

***58th Consultation on International Nonproprietary Names  
for Pharmaceutical Substances  
Geneva, 8-10 April 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***

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***58th Consultation on International Nonproprietary Names (INN) for***

***Pharmaceutical Substances***

***Geneva, 8-10 April, 2014***

**EXECUTIVE SUMMARY**

**INTRODUCTIONS**

**Prof. Derek Calam**, Chair of the INN Expert Committee, opened the 58<sup>th</sup> INN Consultation and welcomed participants. He introduced Dr David Wood, Coordinator of Technologies Norms and Standards, in which section the INN Programme is now located.

**Dr David Wood** warmly welcomed participants on behalf of the WHO, thanking them and their host institutions for the time spent on INN activities between and at meetings. WHO depends on participants' willingness to give WHO the best advice in order to work towards convergence in medicines regulation. The reorganisation within the medicines department brings together all standards work and gives Technologies Norms and Standards a much stronger voice. As with all standards activity, there is a need to educate and this will be the case also with the implementation of a new biological qualifier scheme. Dr Wood stated that he is enormously impressed by the INN Programme and the work of the Secretariat and the INN Experts.

**Dr Raffaella BaloccoMattavelli**, INN Programme Manager, thanked Dr Wood for his generous words and expressed also her pleasure in working with the INN Group. It is a unique highly professional group which is becoming more and more recognised outside of WHO with an increased awareness that what is being achieved is really useful and helpful to society.

**NOMENCLATURE of INNs**

During the Consultation, a total of 119 INNs were discussed, including:

- 80 new INN requests, including 35 for biological substances
- 32 outstanding requests
- 7 previously selected proposed INN, against which a formal objection had been raised

As a result of these discussions, 96 new names were selected, which are planned to be published in List 112 of Proposed INNs, while 13 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. Five amendments are planned to be published in Lists 111/112. Two objections were not retained. Five new stems/sub-stems have been selected and 5 suffixes have been promoted to the pre-stem list

**BIOLOGICAL QUALIFIER SCHEME**

Immediately preceding this Consultation, there was an *ad hoc* meeting to continue discussion of a biological qualifier (BQ) scheme. A document outlining the scheme had previously been drafted, was further refined at the *ad hoc* meeting, and presented to the Expert Committee at this Consultation for comment and approval to go forward to a consultation phase with NRAs and industrial associations.

The document consists of an introductory section followed by an outline of the BQ scheme itself. The scheme would be globally harmonised and would consist of a 4 letter code (with avoidance of certain letters).

Applications for a BQ would be made to the WHO by a prospective marketing authorisation holder (MAH), concurrent with the application to the regulatory authority for licensure of the biological drug. This would take place upon the first application for licensure and in the event that application is made to more than one regulatory authority, then the WHO should be informed of each and, when established, the applicant should inform each authority of the BQ code. The MAH should update the WHO of any regulatory authorities subsequently approving a biological or of any changes to the information captured by the code. Whilst there will be an initial administrative fee for a BQ code, updates would be free of charge in order to encourage manufacturers to provide updated information.

The data pertaining to a particular BQ code would be held in a secure database at WHO with access to the data made available to healthcare workers, doctors, regulators and manufacturers, except for commercially sensitive information. It was noted in discussion that many comments and challenges about access should be anticipated and so there needs to be a good rationale for any decisions made regarding access to the database.

The code could be used for prescribing, especially to control substitution and interchangeability, in labelling, in pharmacovigilance, in reimbursement, in labelling and product literature, and other healthcare matters.

It would apply to all biological medicinal products for which an INN can be issued, e.g. it would not apply to vaccines, and reference should be made to the current INN policy for biological substances, the Biologicals Review (INN for Biological and Biotechnological Substances (a review) -2013- INN Working Document 05.179). It would also be applied retrospectively.

The Expert Committee agreed to the above and following a final review by the Secretariat and a small working group, the scheme can be circulated for consultation.

## **INN FOR VACCINES**

With developments over the years in recombinant vaccines, peptide vaccines and other novel types of vaccine, there is a need to re-discuss the INN vaccine general policies (Bioreview, item 3.10) and Bioreview item 4.23 concerning peptide vaccines/recombinant vaccines. The general policies for vaccines were created 20 years ago and have not been amended or changed since. It states that vaccines are not included in the INN system with their nomenclature being dealt with at WHO by the Expert Committee on Biological Standardisation (ECBS), but notes also that recombinant vaccines could fulfil the prerequisites for an INN application. Also, since peptide vaccines are chemically well-defined they fall within the INN system and indeed many peptide vaccines have received INN.

Item 4.23 attempts to define peptide and recombinant vaccines. With the development of many cancer and therapeutic vaccines involving different approaches including peptides, recombinant proteins and live vectors, some of which have been given INN, it seems appropriate to reassess the general vaccine policies and if feasible, it would be useful to re-define a recombinant vaccine. It should be noted that WHO does not have a general definition of a vaccine. However, many pharmacopoeias have monographs for vaccines.

The *Ph. Eur.* has general monographs for vaccines for human use and vaccines for veterinary use, which include definitions and tend to relate to traditional-type vaccines.

The Chair commented that vaccines may have implications for the Biological Qualifier scheme and suggested that the biological experts should comment on this issue. A closer link between INN and the ECBS would be useful and especially as both committees now fall within the same cluster of Technologies Norms and Standards. There is the possibility of a joint discussion on vaccines in October when both committees meet as the INN programme should not tackle this by itself.

## **PRESCRIRE**

Prescrire is a strong advocate of the use of INN throughout healthcare systems and promotes their use instead of trade names because overdosing with drugs with different trade names but the same INN is a potential risk. Prescrire has provided awareness of INN for many years, including information on INN common stems and special leaflets for patients to encourage their recognition of INN. There has also been a long standing relationship between Prescrire and the INN Programme with representation by INN staff at Prescrire meetings and *vice versa*.

To date, Prescrire has commented on 13 lists of proposed INN (pINN) following the recommendations of the Council of Europe on how to improve the checking of new INN against existing medicine names. A two-step Delphi method is used: first, potentially contentious pINN are scrutinised and second, a risk assessment of potential confusion between these pINN A novel proposed INN and previous INN, brand names, common stems and current or medical language is performed. Following this, results are summarised and a collective position is forwarded to WHO for comment.

The most common issue highlighted by Prescrire is a risk of confusion with other INN or common stems, a risk which is greater than between INN and trade names. Encouragingly, whilst the number of proposed INN addressed by Prescrire has generally increased with time, the number of objections has decreased. Prescrire's analyses also highlight a conflict of their pedagogical approach when no common stem exists, as it has difficulty in explaining to subscribers why no common stems can exist. Another concern is a misunderstanding arising from uncertainty of the potential Action and Use, as on occasions Prescrire can overreact through mistaking the use of the product. Finally, Prescrire finds it unfortunate that many INN never get to market and perhaps unused names should be re-allocated.

Three queries were posed to INN Experts: first, are Prescrire contributions relevant; second, should Prescrire continue to do these analyses; and third, when confusion risks are identified, is 'Tallman lettering' a way to enhance the understanding of common stems?

On behalf of the INN Group, the Chair responded to the first two queries, commenting that Prescrire's contributions are indeed relevant and important, and also that Prescrire's analyses are valuable and should continue. The third query on Tallman lettering was opened to the wider group for comment.

Tallman lettering is used to enhance some parts of words by using capital letters. Its use is not evidence-based and studies in Canada and UK have produced conflicting results. Also, in different regions, a particular Tallman letter can have a different appearance and is only useful for the Roman alphabet and not for Chinese or Arabic; so whilst it has been promoted in the USA by the FDA since the early 90's it is not suitable for global use.

The Chair thanked the Prescrire representative for his enlightening presentation, noting that within the linguistic resources available and the geographical spread of Experts, all attempts are made to deal with pronunciation, but that it does not come out perfect every time.

## **INTERNATIONAL MEDICATION SAFETY NETWORK (IMSN)**

The Prescrire representative also informed the meeting of the work of the International Medication Safety Network, of which he is a member, and whose aim is to improve patient safety through promoting safe medication. The organisation has issued a position statement on INN encouraging the use of INN over brand names. At the organisation's 2013 annual meeting, following proposals from Dr Balocco Mattavelli, IMSN decided to create a liaison with INN and to provide feedback on INN look-alike medication errors. In a USP study of look-alike errors, slightly more than half involved brand names and less than half involved generic names. Most INN errors reported were not especially confusing but occasionally can result in permanent harm or even be fatal. A long standing look-alike error involves morphine versus hydromorphone which gives rise to a serious risk of overdosing.

INN related medication errors occur at all stages of medication use and not only in prescribing. In addition to errors arising from similarity between INN, and INN and brand-names, errors occur through alphabetic neighbourhood, especially with electronic prescribing. The risk of confusion can be managed by improving the legibility of INN and where confusion exists by alerting users and by referring to a drug by both its INN and brand name. IMSN's position statement on this issue includes a risk analysis as to whether an INN should be changed, but recognising that this is a risky proposition. This last point is relevant to *trastuzumab emtansine* versus *trastuzumab* for which serious and fatal dosing errors occurred during clinical trials, resulting in the US FDA adding an extra prefix, 'ado', to *trastuzumab emtansine*, and thus raising the question as to whether the INN itself should be changed.

## **COLLABORATORS UPDATES**

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

2014 is the 50<sup>th</sup> anniversary of the Convention on the Elaboration of a European Pharmacopoeia (Ph. Eur.) and the start of the EDQM. A tri-annual international conference will be held in October in Strasbourg to mark the event, with plenary sections and workshops on a range of subjects. Details of the meeting and the draft agenda are available on the EDQM website.

As part of its anti-counterfeiting activities, the EDQM recently launched a new database called Know-X, which collates reports on counterfeit/falsified medicinal products. It further supports the Medicrime Convention by fostering collaboration and information-sharing between officials in relation to the detection and testing of counterfeit medicinal products, and to aid governments in the management and prevention of specific risks created by counterfeit/falsified medicines.

Supplement 8.2 of the European Pharmacopoeia was published in January 2014.

Finally, EDQM is now on Twitter (see @edqm\_news), providing posts about press releases, health campaigns and employment opportunities.

### ***Federal Institute for Drugs and Medical Devices (BfArM), Germany***

The Chair welcomed a new participant to the Consultation, from the German drug regulatory authority, the Federal Institute for Drugs and Medical Devices (BfArM), who will advise on publications. As manager of the BfArM drug substances database which has more than 40K substances including excipients and plastic for packaging, his main task is to give IUPAC names for substances and adding new INN to the database.-If discrepancies are detected, comments are submitted to the INN Secretariat.

#### ***International Union of Pure and Applied Chemistry (IUPAC)***

The revision of the Blue Book of organic compounds is now complete and was published at the end of 2013. It has taken 12 years to complete, contains 1,568 pages and weighs 2.5 kg. It does not make many changes, but importantly for regulatory authorities, it provides a preferred IUPAC name. Publications in journals have no obligation to use these but for patents and INN Definitions, the obvious implication is to use the preferred IUPAC name. It was prepared by the late Prof Henri Favre and Dr Warren Powell, both of whom developed the revision and responded to comments, although all final work and proof reading had to be by Dr Powell.

#### ***International Union of Biochemistry and Molecular Biology (IUBMB)***

Since the last INN meeting, 193 new enzymes have been added to the enzyme list, 74 have been revised with new information, including one new sub-subclass, 8 have been transferred following better classification and 6 have been deleted as they were already present in the listing.

#### ***Japanese Pharmaceuticals and Medical Devices Agency (PMDA)***

The responsibility for the Japanese Pharmacopoeia (JP) and Japanese Accepted Names (JAN) lies with the Division of Pharmacopoeia and Standards for Drugs of the PMDA. Preparation of JAN takes place in consultation with the JAN Expert Committee, which meets four times per year, and some of whose representatives are also members of the INN Expert Committee. Over the last 6 months, the Division has received more than 50 JAN applications, with about 15% for biologics. The latest total revision of the JP is the 16<sup>th</sup> edition published in 2011. Supplement I was published in English in April 2013 and Supplement II was published in February 2014, containing 1,896 monographs; an English version will be available online later in the year. The JP 17<sup>th</sup> edition is due to be published in spring 2016. The JP also has also been given legal status, as MHLW Ministerial Notification No. 519.

#### ***United States Approved Names (USAN)***

The 2014 winter USAN Council meeting took place on January 16-17, 2014 in Phoenix, Arizona, at which names for 31 drugs substances were proposed and approved. Twenty-seven INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 58<sup>th</sup> INN Consultation.

A teleconference on monoclonal antibodies with INN Experts, INN programme staff, FDA staff and the USAN Council and staff was held on March 17, 2014. Items discussed were the determination of the origin of the mAb and possible guidelines for chimeric and humanised designations.

USAN has begun planning for the summer 2014 USAN Council meeting scheduled to occur in July 2014 in Chicago, Illinois. From January 2014 through March 2014, USAN staff processed, researched and made recommendations for 36 new USAN applications and forwarded this information to the USAN Council. Through March 2014, 21 USAN, 7 modified USAN and 2 revised USAN were adopted during 2014. Revenue was also realised for an additional 9 negotiations.

### ***United States Food and Drug Administration (FDA)***

The FDA is tracking safety for biologics and any draft releases have to go to the US department of Health & Human Services (HHS) for approval. Regarding the teleconference on mAbs mentioned by the USAN representative, it should be noted that *ado-trastuzumab emtansine* is neither a USAN nor an INN, and that the *ado*- tag that FDA generated was for safety purposes, the FDA being allowed to designate such an alternate name.

### ***United States Pharmacopoeia (USP)***

Dr Roger Williams is stepping down as CEO of the USP and will be succeeded by Dr Ron Piervincenzi who will take over the leadership as of Feb 1, 2014. Dr Piervincenzi is a graduate of Duke University and arrived at USP from the McKinsey pharmaceutical group.

The USP is also concerned with pharmacovigilance and substituted drugs globally and recently opened a Center for Pharmaceutical Advancement and Training in Ghana to combat falsified, substandard and counterfeit medicines in sub-Saharan Africa.

### ***WHO Collaborating Centre for Drug Statistics Methodology, Norway***

The Centre has recently had its first semi-annual meeting and the minutes are waiting to be approved. Many anti-HCV (hepatitis C) drugs are appearing now and the Centre has requests from companies that have single and combination products on how to classify these into the Anatomical Therapeutic Chemical (ATC) classification system.

### ***World Customs Organisation (WCO)***

One of the most successful instruments within the WCO is the Harmonised System (HS) adopted by 150 Contracting Parties and which was created to facilitate international trade. It forms the basis for custom tariffs and 98% of international trade is based upon it. Similar to INN substances, each commodity is assigned an HS code and the 2012 version of the HS has 5205 assigned 6-digit subheadings. It is very important for WCO to provide harmonised information and the correct classification for INNs. HS classification is sometimes obvious but on occasions it may not be clear and every year the Scientific Sub-Committee of the WCO provides its advice to the HS Committee regarding, among other issues, the HS classification of INN products. The work of WCO is international and is in a position to improve harmonisation; with its work and experience on INN, WHO could also contribute to global harmonisation.

## **UPDATE on IDMIS**

The INN Experts were shown improvements to the online IDMIS system, covering earlier access to applications pre-Consultation and improved handling of publication data post-Consultation. Also, consistency checks are made for chemical drugs pre-Consultation, in preparation for future publication and to assist in naming substances during the Consultation. The possibility of assembling more publication information on biological substances pre-Consultation was considered, as this would make it more efficient in constructing the correct name, but would be a lot of work.

Changes implemented pre-Consultation will help minimise any delay in assessing applications and to improve the naming process; however, care should be taken in not building in too much that might impede progress in pre-Consultation assessment. There should be no delay in consideration of applications as Experts meet only twice a year and generally the information within an application is enough to make a decision.

**CLOSE of MEETING**

The Chair was grateful for all for contributions, both before and during the meeting. There has been good discussion providing plenty of material to reflect upon, especially on the development of a BQ scheme. Thanks were given also to the Secretariat for developments in the IDMIS system, making it more and more effective.

The Secretariat in return thanked the Chair for his role in the highly efficient running of the meeting.

**NEXT MEETING**

The 59<sup>th</sup> INN Consultation will take place at WHO headquarters, Geneva on 14-16 October, 2014.



**OPEN SESSION for STAKEHOLDERS**  
***58th Consultation on International Nonproprietary Names (INN) for***  
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Stakeholders were welcomed by **Prof. Derek Calam**, Chair of the INN Expert Committee. These Open Sessions continue to grow in popularity with this being the largest. They provide an opportunity for applicants to explain their requests where INN experts have difficulties. Other stakeholders present their wider views on various aspects on nomenclature. It was stressed that this is a closed meeting and any information disclosed or issues discussed should not made public until the official record is available.

**Dr Lembit Rägo**, Head of Regulation of Medicines and Health Technologies, similarly welcomed participants. Dr Rägo felt partly responsible for establishing these sessions to enhance transparency and allow stakeholders to present their arguments directly to the INN experts to help them make decisions. The first five presentations from associations on nomenclature issues show a keen interest in the work of the WHO and that those associations are willing to share their views, which helps build consensus and a mature decision making process.

## **BIOLOGICAL IDENTIFIERS**

### **Generic Pharmaceutical Association (GPhA)**

The GPhA addressed naming issues of biosimilars and biologics in general, all of which should receive the same sort of treatment when it comes to INN. Biosimilar medications provide patient access to affordable alternatives within healthcare systems and since their first licensure in the EU in 2006 they have had a very positive impact on healthcare. There is a competitive market place for biosimilars and it has been estimated that biosimilars could deliver savings of \$20 billion in the USA once the market stabilises.

Globalisation of naming is important and in addition to the INN, products will have a brand name and other unique identifiers such as the manufacturers name and the lot (batch) number, including in the USA a national drug code (NDC) number that will distinguish different products with the same INN. Products also have bar codes and soon 2D barcodes, but the INN is the only common identifier for drugs with the same active ingredient.

Globalisation promotes safety across the board and creating a new naming convention with unique INN will instil uncertainty and cause problems. In discussions with healthcare providers such as physicians and pharmacists it would appear that even a small appendage to an INN can make people think that it is a different drug altogether. The current INN system is working well and for example, the EMA has approved a biosimilar of a mAb with the same INN as the reference product. This is important for recognition under the biosimilar pathway. Indeed, more than 99% of post market reports on Retacrit® within the EU were identified correctly as Hospira's product without the need for INN differentiation. A further issue with non-identical INN for biosimilars is the exclusion of certain products with an alternative Greek suffix from reimbursement in several EU countries; this ultimately impacts on availability to patients. Thus, adding more complexity to the INN is not recommended although GPhA could consider an alternative unattached qualifier that includes the full company name of the marketing authorisation holder rather than a random code.

In summary it is important that WHO guidance for INN is scientifically-based and takes the clinical impact into consideration as well as is applied all biologicals and not only biosimilars, harmonised globally by the INN Programme.

### **European Generic medicines Association (EGA)**

The EGA appreciated the efforts being made by the INN Expert Committee and Programme to maintain a globally harmonised naming system for biologics. It quoted the EU naming system as a reliable model for naming of medicinal products (biosimilars included) with two options for the name of the product – an invented name or the common name accompanied by a trademark or name of the marketing authorisation holder. The INN is stated in addition to and separately from the product name in all labelling. The INN is usually a shared name between biosimilar products and the respective reference product. There is ample evidence that this system works in the EU, with several examples from pharmacovigilance studies of the successful identification of specific biosimilar products by their trade name. A recent EC survey also showed that member states support the current EU thinking that biosimilars should be closely aligned with their reference product and that biological products, including biosimilars, in the context of ADR reports, can be identified.

The EGA acknowledged that outside of the EU, some countries want a second level of differentiation in addition to the brand name, e.g. where a product name is not required separate from INN or to avoid inadvertent switching where INN prescription policies are in place. The EGA welcomed the consensus reached on key principles for this second level of differentiation in which the INN system would stay intact, with further product identification through an additional component being independent of the INN and which is applied retrospectively to all biologicals and not just biosimilars, and is voluntary for regulatory agencies. The EGA has had positive discussions on this with IFPMA and GPhA.

EGA presented three options for an additional component: a BQ code incorporating 4 random letters, a 4 letter code proposed by the company, or a company name as registered with the INN Programme. Various parameters of these options have been evaluated from a patient/physician perspective with the conclusion that the option of the company name identifier is the best solution as it was the easiest to recall and to implement. In conclusion, a thorough discussion with all stakeholders is necessary and the proposed solutions need to be tested with various stakeholders. Any system will need promotion and training. The EU system is a model for the world with clear differentiation (i.e. unique product name) and in countries where a product name is not mandatory, then EGA supports combining the INN with the company name.

### **Asociación Latinoamericana de Industrias Farmacéuticas (ALIFAR)**

ALIFAR is a non-governmental organisation founded in 1980. It is a regional body with 15 Latin American member countries representing approx. 500 enterprises. It is recognised by the Pan American Health Organization (PAHO) and has been a participant of the Pan American Conference on Harmonisation of Pharmaceutical Regulations since 1997. The organisation subscribes to what has already been said by previous speakers and is grateful for the opportunity to provide the Latin American perspective. Overall, ALIFAR does not understand the rationale to change something that is working. The INN should always be based on scientific criteria and this proposed modification is confusing. The main concern is for pharmacovigilance, and since this and traceability concerns are regulatory aspects, regulatory tools are the appropriate way to control these issues. The imposition of different or distinct INN for biosimilars will not improve safety, will only cause confusion and will likely affect the biosimilar market. In Latin America it will affect price, reduce access and

availability, and ALIFAR acknowledged and supported the efforts of WHO and PAHO in these points. ALIFAR is not comfortable in changing criteria for INN which has been in place since 1953, and INN classification should not be used to differentiate biological products with the same active ingredient.

### **International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)**

The IFPMA remains supportive of the WHO development of a biological qualifier (BQ). A BQ can support the goals of the INN system and help retain its integrity. Used in conjunction with an INN, it will support traceability in prescribing, dispensing and reporting adverse events on a global basis at both class and product levels, and between biotherapeutics. A BQ will help the challenge faced by having global variations in policy on the use of INN and trade names. For example, in the EU there is evidence that brand names are not always used in prescribing and dispensing biotherapeutics, as is recommended, and that in these cases, only INN are being used.

The IFPMA contends that the BQ should be given to all biotherapeutics and not just similar biotherapeutic products. It should be globally consistent and durable, identifiable or used consistently alongside the INN. It should also be linked to the ‘umbrella’ authorisation of a medical product, covering all presentations and line extensions. It should be non-discriminatory of the regulatory pathway involved and should be short and easy to record and remember. The WHO proposal for a 3 or 4 letter BQ has the potential to meet these needs.

On the other hand, a BQ should not include elements subject to change. It should not be meaningful and it should be a globally unique link to the ‘umbrella’ global safety authorisation, which is currently lacking. The presence of a BQ does not preclude regulatory authorities adding more identifier information although a global harmonised approach is preferred. A consistent naming approach should involve interaction between the MAH, WHO and the NRA, with the WHO taking the lead. The WHO should make a BQ publicly available online, including an annex to existing INN lists, but excluding confidential information. A link to a drug dictionary should be considered.

A BQ should be used by prescribers, dispensers, for AE reporting, by the pharma industry, by NRAs and by scientists. It should be linked to the INN, and WHO guidance and educational material for NRA’s, manufacturers, prescribers, pharmacists and patients would be needed.

In conclusion, the IFPMA supports the development of a BQ coding system that is applied to all biotherapeutic medicines, should be non-discriminatory, non-proprietary and globally applicable, with BQ data made publically available.

### **Alliance for Safe Biologic Medicines (ASBM)**

Since the previous Open Session in October 2013, at which ASBM presented, ASBM has taken part in a European Prescriber Study the results of which were released in Brussels in March 2014. The issue of biologics identification though is truly global and ASBM continues to be approached by people from around the world. Distinguishable INN support prescribing, dispensing, pharmacovigilance and manufacturer accountability. The ASBM backs the use of a BQ and it is interesting to note that other countries such as Japan and Australia are working on their own approach, but support a global WHO led scheme.

The European Prescriber Survey involved 470 prescribers amongst 5 western EU member states. What became apparent was a misconception that an identical INN means an identical drug, a finding consistent with a previous US study. Also a majority of respondents believed that biosimilars with an identical INN to its reference biologic, were approved for the same indication, which is not necessarily the case. Further, a significant number of physicians used

the INN only for biologics, which could result in patients receiving the wrong medicine. Prescribing by INN is encouraged throughout the world and frequently it is at the discretion of the prescriber whether to use the INN or the brand name. From the EU study, in reporting AEs, 17% had used the INN only. This can result in the pooling of adverse events, false attribution and other difficulties. The survey pointed to a clear need for education. This challenge in nomenclature will increase as biosimilar use increases. It is a global problem and needs a global solution, and the ASBM looks to the WHO to take an important lead for this important decision.

## **DISCUSSION on BIOLOGICAL IDENTIFIERS**

In opening discussion on a biological qualifier, the Chair highlighted the huge task that WHO/INN faces in attaining a global solution. The focus of discussion was primarily on the added value of a BQ in traceability, which is probably the most important aspect throughout the chain of prescribing to AE reporting.

The need for a scheme specific to the traceability of biologics compared to chemical generic drugs was questioned however, as there has to be as much care with switching of some chemical drugs as there has to be with biologics. This point was accepted to a degree, but for biological drugs, there is an additional layer of complexity in that these are complex entities, manufactured in a living system of which control is different and difficult, that characterisation is less robust than for chemical drugs, that different regulatory pathways are used and that adverse events could be long term.

To add to the debate, it was pointed out that pharmacists in the USA have taken a strong view on this and are not in favour of changing or adding to the INN, as they feel that their IT systems storing the National Drug Code (NDC) and the batch number are sufficient for traceability. However, even in the EU system, much of which is established in law, there is not full electronic recording; the full extent of AE reporting is not known and a full traceback in the EU cannot be guaranteed.

It was also commented that since education on a novel BQ scheme will be needed, it should be possible instead to train prescribers and dispensers to use INN plus trademarks, and possibly batch numbers also, to enhance traceability. But since the proposal is intended as a global scheme and different brand names are used around world, the BQ would be one item used globally independent of the brand name. Participants were also reminded that NRAs had requested WHO to develop a global scheme and with some NRAs already embarking on their own scheme, there is a clear need for a BQ.

As a representative of one such NRA developing its own scheme, the Australian TGA representative informed participants that the TGA's motivation in developing a biosimilar identifier was primarily to aid tracing and prescribing. It is a conservative approach as there is a certain level of redundancy in a BQ scheme but it allows internal cross-checks.

Looking ahead, it is unclear exactly how a BQ will work in traceability. With an increasing number of companies manufacturing active pharmaceutical ingredients for sale to others for final formulation, company names are not very useful for traceability as they often change when companies get sold. This unique BQ route for the site of manufacture of an active pharmaceutical ingredient (API) could be the way forward but will depend also on the maturity of the regulatory authority, many of which do not assess drugs and their manufacture to the same extent as others.

The Chair was grateful for the discussion noting that so much more time could be spent on it. Although the INN Committee was asked to look into and develop a scheme for global use, we are all realistic and that with different problems in different member states, it is unlikely that more than a fraction of WHO member states will pick up and use whatever acceptable solution gets developed. Ultimately however there is a strong view that there is a problem and that the solution should be at the global level and not be left for a few regulatory authorities to develop their own system.

## INDIVIDUAL INN APPLICATIONS

### Cytos Biotechnology AG

Cytos has previously had an application for an INN for its substance CYT003 turned down on the basis that it was a mixture. Having objected to this decision, it now presented further details of its compound and argued that an INN should be appropriate. CYT003 is a unique compound for targeted delivery of a Toll-like receptor 9 (TLR9) agonist oligonucleotide. It comprises a synthetic A-type CpG oligonucleotide encapsulated in a bacteriophage Q $\beta$  icosahedral capsid containing 180 identical Q $\beta$  coat protein subunits. The capsid protects the CpG oligonucleotide from degradation in the serum and, following capture by dendritic and B cells, allows efficient delivery of the TLR9 agonist to this relevant TLR9-positive compartment in local lymph nodes.

Capsids are produced in *Escherichia coli* and disassembled into subunit dimers. Purified dimers are reassembled into capsids in the presence of aggregated CpG oligonucleotides, encasing them inside the capsid with the oligonucleotides bound to the inside of the particle. Purified dimers do not form capsids in the absence of the oligonucleotides. The oligonucleotide containing capsids are characterised by size exclusion chromatography, electron microscopy and oligonucleotide content, with batches of CYT003 having a highly consistent oligonucleotide content. Thus CYT003 is a highly defined drug substance consisting of a protein coat and a TLR9 agonist oligonucleotide, with the capsid being essential for virus-like mediated delivery to the correct cell type and the oligonucleotide to exert the desired biological activity.

The company also argued that peptide vaccines set a precedent for this type of drug substance and that *amilomotide* especially, a virus-like particle of bacteriophage Q $\beta$  coat protein coupled with multiple copies of a human beta-amyloid peptide fragment on the capsid surface. The principle difference between CYT003 and *amilomotide* is the location of the oligonucleotides inside the surface (in CYT003) rather than the peptides of *amilomotide* being bound on the outside.

The company proposed also a new stem for this class of substance, along with proposed INN.

### Epizyme Inc

Epizyme has previously lobbied the INN Expert Committee for a novel stem for protein methyl transferase (PMT) inhibitors. PMTs regulate gene expression by methylation of histones and many have a genetic link with human disease; as such, they form a large class of novel therapeutic targets. Epizyme has two PMT inhibitors, EPZ-5676 and EPZ-6438, in clinical development, the former for leukaemia and myelo-proliferative disorders, and the latter for B-cell lymphoma, follicular lymphoma and advanced solid tumours. Many other companies are similarly developing PMT inhibitors.

At the 57<sup>th</sup> INN Consultation, the stem *–metostat* was selected by WHO for its new drug substances, rather than the requested novel *–adomet*, *–isemat*, *–edomet* or *–emetar* stems. The

company however feels that the *-stat* class is inappropriate. First, the *-stat* class includes HDAC inhibitors which have a similar patient population as PMT inhibitors and prescribing an HDAC instead of a PMT inhibitor has the potential for severe myelosuppression. Second, the *-stat* stem is overcrowded and inhibitor classes with fewer targets than PMT have a unique name, and third, *-metostat* is in conflict with existing company trademarks, e.g. MetaStat Inc. Consequently, Epizyme expressed disappointment of the selected *-stat* stem and is re-requesting that its previous stem suggestions are re-considered, or a further suggested novel stem *-statomet*, which would differentiate this new class of inhibitor from the general *-stat* class.

### **Bayer Pharma AG**

Bayer has made an application for the INN *octocog alfa* for its new Factor VIII preparation – BAY 81-8973. At the 57<sup>th</sup> Consultation, the application was deferred for further discussion at the 58<sup>th</sup> meeting.

*Octocog alfa* is the same INN as the currently marketed Bayer Factor VIII product Kogenate®. BAY 81-8973 and Kogenate® have the same FVIII amino acid sequence, are produced in the same cell substrate in perfusion-based bioreactors, have the same molecular formula, the same proteolytic processing, the same heavy to light chain ratio and the same post translational modifications (glycans and sulfation).

BAY 81-8973 is a next generation FVIII product for which human biological reagents, plasma and albumin, have been removed from the manufacturing process and an additional viral clearance step has been added to the downstream process. In the glycan analysis, the glycoforms are highly similar with some minor variations in levels of specific antennary structures whilst the overall level of sialylation is slightly higher in BAY 81-8973 but both substances within the company's specification. Minor quantitative differences are also observed between different batches of the same products and there are no major differences from a clinical perspective.

Bayer considers that despite the small differences in glycoform structure that *octocog alfa* remains the appropriate INN for BAY 81-8973.

### **GENFIT**

At the 57<sup>th</sup> INN Consultation, the name *orlefibrate* was selected for GENFIT's candidate drug for metabolic liver diseases, GFT505. The company finds this name inappropriate as it felt there are functional differences between GFT505 and fibrates and there is potential confusion between *orlefibrate* and *clofibrate*. GENFIT now presented further information on GFT505 with apologies that it had not included this in the original application.

GFT505 is a drug candidate for metabolic diseases including liver disorders and has recently successfully completed Phase IIa trials for treatment of non-alcoholic steatohepatitis (NASH), a condition that can lead to cirrhosis, liver failure and liver cancer.

The *-fibrate* class is defined as *clofibrate* derivatives, which are mostly specific PPAR $\alpha$  activators; in contrast, GFT505 is a first-in-class dual agonist of PPAR $\alpha$  and PPAR $\delta$ . Fibrates themselves are not effective in NASH and those on the market are not for treatment of NASH.

Studies show that GFT505 displays different specific effects on human monocytes and human fibroblasts compared to *fenofibrate* with the PPAR $\delta$  activity of GFT505 being essential in NASH protection. Furthermore, the protective effects of GFT505 against NASH in a mouse model are not reproduced by *fenofibrate*.

In addition to *-fibrate* being an inappropriate stem, the selected name *orlefibrate* is felt to be in conflict with *clofibrate*, *fenofibrate* and *orlistat*, which presents a risk of prescription error. Consequently, GENFIT proposed several alternative stems and names, but all of which include a *-fibr-* infix.

## **CLOSE of MEETING**

The Chair thanked all stakeholders for attending the meeting and noted that all presentations and discussion will be considered during the 58<sup>th</sup> Consultation. It was unfortunate that time was short due to the large number of presentations but nevertheless, these informal meetings are highly valuable to the INN Experts.