 has a distinct isoform and glycosylation profile compared to follitropin alfa and beta.

FE 999049 also displays distinct pharmacokinetics with a considerable slower plasma clearance which, along with its increased potency, has resulted in a completely different dosing regimen from follitropin alfa and beta. Thus, FE 999049 requires a distinctive INN, possibly a unique prefix, separate from and instead of the 'delta' suffix, to avoid accidental substitution.

In discussion, it was noted that EGA (above) had argued elegantly to stick with scientific evaluation of INN. In this case FE 999049 has an identical amino acid sequence and therapeutic use to follitropin alfa and beta and as such INN rules say that it should have the same INN but distinguished by a Greek letter suffix. It was felt that what is being proposed is more a regulatory matter. FE 999049 clearly has differences from follitropin alfa and beta, but there are differences between alfa and beta also, although to a lesser extent, but scientifically speaking it would seem that the INN should indeed be follitropin (delta).

There are many complex issues associated with SBPs, whether standalone or biosimilar. What we have here is a switch from CHO to a human retinal-derived cell resulting in considerable differences in post translational modification. This raises the question as to whether there are circumstances when the INN needs to indicate the source/cell system; there is no solution as yet but it is a topic for discussion.

GSK

GSK made representation to highlight a concern they have with regard to a global approach to nomenclature for recombinant protein cancer immunotherapeutics, especially their lead compound MAGE-A3 ASCI. MAGE-A3 is in phase III development in 37 countries for the treatment of non-small cell lung cancer and for melanoma. For product registration in the USA, CBER, the relevant competent authority, requires a USAN. The USAN Council has established a naming system for cellular and non-cellular immunotherapeutic products such as MAGE-A3, with *Astuprotimut-R* being selected as the USAN. For INN, MAGE-A3 was initially considered as a peptide and thus have the stem *–tide* with the substem *–motide* for immunological agents for active immunisation. GSK expressed concern that for a portfolio of compounds with a similar mode of action, different non-proprietary names for the same substance will be created by international (INN) and national nomenclature bodies. GSK is also concerned that considering MAGE-A3 as a peptide is inappropriate as this is a recombinant protein of 450 amino acids expressed in E coli and should be treated as a protein and not a peptide.

A globally unique non-proprietary name is also highly important for safe prescribing, good communication between regulators and healthcare personnel, and for pharmacovigilance. Furthermore, the lack of a single global non-proprietary name could impact patient treatment as regimens can last for several months. GSK implored the INN Committee to work with national nomenclature authorities to seek harmonisation and provide a single scheme for MAGE-A3 and other immunotherapeutic proteins.

In response, the INN noted that indeed the INN programme needs to work with other authorities, but that GSK applied first for a USAN which has a naming scheme that is not acceptable to INN policy. Also, the INN has a sink stem for peptides but not for proteins and so when an application is made for a protein for which there is no distinct mode of action (MoA) or relevant stem, often the sink peptide stem gets used.

GSK commented that the presumed MoA of compounds such as MAGE-A3 – when administered in combination with an immunological adjuvant system - is the activation of a cellular and humoral immune response that is directed against tumor cells bearing the antigen. The MAGE-A3 compound has no direct pharmacological activity on the tumor.

IFPMA

The IFPMA participated at the stakeholders meeting in order to emphasise the role of the INN in national prescribing and pharmacovigilance practices. The IFPMA confirmed their support for the INN system and the principle of clear identification, and safe prescribing and dispensing of medicines worldwide. However, the IFPMA feels that this is not happening for biologicals within the current INN system and recommend that the INN Committee along with the WHO pharmacovigilance committee provides global guidance on the use of unique identifiers that would complement the INN.

UK, Greece and Portugal require manufacturers to append the brand name to the INN for similar biological medicines and France is soon to follow suit. In the USA, a unique non-proprietary name, tbo-filgrastim, was provided to distinguish the product from a similar and previously licensed product – Neupogen (filgrastim) – in order to differentiate the products and minimise medication errors. Around the world, epoetin is variously named epoetin alfa, epoetin zeta and epoetin lambda for apparently similar products. Overall there appears to be a weakening of the INN system for biologicals, and whilst the role of the INN in pharmacovigilance cannot be ignored, the IFPMA would like to see good practice guidelines to help in prescribing and reporting of adverse events. There is no one way to ensure this but an effective way to help trace products is needed; the INN has been used in the past to do this but it will not work for biosimilars.

Pharmacosmos

Pharmacosmos, a small specialist Danish company, participated in the stakeholders meeting to petition the INN committee for an INN for iron isomaltoside 1000, the active ingredient of Monofer® used for treatment of iron deficiency anaemia. Previously, an INN request had been turned down due to insufficient definition of the compound. Pharmacosmos thus wished to provide further documentation to define it more precisely.

The isomalto-oligosaccharide in the complex is a mixture of linear chains of linked glucose units of average size 5.2 units and average molecular weight 1000 Da; reducing sugar units have been eliminated by hydrogenation. The appropriate systematic name is 6-O-D-glucityl α-D-isomaltopentaoside iron complex. Pharmacosmos acknowledges that nanoparticle materials are difficult to describe and define but pointed out that the name iron isomaltoside 1000 has been accepted as the substance name in 22 EU countries and appears in the scientific literature. Also, the company notes that ferric carboxymaltose has been assigned an INN and is comparable to iron isomaltoside 1000. Structural studies including NMR analysis, UV adsorption, electron microscopy, dynamic laser light scattering and gel permeation chromatography have been used to define the compound in detail. In conclusion, the company felt that it is chemically well described and sufficiently defined to warrant an INN.

Following this sixth representation, the Chair closed the meeting, thanking all those who participated. The presentations are very helpful to the Expert Committee in discussing applications and find it useful to have the additional information which they will take into account during deliberations. It has also been useful to hear general comments about the INN system although there are limits to the actions that WHO can take, and cannot force applications to be made. All national regulatory authorities have their responsibilities, including in pharmacovigilance. Traceability and recording of adverse events are a concern to the INN Experts; however, there is probably less that the INN Committee can do than is thought, but it will try to do as much as possible.