

***57th Consultation on International Nonproprietary Names
for Pharmaceutical Substances
Geneva, 22-24 October 2013***

Executive Summary

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms (TSN)

Regulation of Medicines and other Health Technologies (RHT)

Essential Medicines and Health Products (EMP)

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EXECUTIVE SUMMARY

INTRODUCTIONS

The 57th INN Consultation was opened by **Mr Kees de Joncheere**, director of EMP, who followed with an update on continued reforms within WHO. During the summer of 2013, three pillars of work were created within EMP: innovations for health technologies, national policies for access and use of medicines, and regulation of medicines and health technologies. The INN Programme is situated in this latter group, led by Dr Lembit Rägo, in the team covering technology standards and norms, led by Dr David Wood. New cost effective strategies and lines of management are also being implemented.

Mr de Joncheere noted the increasing importance of the work of the INN Expert Group, especially in light of the growing complexity of new medicines; he also noted that this meeting would assess a record number of applications. Ways of helping the INN Expert Group work more efficiently are continuously sought and recent advances in the IT area have helped in this regard. Participants can expect a busy schedule and Mr de Joncheere expressed his gratitude for all the energy and effort that goes into the work of the Committee.

Dr David Wood, who is to lead the new technologies standards and norms team, expressed his pleasure at being involved with the INN Programme and the INN Expert Group. He had worked previously as a virologist at NIBSC (UK) involved in the batch release of a number of vaccines and has been with the WHO for 13 years, now leading the Biologicals unit and the Expert Committee for Biological Standardization. This has involved occasional interactions with the INN Programme and he is looking forward to working directly with its Experts.

The Chair, **Professor Derek Calam**, similarly welcomed the members of the INN Expert Group, The INN Biological Advisory group members and observers to the meeting. The Chair spoke warmly of Professor Henri Favre of IUPAC, who had died in July 2013 and who had been a long term advisor to the INN Committee on chemical nomenclature, and called for a moments silence in his memory. This meeting will consider over 100 applications and debate major policy decisions in the biologicals field and the Chair expressed his gratitude for all contributions made since the last meeting.

Dr Raffaella Balocco-Mattavelli, INN Programme manager, noted that the front page of the WHO's website contained an article on INN since this was the 60th anniversary of the INN Programme and that this meeting would consider its 10,000th application.

NOMENCLATURE of INNs

During the Consultation, a total of 132 INNs were discussed, including:

- 107 new INN requests, including 47 for biological substances
- 23 outstanding requests
- 2 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 112 new names were selected, which are planned to be published in List 111 of Proposed INNs, while 14 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. Two amendments are planned to be published in List 110 of Proposed INNs. One request has been withdrawn. Three new stems have been selected and 6 suffixes have been promoted to the pre-stem list.

CELL THERAPY NOMENCLATURE SCHEME

Following from a first draft of an INN nomenclature scheme for cell therapy products, various comments had been received from individual experts and from interested agencies. These have been

integrated into a second version which was presented to the INN Expert Group by the INN Secretariat. The scope of the current draft includes allogeneic and xenogeneic but not autologous cell therapies; minimally manipulated haematopoietic products, combination products and prophylactic vaccines also would be outside the scope. Autologous cells however need further consideration as most cell therapy experts are in favour of their inclusion. Residual, contaminant cells and biological substances such as cytokines that are part of a cell therapy drug product would not be reflected in the name but be described in the description.

The suffix, or the stem, *-cel* would be used for all cell therapy products. A close preceding infix would designate the type of the cell therapy product, i.e. *-lo-* and *-xo-* would designate allogeneic and xenogeneic cells respectively. If autologous cells become included, they could be designated by *-to-*. If *-to-* is in conflict with *-tu-* for tumour, another infix could be selected for autologous cells, e.g. *-ato-*. In contrast to this tentative scheme, the USAN scheme uses single terminal uppercase letters to designate the type of cell therapy product. An additional infix would further describe the cell type, e.g. hepatocytes would be *-ep(a)-*, fibroblasts *-fi(b)-* and tumour cells *-tu(m)-*, although it was commented that the suggested *-leu-* was too broad for lymphocytes. Tumour cell types would be further defined with an infix for the type of tumour cell, e.g. *-mel(a)-* for melanoma and *-glio-* for glioma. Stem cells would be designated by the infix *-tem-*. Infixes to define the type of stem cell, and/or the origin/source of the stem cells have been broadened based upon comments received and brings it in line with the USAN scheme. A further modification is where the product contains cells differentiated from stem cells into a specific cell type. In such cases there would be an infix for the differentiated cell type plus *-def(i)-* to indicate that they had been differentiated from stem cells.

Genetically modified cells would have a two word name with the first word describing the nature of the gene being used to make the modification following the same approach as is used for gene therapy products. The second name would describe the cell as outlined above. Comments received however stressed that if genetic manipulation was to be part of the name then other types of manipulation should be highlighted such as selection, fusion and pulsing. Consequently, an appropriate infix would be used for these as required and would likely be the first infix in the name. The various infixes describe in this second draft are not final and can be modified or further infixes can be proposed.

In discussion, various issues concerning this new draft were debated, with the inclusion of autologous cells within the scheme being at the forefront. In one respect, if every distinct autologous cell product was to be named names would be on a patient basis, which would be both undesirable and impractical. On the other hand if there was a single name for a specific autologous cell regardless of the patient, this would essentially be naming a process rather than a defined product, which again many felt to be undesirable. To date the majority of licensed cell therapy products are autologous cells. Concerns about labelling and shipping autologous cells, sometimes across national boundaries, had been voiced and it was clear from comments received that cell therapy experts wanted autologous cells to be included in an INN nomenclature scheme. From a practical point of view, it may be that the number of applications for INN for autologous cells may not be high as many are derived in hospitals and not in commercial settings.

Inclusion of the infix *-tu-* for tumour cells alongside an infix for the tumour type was felt to be redundant, especially in the face of an increasing number of possible infixes although one opinion received had recommended retention of the *-tu-* infix so that this feature of a cell therapy product would be highlighted to prescribers. Following from this, a common concern was the number of potential infixes that might be used which will result in increasingly long and complex names.

A final point of concern was the lack of harmonization between the existing USAN scheme and this tentative INN scheme. Having two similar but distinct nomenclature schemes for cell therapy products would likely result in confusion and steps should be taken to harmonize them.

Bringing the discussion to an end the Chair sought consensus on the points discussed. First, there was strong opinion from cell therapy experts to include autologous cells, and it was agreed by the meeting to do so. Second, rather than dropping the *-tu-* infix, it was agreed to retain it but to advise stakeholders that the Committee was considering its removal and to seek comment on this. Third, it was agreed that designation of stem cells would be included in the name and that the scheme as

described would be followed, including an infix for differentiated cells. Fourth, genetic manipulation would be included as described but thought needs to be given to the value of requiring a separate INN for the vector, prior to obtaining an INN for the manipulated cell. Finally, a meeting needs to be arranged with US FDA colleagues in order to look at bringing the USAN and WHO schemes together.

INN QUALIFIER for BIOSIMILARS

A major topic for discussion during the Consultation was the proposal for nomenclature for Similar Biotherapeutic Products (SBPs, but also frequently termed biosimilars); this discussion followed on from a one day meeting on SBP nomenclature held alongside the 56th INN Consultation in April 2013.

The Chair had recently updated the WHO's Expert Committee on Biological Standardization on 'INN and biosimilars' and used his presentation by way of introduction to the issue. Assigned INN are not restricted to one manufacturer or one product, and the same substance obtained by different synthetic routes and with different impurities has the same INN. Importantly the INN Committee does not review registration dossiers and does not receive applications for INN for (non-biological) generic substances. INN for biological substances now comprise more than 40% of applications and are assigned according to established general principles with biological substances of increased complexity such as glycoproteins and gene therapy products receiving a two word name. With regard to biosimilars, this is a regulatory concept whereby their registration is based upon a comparison of their quality, non-clinical and clinical attributes with a previously registered similar substance. Whilst they are a type of generic, their manufacture from living biological sources gives them a level of variability not seen with true generic compounds. Note however that no application has been received for an INN for a biosimilar that is a non-glycosylated protein such as insulin and somatropin.

Biosimilar regulatory routes exist within some jurisdictions but not in others and likewise the same substance may be viewed as a biosimilar in one jurisdiction but not in another. Whilst issues such as substitutability, reimbursement and pharmacovigilance are not the responsibility of the INN Expert Group the INN can have an impact on these, but by itself the INN alone is unlikely to be sufficient for biosimilars. Consequently, some drug regulatory authorities have requested the INN Programme to develop and administer a voluntary and global nomenclature system applicable to biosimilars.

Following this introduction, Dr Patience Holland, reported on the outcome of the April 2013 INN SBP meeting.¹ The meeting comprised regulatory experts from agencies worldwide and various INN Expert Group experts especially those with expertise on biological substances. They considered the formation of a coding system for SBPs for use worldwide which would be established and managed by the INN Programme. Whilst diverse views were expressed by participants, there was a majority view that in principle the INN Secretariat should explore the practicalities of delivering a unique qualifier for SBPs. Two schemes were proposed, one comprising a unique global qualifier assigned by the INN Secretariat, and one in which detailed information concerning a biosimilar would be captured in a publically accessible database administered by the INN Secretariat. It was further highlighted that any codification scheme should apply to the drug substance and not the drug product despite it being the drug product which gets registered.

Following on from the April SBP meeting, and based upon recommendations and comments from interested parties including regulators, the INN Secretariat has been investigating a practical solution to creating a biosimilar qualifier. First, participants were reminded that the INN Programme has a clear mandate to ensure unambiguous identification of pharmaceutical substances, both chemical and biological, and so to take a lead in this venture. Many experts have voiced that the best way to distinguish between an SBP and its reference product, and between one SBP and another, is through nomenclature, with involvement of the INN Programme in developing a unique global biological qualifier (BQ). It is also important that the assignment of non-unified qualifiers by individual regulatory bodies is avoided.

¹ The minutes of the meeting are available online at http://www.who.int/entity/medicines/services/inn/56th_Executive_Summary.pdf.

The embryonic scheme developed by the Secretariat involves submission of an application to WHO providing the applicant's name, the INN of the substance, the manufacturing site and the drug registration authority that will licence the SBP. For the BQ itself, a random sequence of a specified number of letters would be chosen taking into account INN principles, i.e. stems, numerals, company names, common names, brand names and unacceptable visual formats would not be allowed, and the BQ should be unique. BQ's could be published as an annex to INN Lists and/or in an accessible global database. Stakeholders would include pharmaceutical companies, drug regulatory authorities (DRAs) and others. Two possible scenarios for obtaining and assigning an INN-BQ were presented. One would be where a company applies to the INN Programme for a BQ prior to submitting its biosimilar dossier to a DRA. Following approval of the dossier, the DRA informs the INN of its decision whereupon the INN Programme would publish the BQ. A slightly varied process would see the DRA, following a marketing authorisation application, requesting the sponsor to make an application to the INN Secretariat for a BQ. The DRA is informed by the INN Secretariat of the proposed BQ, which in turn is informed by the DRA of its acceptance upon authorization of the biosimilar, followed by publication of the BQ by the INN Programme. Some stakeholders are more in favour of the first scenario. It was also highlighted that such a scheme would be a separate and distinct activity from INN applications and that a BQ would not be part of the INN.

The meeting was also informed that the Therapeutic Goods Agency (TGA), Australia, is developing a guideline for biosimilars which has led the TGA into devising a naming scheme involving the Australian Adopted Name of the reference product plus an identifier that would consist of the prefix *sim-* plus a three letter code, preferably with the code assigned by INN/WHO. The reason for this approach is because prescribing in Australian hospitals is by INN on a cost basis, and consequently the TGA wants a means of identifying between a biosimilar and its reference product and between other biosimilars. The TGA is not committed to its identifier policy and will harmonize as much as possible with any scheme devised by the INN Programme.

Prior to initiating general discussion, the Chair reminded the Committee that it had one fundamental decision to make during this meeting and that was whether or not to recommend the Secretariat to proceed further with the development and implementation of a scheme for a biological qualifier, for at least some biological substances. Participants were also reminded that a biological qualifier would not be part of the INN and that selection and administration of a biological qualifier would be a parallel activity by the INN Secretariat which would not impact on the INN Programme itself.

It was raised that for such a voluntary scheme to work there would need to be global acceptance and that regulatory agencies should have the same standards for approval of biosimilars although effort would be required to achieve such harmonisation. Also, an additional code administered by the INN Secretariat would easily be viewed by the outside world as being part of the INN and so the idea of it being a parallel activity to and distinct from INN nomenclature needs to be explained formally and clearly.

Representatives from Japan and Australia, where a biological identifier is in place or is being developed agreed that a global system was desirable, especially when one biosimilar drug substance is used by different manufacturers to produce a drug product, and would conform to a unified system.

In contrast, the European Medicines Agency representative thought it unlikely that a biological qualifier would be used in the EU but could not state categorically that it would not be. The considerable experience with biosimilars within the EU has created a high level of confidence that biosimilars have good equivalence with the reference product and the EU view is that the posology should be the same, i.e. alignment of a biosimilar with the reference product. The EU also has a strong desire to retain the brand name for pharmacovigilance and it is now in legislation that the invented name, as a key element in prescribing, plus the batch number are required for an adverse event report. The EU representative noted that the main drive for an additional code appeared to be added safety, but with many biosimilars now appearing on the market it could be confusing for prescribers as to what a biosimilar actually is, when confronted with multiple qualifiers.

A concern was raised as to whether the INN Secretariat should be taking on this task, especially as it was being emphasised that a biological qualifier would not be part of the INN. It would appear on the

surface that regulators would be better placed for this; they are privy to the details of a regulatory dossier, are more in touch with manufacturers, with batch variation and with manufacturing updates. Furthermore, much of the information that might appear in a BQ would be available in for example the EU's European Public Assessment Report (EPAR). Thus, the INN Secretariat needs to be careful in taking on this extra commitment, and several INN Experts stressed the need to keep this scheme separate from INN activities, possibly even through separate meetings of the INN Expert Group.

On a more positive note, the basic idea of a BQ appeared acceptable to the INN Expert Group, would help link a biosimilar to its reference product and to other biosimilars, which in turn would contribute to decreased mis-prescribing and improved pharmacovigilance. Indeed, it was mooted by more than one Expert that such a scheme should apply to all biological medicinal products and not just to biosimilars. A three letter code was considered to be somewhat limited and a four letter code would provide a far greater number of combinations, or a coding system based upon the Anatomical Therapeutic Chemical (ATC) classification system may be useful.

The Chair acknowledged that the situation is complicated and asked the Experts on the basis of what had been presented and discussed during the meeting if they wished to request the Secretariat, to take the idea of a BQ forward in principle, and to explore the application and administration of a system in more detail. There was consensus that this should be done. Following from this, the Chair outlined four key issues to be considered: the nature of the BQ, what information it should convey, who makes an application for a BQ, and who should have access to the BQ information. Finally, there should be information on who is going to use the code and how. From a practical viewpoint, it would be useful to convene a smaller group to explore these issues and report back at the next INN Consultation, but this would be for the WHO Secretariat to arrange.

COLLABORATORS UPDATES

British Approved Names (BAN)

Supplement No. 2 of the BAN 2012 was published in August 2013. Also, the British Pharmacopoeia is celebrating its 150th anniversary in April 2014 and details of the event will appear on its website.

European Directorate for the Quality of Medicines and HealthCare (EDQM)

The 8th edition and supplement 8.1 of the European Pharmacopoeia were published in the summer of 2013, 8.2 will be published at the end of the year, and three further supplements will appear in each of the next two years. With the increasing number of biological medicinal products coming to market, the Ph.Eur. has started drafting monographs for biological substances still under patent, under the P4Bio procedure, in order to speed up the delivery of new biological monographs.

At the international level, the Ph.Eur. continues to work with the Japanese and United States Pharmacopoeias within the PDG, and also supports the WHO initiative for global pharmacopoeial harmonisation.

Ukraine became the latest (and 38th) full member of the Pharmacopoeia in January 2013, and South Africa joined as an observer in June 2013, bringing the number of observers to 25. Ukraine also joined the EDQM's Standard Terms, providing translations for dosage forms, routes of administration and packaging items; Standard Terms now operates in 32 different languages, most of them being European.

The EDQM also has other healthcare responsibilities, having taken over various initiatives from the Council of Europe, including the provision of guidelines for blood donation and transfusion, and for organ transplantation, and is involved in promoting the importance of these services in member states. The Council of Europe continues to coordinate and implement the MEDICRIME convention, a binding international instrument to fight counterfeiting of medicines and other related crimes, which encompasses not only the manufacture but also the supply and handling of counterfeit medicines. The EDQM contributes to MEDICRIME at the practical level through eTACT, its mass serialisation initiative for tracking individual packs from manufacture to end-user, and is setting up a 'fingerprint'

database of Active Pharmaceutical Ingredients and excipients to help OMCLs detect counterfeit substances.

European Medicines Agency (EMA)

The main objective of the EMA's (Invented) Name Review Group is to consider whether the invented name proposed by a product's manufacturer could create a public-health concern or potential safety risk and forms part of the Agency's role in evaluating the safety of medicinal products in the centralised marketing authorisation procedure. It reviews almost 500 invented names per year, with an acceptance rate of 50-60%. The Group examines similarity to INN or inclusion of INN stems as these could form grounds for rejection. The EMA's 2007 guideline on the Acceptability of Names for Human Medicinal Products is currently under revision with the final version expected to be published late 2013/early 2014. Clear reference is made to the World Health Assembly Resolution WHA46.19 with respect to the protection of INN and to the avoidance of similarity to INN or inclusion of INN stems. The Group is committed to work with and uphold INN and is grateful to the WHO for its review of the draft guideline.

International Union of Pure and Applied Chemistry (IUPAC) and International Union of Biochemistry and Molecular Biology (IUBMB)

Recent IUPAC publications include 'A Brief Guide to Polymer Nomenclature' (*Pure Appl. Chem.* **84** [2012]) and 'Nomenclature of Flavonoids (IUPAC Provisional Recommendations)' published on their website. Revision of 'Nomenclature of Organic Chemistry (IUPAC recommendations 2013 and Preferred IUPAC Names)', commonly referred to as the Blue Book, is almost complete and will be published soon by the Royal Society of Chemistry. It was edited primarily by the late Prof Henri Favre who had worked on it since the early 2000's; Dr W H Powell is a co-editor. The latest revision of 'Atomic Weights of the Elements' will be published in 2013.

Publications in preparation include 'A Brief Guide to Organic Nomenclature', 'A Brief Guide to Inorganic Nomenclature', the 2nd Edition of 'Carbohydrate Nomenclature' and 'Inorganic Preferred IUPAC Names' (PINS).

The IUBMB has been considering enzyme nomenclature for more than 40 years and produces an index to enzyme catalysed (EC) reactions for isolated, characterised enzymes. The EC list now covers more than 5000 reactions with the EC number defining the reaction and not the enzyme structure. Each enzyme will also have its own CAS number. The list was last published as a book in 1992 and since then is available on the internet only; approximately 300 new entries are added each year.

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

Japanese Accepted Names (JAN) are created after consultation within the JAN Expert Committee which consists of 16 members; membership includes organic and biological chemists, a patent officer, and meets quarterly. In recent years, the number of submissions to the Committee is averaging about fifty per year with about 15% of these being for biological substances. The Japanese Pharmacopoeia is revised periodically with the 16th Edition (JP16) being published in 2011. Since then Supplement I to JP16 was published in September 2012, Supplement II is due to be published in the spring of 2014 whilst the 17th Edition is scheduled for publication in 2016. An English version of the 16th Edition and Supplement I are available on the web.

United States Approved Names (USAN)

The 2013 summer USAN Council meeting took place on 11-12 July in Chicago, IL, at which names for thirty-three drug substances were proposed and approved. The entire USAN stem list has been reviewed and revised based upon input from the USANC and the FDA's Division of Medication Errors Prevention and Analysis (DMEPA). The updated list has been posted on the USAN website. Key changes include the conversion of the stem list to MS-Excel format; columns show the syllables of stems and the positions in which they are used, a review of the example names used for each stem, a review of the stems, substems and definitions and their relationships to one another within the stem list. These changes were implemented to improve consistency of information provided and to address

DMEPA's concerns. The monoclonal antibody nomenclature scheme has also been removed from the stem list.

Thirty-seven INN applications for proposed USAN were prepared and forwarded to the INN Programme for discussion at this Consultation. Planning for the 2014 USAN Council meeting has begun; this is scheduled for 17-18 January 2014 most likely in Phoenix, AZ. In September 2013, the American Medical Association relocated its headquarters to 330 N Wabash, Chicago and the USAN staff offices are located on the 43rd floor of this landmark building.

Up to September 2013, USAN staff had processed, researched and made recommendations for 79 new USAN applications and forwarded this information to the USAN Council. Up to October 2013, 78 new USAN, 25 modified USAN and 6 revised USAN were adopted during the year, and revenue was realised for an additional 8 negotiations.

The Chair expressed his gratitude to the USAN for the significant contribution it makes to the work of the INN Committee as more than half of INN applications are channelled first through USAN which does most of the preparatory work.

United States Pharmacopoeia (USP)

The Nomenclature, Safety and Labeling Expert Committee has a responsibility for naming drug products including compounded products. Recently there was an unfortunate event in the US when certain injectable compounded products gave rise to fungal infection and meningitis, of which some cases were fatal. The General Chapter on compounded products had not been adhered to, constituting a violation.

The USP also develops non-USA monographs, i.e. monographs for medicines legally marketed outside of the US, and intended to treat specific neglected diseases as listed on its website; these monographs will eventually appear in the new Medicines Compendium. The USP is further broadening nomenclature with the introduction of its new Herbal Medicines Compendium.

Finally with regard to biosimilars, the USP is waiting for an official FDA position on nomenclature. The USP has not changed its position on this which is aligned with the GPhA from the perspective of standards, identity, purity, potency and strength, and biosimilars are considered to be 'generic' unless shown otherwise. To date, no biosimilars have been approved in the US as no sponsor has chosen this route although it is known that such products are in manufacturers' pipelines. The US Affordable Care Act of 2010 provides for the feasibility of having biosimilar medicinal products but does not provide any detail, simply that people should have access to affordable medicines and that the FDA should address this. A monograph for *filgrastim* becomes official late 2013 and if *tbo-filgrastim* complies with the identity test for *filgrastim*, then essentially it is mis-branded.

World Intellectual Property Organisation (WIPO)

The WIPO representative thanked the INN team for the successful ongoing collaboration between the INN Programme and WIPO.

In particular, WIPO continued to circulate information concerning the publication of new lists of proposed and recommended INNs to WIPO Member States in implementing a decision taken by the WIPO Standing Committee on the Law of Trademarks, Industrial Designs and Geographical Indications at its nineteenth session held in Geneva from July 21 to 25, 2008. Most recently, WIPO circulated electronically information on List No. 109 of Proposed INNs to its Member States on July 16, 2013.

UPDATE on IDMIS

The INN IT expert reminded Experts of the INN online repository which consists of two areas – a personal folder for sharing files and which can be accessed only by an individual Expert and INN staff, and a public folder which contains INN applications, meeting agendas and meeting presentations, accessible by but restricted to INN Experts and staff.

A proposal on how a biological qualifier (BQ) could be physically handled was presented. The application for a BQ would be online using a form similar to the current INN application form and a code, say a random four letter code, would be generated in real time during the application. There would be a facility for self-checking the form and the code generated. The form would be further checked and approved by WHO but the code would only go live when a regulatory agency approves a marketing authorisation and the INN for the product. The code produced would be random and would not be linked to the type of substance or to the manufacturer. A fee would be payable upon application to cover establishment of the system and administration costs.

CLOSE of MEETING

The Chair noted that the Consultation had had a very full agenda with 107 new applications, and thanked everyone for their hard work in getting through this. Progress was also made on administrative aspects of nomenclature for SBPs and by the next Consultation an outline of a possible scheme should be tabled.

The Chair was in turn thanked for his efficient efforts in steering everyone through such a busy agenda.

NEXT MEETING

The 58th INN Consultation will take place at WHO, Geneva on 8-10 April 2014.

OPEN SESSION for STAKEHOLDERS

57th Consultation on International Nonproprietary Names (INN) for

Pharmaceutical Substances

Geneva, 22 October 2013

Stakeholders were welcomed by Professor Derek Calam, Chair of the INN Expert Committee. Stakeholders' open sessions give applicants and interested parties the opportunity to explain their applications in detail or to provide comment on INN policy issues. These meetings appear to be welcomed by stakeholders and on this occasion ten companies and groups were present to make representation to the INN Committee; the first four addressed biosimilar identifier issues whilst the remaining six provided scientific information on specific INN applications. The Chairman stated that the meeting is "open" to participants, but what is discussed should remain confidential and should not in any way be made publicly available.

The Programme manager Dr Raffaella Balocco-Mattavelli welcomed the stakeholders on behalf of the Director and Coordinator of the INN Programme. With such a large number of presentations time will be an issue, but this remains an important opportunity for open discussion between stakeholders and INN experts. As is the norm for WHO groups, names of experts remain confidential.

BIOLOGICAL IDENTIFIERS

Generic Pharmaceutical Association (GPhA)

The 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. The Association felt that adoption of unique non-proprietary names for biosimilars could jeopardize patient safety, inhibit market competition and disrupt the current global naming system. The Association found the current INN system to be working well in the EU for all biologics; where biosimilarity is established the same INN is assigned and in highly regulated markets in general, if comparability is shown, no new INN is required. In the USA, where a biosimilar regulatory process has yet to be formally established, non-proprietary names are not used for interchangeability. In addition there should be consistent nomenclature between a biologic that is shown to be comparable following a manufacturing change and a biosimilar shown to be comparable to the originator product, i.e. no new INN should be required. It was the view of GPhA, some of which was based upon scientific studies, that if unique non-proprietary names are assigned to biosimilars, that it would undermine the whole concept of comparability and public health benefits.

European Generic medicines Association (EGA)

The EGA recognises that the INN Programme has made great contributions to public health so that a pharmaceutical substance has a common name worldwide, but it expressed concerns that the current debate could have an adverse impact on the system. The EGA's position is that biosimilars should be assigned the same INN as their reference product and where the system is working well, e.g. in the EU, changing it will only cause confusion, compromise patient safety and limit patient access. However, if addition of an identifier which is not part of the INN is considered, it needs to be applied in a non-discriminatory manner and equally to all biologics, not only to biosimilars.

The existence of biosimilars is to improve patient access to biological medicines and reduce healthcare expenditure. Across the EU, there is disparity of access to biologics due to unaffordability in lower income member states whilst in other states patient access to treatment has increased considerably, e.g. the availability of biosimilar GCSF in the UK. Different INNs are likely to increase confusion; for example, *epoetin zeta* is an EU approved biosimilar with *epoetin alfa* as reference product. The manufacturer of *epoetin zeta* had requested this INN before a biosimilar regulatory pathway was in place and is now faced with considerable challenges in having it included in

government tenders for *epoetin alfa* or to get reimbursement at all as it is considered a ‘new INN’ in some countries. Further, the INN only identifies the active substance not the finished drug product and was never intended to be a unique tool for traceability; in the EU, legislation mandates the name of the medicine and the batch number for adverse reaction reporting, and data demonstrates that the current system operates well without a unique INN.

It is the regulators who make the assessment of biosimilarity and they are best placed to assess the scientific appropriateness of the INN. The EGA maintains that the brand name is the best and most easily understood non-INN identifier but if new identifiers are introduced they should apply in a non-discriminatory manner and to all biologics and not just to biosimilars.

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

Both originator and biosimilar biotherapeutics are produced by companies that are members of IFPMA which strongly supports the goal of the INN system in providing a unique and universal non-proprietary name for each marketed pharmaceutical substance. In the case of biotherapeutics, products by different manufacturers need to be distinguishable from one another throughout their usage to promote patient safety. The IFPMA welcomed the creation of a distinguishable INN for all biotherapeutic medicines, including a unique product identifier. Such an identifier should be available globally and would require close interaction between applicants, WHO and regulators. The identifier should be non-proprietary and be able to distinguish between different SBPs, between SBPs and reference products, and between SBPs, reference products and non-comparables. A distinguishable INN would enhance global safe prescribing and the WHO should recommend that NRAs require assigned identifiers to be included alongside the INN in healthcare systems and practices, including labelling. The identifier code should be durable and linked to the medicine; it should have a short consistent format, e.g. 3 letters, and should not be intentionally meaningful or related to the company.

It was also recognised that a universal combination of INN plus identifier would need to be integrated into differing regional nomenclature systems where necessary and clear communication to all INN stakeholders regarding such a system would be essential. The INN and unique identifier should always appear together and should be used in pharmacovigilance track-and-trace systems whilst additional measures such as brand name and batch number should continue to be encouraged. Finally, as many follow-on versions of reference products have been authorised through pathways that did not meet WHO SBP guidelines, distinguishable naming should also apply to these types of biotherapeutic medicines.

Alliance for Safe Biologic Medicines

Safety of biologic medicines is paramount and the Alliance exists to ensure that patients are at the forefront. Serious adverse reactions occurred with a specific innovator biologic and despite the three versions on the market at the time having distinct INN, it took many months to determine the responsible product. Thus, if biologics have the same INN, it will be even more difficult to assess the responsible product when AE's occur. In a survey of US physicians, the vast majority preferred a name to a number and most felt that if an INN was identical, that the structure was identical and so the medicines can be easily switched. A resulting concern of the Alliance was that there would be inappropriate substitution. Tracking and tracing can be complex and if an AE occurs months following treatment, identifying the drug responsible can be challenging; thus it is important to trace back to identify the responsible drug and to take appropriate action.

A white paper produced by the ASBM/FDLI in 2012 recommended that all biologics should receive distinct non-proprietary names with biosimilars and their reference products having a shared root but distinguishing suffixes. Whilst the FDA has begun to use three letter prefixes for some biotherapeutics, the Alliance prefers distinguishing suffixes so that drugs are grouped together alphabetically; this is easier for doctors and nurses. Multiple layers of redundancy are important also to ensure safety of patient and in a letter from the Alliance to WHO, whilst suggestions were made along with suffixes, any system would suffice. Having a unique non-proprietary name would provide for an improved level of safety for patients.

INDIVIDUAL INN APPLICATIONS

Pharmacosmos A/S

An initial application in 2012 for an INN for an iron/carbohydrate complex was turned down through lack of definition of its structure. Following the submission of further documentation, the INN *ferric derisomaltose* was proposed at the 55th Consultation but that the Definition should be further clarified before publication, specifically concerning the carbohydrate structure. This information was provided shortly before the 56th Consultation. After the Consultation, the Company was then informed that there was insufficient information concerning the iron moiety. During May 2013 this further information was provided but the Company was then informed shortly thereafter that the INN Experts could not reach an agreement regarding the description to be published. The Company had therefore attended this stakeholders meeting in person to present a description based upon the adopted description for *ferric carboxymaltose* which is similar to its own *ferric derisomaltose*. Beyond this the Company was unsure how it should proceed.

The Chair acknowledged that this had been an unusual situation. Some of the concern of the Experts had centred around the inclusion of the term ‘penta’ which suggested the existence of 5 units whereas the structure is not a uniform compound, and indeed some Experts had questioned whether this was a mixture or not. This further information was appreciated by the INN Committee which would give it due consideration at the forthcoming 57th Consultation.

Ferring Pharmaceuticals A/S

Ferring Pharmaceuticals manufacture a recombinant follicle stimulating hormone (FSH) expressed from a human cell line. In comparison to other recombinant FSH, the drug substance of Ferring’s FSH has significantly different glycosylation (concerning terminal sialic acid linkages) resulting in a distinct PK profile and a different dosing regimen and dosing unit. The Company had previously requested an INN with a unique prefix and had rejected *follitropin delta* as the *delta* suffix did not distinguish it sufficiently from other FSH. Because Ferring’s FSH has a personalised and scientifically unique dosing regimen, the Company was concerned that prescribers will overlook the suffix resulting in mis-prescribing and over dosing. Indeed the Ferring FSH would not comply with a recent European Pharmacopoeia monograph on FSH as the reference is CHO cell derived. The Ferring representative also cited the introduction of a unique three letter prefix by the US FDA to avoid unintentional substitution of specific biotherapeutics by pharmacists using drop-down menus as an example of the need to distinguish closely related biologics in some instances.

In discussion, INN experts highlighted that INN are based upon structure, that the Greek letter suffix highlights differences in glycosylation and that regulatory agencies such as the FDA should not be altering INN even for supposed safety reasons. Where other biologics have the same stem but distinguishing names it is because of differences in amino acid sequence, in some cases involving only one amino acid.

Bellicum Pharmaceuticals Inc.

Bellicum made representation concerning an INN for AP1903 which is the first compound in a new class of rationally designed ‘dimerizer’ agents and stressed that it should not be classified as an immunosuppressant despite its derivation from FK506 (*tacrolimus*) a registered immunosuppressive drug. Various modifications of FK506 including a final dimerization step have abolished its immunosuppressant activity and AP103 has no biological activity in humans by itself. The function of this new compound is to dimerize specifically designed chimeric proteins expressed in genetically altered cells used in cell therapy. Following treatment of cell therapy patients with AP1903, dimerization of the cell surface proteins engineered into the therapeutic cells would result in their self-destruction and AP1903 has resolved GVHD in a patient within 30 mins. Another application, DeCIDE, is as an activation switch for dendritic cell vaccines which results in the production of large amounts of IL-12. The Company were present to request the INN Committee to avoid use of the stem

–*imus* (for immunostimulants) and proposed a new stem –*dimir*, with AP103 being assigned the INN *rimidimir* (or other suggested alternatives).

The Chair informed the Company that the Committee will certainly take these arguments into account when the application is assessed during the forthcoming INN Consultation.

NPO Petrovax Pharm LLC

Petrovax is a Russian biotechnology company which participated in the meeting to explain the structure and activity of its prolonged action hyaluronidase for which they have submitted an INN application. Substance 9575 is a conjugate of hyaluronidase with a water soluble synthetic polymer whose formation and structure is part of the company's IP. HPLC analysis of the conjugate shows a single molecular species. Compared with hyaluronidase on its own, the conjugate has improved thermostability and prolonged activity in serum. The hyaluronidase for 9757 is sourced from bovine testes and the drug product is marketed in the Russian Federation as Longidaze®. Longidaze® is indicated for therapy and prophylaxis of diseases accompanied by connective tissue hyperplasia and has been used successfully in surgery for scar treatment. In summary, substance 9757 comprises a single molecular species and should be eligible for an INN.

Baxter Healthcare Corp.

BaxterHealthcare had an application for an INN for its recombinant porcine factor VIII (OBI-1) turned down due to the heterogenous nature of the substance. The company had written to WHO for reconsideration and made representation at this meeting to clarify the situation. OBI-1 is a B-domain deleted porcine Factor VIII expressed as a unique single chain amino acid sequence. Like all other Factor VIII products, it undergoes post-translational cleavage to produce an active native heterodimer. Also in line with other recombinant Factor VIIIs, OBI-1 undergoes proteolytic truncation of the heavy chain C-terminus producing specific variants with 24 or more amino acids fewer, all of which have Factor VIII activity. Such variants are a common characteristic of recombinant Factor VIIIs including *octocog alfa* and *moroctocog alfa*. Indeed the Genentech patent for *octocog alfa* notes that it has multiple degradation forms due to proteolytic processing. Like OBI-1, *moroctocog alfa* has a deleted B-domain and similarly contains variants due to proteolytic degradation.

In conclusion, all recombinant Factor VIII products contain these degraded variants but are derived from a single expressed product, and the Company requested reconsideration of their application for an INN; six names were proposed.

Epizyme Inc.

The Company has submitted applications for two of its leading small molecule compounds, one for leukaemia (EPZ-5676) and one for lymphoma (EPZ-6438). Their design of novel anti-cancer drugs makes use of human genomics, epigenetics, and basic cancer causing mechanisms, an approach that contrasts with most anti-cancer drugs, which target rapidly dividing cells. These novel drugs target protein methyltransferases (PMT), a large class of enzymes that methylate histones, affect gene transcription, and many of which have known genetic linkages to cancers. The development of inhibitors of PMTs is an active area of research as they have promise as anti-cancer agents and EPZ-5676 and EPZ-6438 are expected to enter phase II studies in 2014. Both have similar mechanisms of action and inhibit the hypermethylation associated with MLL-r leukemia and lymphoma respectively.

To date there are no INN for PMTs or inhibitors of them and due to the large number of PMTs and the possible development of dozens of PMT inhibitors, Epizyme is proposing that a new stem is created for them; avoiding pre-existing stems would help avoid confusion regarding indications and patient populations.

Summary

Following this final presentation, the Chair drew the session to a close. There had been very interesting presentations; the information and comments provided by the first batch will be taken into account when biosimilars are discussed during the INN Consultation whilst the information presented regarding individual INN applications will also be used when the applications are re-considered, or

considered for the first time. The Chair was grateful to all those who took time to attend the meeting; the information provided was highly valuable to the INN Committee and hoped that the decisions that get made would be acceptable to all.