

**75<sup>th</sup> Consultation on International Nonproprietary Names for Pharmaceutical  
Substances**

**Geneva, 18-21 October 2022 (hybrid face-to-face/virtual meeting)**

***Programme on International Nonproprietary Names (INN)***

***Access to Medicines and Health Products Division (MHP)***

***Health Product Policy and Standards Department (HPS)***

***World Health Organization, Geneva***

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### **EXECUTIVE SUMMARY**

#### **OPENING REMARKS**

The 75<sup>th</sup> INN Consultation was opened by Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products and welcomed all participants on behalf of Dr Clive Ondari, Director, Health Products policy and Standards (HPS) and Director of the INN Programme, and the Assistant Director General, Dr Mariângela Batista Galvão Simão, who sent their apologies for not being able to attend in person. It was a pleasure for Dr Balocco to see many of the INN Experts and Advisors around the table and hoped that everyone would be present face-to-face at the next meeting this was much better than virtual attendance. She reminded Experts that they must work independently and not on behalf of their organisation, and encouraged them submit their comments on applications pre-meeting as the number of requests was very high and increasing with each Consultation.

#### **ELECTION of CHAIR, VICE-CHAIRS and RAPPORTEUR**

Mr Adrian Evans was proposed, seconded and elected unopposed to the Chair. Prof. Menico Rizzi was elected vice-chair for biologicals and Professor Vicente Rodilla Alamà was elected vice-chair for chemicals. Dr James Robertson was elected as rapporteur.

The Chair looked forward to a fruitful discussion. With the meeting split between those in the room and those online, and with several new attendees, a tour de table was held.

#### **74<sup>th</sup> NOTES of CONSULTATION**

The Notes of the 74<sup>th</sup> Consultation were adopted without objection and the Chair thanked the Rapporteur for his excellent work.

#### **NOMENCLATURE of INN**

During the 75<sup>th</sup> INN Consultation, a total of 259 INN requests was discussed, including:

- 212 new INN requests, including 121 for biological substances
- 47 outstanding requests

As a result of these discussions, 247 names were selected, which are planned to be published in Lists 128 (COVID-19-related requests only) and 129 of proposed INN (p.INN). Six requests did not fulfil INN criteria (No INN) and 6 requests were deferred for future discussion.

Ten new stems/substems were selected, 13 suffixes were promoted to the pre-stem list and it was decided to review the description of one stem.

#### **MONOCLONAL ANTIBODY NOMENCLATURE: -BART VERSUS -TUG SUFFIXES**

The new nomenclature scheme for monoclonal antibodies (mAbs) provides for four distinct suffixes. However, issues had cropped up regarding two of them, *-tug* and *-bart*. The suffix *-tug* is used for monospecific full-length immunoglobulins with unmodified constant regions and identical sets of complementarity-determining regions (CDRs) that recognize the same epitope; basically, this group includes all natural immunoglobulin molecules. The suffix *-bart*

is used for monospecific full-length immunoglobulins with engineered amino acid changes in the constant regions and identical sets of CDRs that recognize the same epitope; by definition, mAbs falling into the *-bart* category would not occur in nature. The *-bart* stem was also designed to cover mixed allelic variants not seen in nature, but it now seemed that some previously undocumented combinations of variants were indeed naturally occurring and therefore some mAbs assigned as *-bart* possibly should have been assigned *-tug*.

Assigning *-tug* versus *-bart* is determined from the mAb protein sequence using a specific algorithm to compare the CH1, CH2 and CH3 domains with the germline DNA sequences to determine whether they all fall into the same allelic cavity; if they did not then it was not a naturally occurring mutation, which then suggested the appropriate suffix was *-bart*. But as more naturally occurring immunoglobulins get sequenced, combinations not seen before were being found, and mAbs previously assigned *-bart* should perhaps be *-tug*. However, the suffix assigned had to rely on data available at that time – specifically the germline sequences provided by the international ImMunoGeneTics (IMGT) information system. Also, where there was no evidence to show that the sequence had not been mutated, it was assumed that it had, and when assigning *-bart* under those circumstances there had to be an extra check with the applicant as to whether the mAb had been specifically mutated.

It was inevitable that some teething issues occurred with the new suffixes but redesigning the definition of *-tug* should fix this, although the weakness was in not having the necessary tool to determine if an allele was a natural variant or not.

In detail, when two or more germline sequences match a mAb domain sequence with the same score, the heuristic approach had been to select the germline assignment with the lower number. IMGT-GapAlign tended to show these first. A CH1 domain matching IGHG1\*03 and a CH3 matching IGHG1\*01 actually matched IGHG1\*08 in both domains (CH2 was the same in all cases). However, a CH1 matching IGHG1\*01 and a CH3 matching IGHG1\*03 is not currently listed as an allelic variant in IMGT. Serological allotype assignment had suggested that this combination did occur naturally, but it had not been included in IMGT because the DNA sequence had not been obtained and confirmed. This combination would be added to IMGT as IGHG1\*15 in the future, confirming that this combination should be assigned as *-tug* and not *-bart*.

Domain	Position in domain	IGHG1*01	IGHG1*03	IGHG1*08	IGHG1*15
CH1	97	K	R	R	K
CH3	16,18	D,L	E,M	D,L	E,M

## CELL THERAPY SUBSTANCES

In a breakout session during the Consultation, a small number of Experts discussed the naming of cell therapy substances, focusing on the content of the Definition that accompanies the name, the length of names, and the growing use of abbreviations of cell INN by authors in scientific publications.

Recently, an INN applicant for a cell therapy had requested to alter the Definition of a proposed INN in order to accommodate changes, or future potential changes, in their manufacturing process. This had triggered concern amongst the Experts that ongoing changes to manufacture could impact the final cell substance to the extent that a new INN would be required; this would certainly be the case if a regulator assessed that manufacturing change altered the product. The Experts believed that when INN get requested very early in development of a cell therapy, the chances would be high that changes would be made to manufacturing processes. Early requests

for INN could be driven by pressure from regulators to obtain an INN or applicants wanting the INN for research publications or commercial reasons. Furthermore, applicants were often unwilling to provide decisive data as to how the cells were manufactured and this resulted in an incomplete Definition. In such cases, the INN process was best put on hold. It was suggested to amend the INN application form to make clear that the Definition of the cell substance, including how it was manufactured, could not change significantly and if it did, a new INN may be required.

The Experts also discussed how to keep cell substance names short and pronounceable. Some two-word names were very long and it had been noticed that in the literature, abbreviations of long INN were being used, for example 'AXA', instead of *axacabtagene autoleucl*. Some early cell INN were acceptable, being not too long, but with time their length has increased. Genetically engineered cells especially have long two-word names. There is a need to find the correct balance between what information can be contained within the INN name versus the full information present in the Definition. One suggestion was to copy the approach used for fusion proteins whereby single letters rather than syllables were used as infixes; however, single letters are essentially codes and many users do not know what they infer.

It was decided that the INN Experts should publish a letter in a scientific journal updating the cell therapy industry on the precise information that is required for cell therapy INN, and at what stage this is required. The letter would also highlight that INN should never be shortened in scientific literature. This could be followed up by a position paper on this topic covering all issues in full detail.

An exercise could also be performed by assessing current names, especially long ones, on how they could have been created shorter and more pronounceable, perhaps by using fewer infixes in the name and relying more on the full account of the substance in the Definition. It needed to be borne in mind that the cell nomenclature scheme had been developed alongside the United States Adopted Names (USAN) scheme and any changes should remain harmonised with that scheme.

## **PEPTIDES**

At the Open Session accompanying this Consultation, there had been a presentation on INN for an immunomodulating multi-peptide substance. The INN approach with such substances is to name each peptide using the *-motide* stem, as INN are not assigned to mixtures. In contrast, USAN provides a single non-proprietary name to mixtures of peptides using the stem *-imut*. A group of INN Experts met virtually in June of this year to discuss a way forward for the INN to harmonise with the USAN scheme. With many opinions expressed, the outcome could be summarised as follows. First, assigning INN to a mixture of peptides containing up to, for example, 5 peptides, should follow current INN rules with each peptide being named individually with the *-motide* stem. Second, given the concern in printing multiple INN on the packaging of medicines and pressure to name mixtures with a single INN, well-defined mixtures with more than 5 components could be given an individual name with a stem that may be *-imut*. This approach would only be acceptable if each component of the mixture was well defined, including the comparative ratios of each peptide. If the mixture was not well defined, then no INN would be assigned. This would require a clear explanation of what was required in order to be considered 'defined'. The idea of using the INN approach to demonstrate that the substance had a single name, but was in fact a mixture, was mooted, but the additional letter could not be 'M' as this is used for INN Modified and could not be used for 'mixture'.

*In discussion*, a major point was the number of components present that would trigger a single INN in the event a mixture of peptides could be named. Five was suggested initially, as most

such mixtures have no more than this. Whilst there was support for this type of approach, it was argued that even if the substance comprised only two peptides, then it was a mixture and so anything beyond a single peptide would need to be named accordingly. That is, a single peptide would have a *-motide* name, but two or more would have, as per the USAN approach, an *-imut* name (or whatever suffix gets harmonised with USAN). It was re-emphasised that a clear definition of the substance would be important. With regard to harmonising a suffix with USAN, it was highlighted that the stem *-imut* (for immunotherapy) would clash with the pre-existing INN stem *-imus* (for immunosuppressants); however, there was also the opinion that the two could co-exist.

The EMA representative indicated that they would approach such mixtures in the same way as multi-component vaccines. For example, the 23-valent pneumococcal vaccine was named with a common name (generic descriptor) that is distinct from the applicant's invented name; the descriptor was then defined within the product summary of product characteristics.

With a pragmatic solution being required, and with no clear consensus, the Chair requested that the Experts seriously consider the proposal that a single peptide substance was named with *-motide* and that a mixture of two or more peptides be assigned a different single suffix. A final decision on this is needed and discussion should continue post-meeting including collaboration with USAN and the Center for Biological Evaluation and Research (CBER) on this issue.

### **SCHOOL of INN (SoINN)**

The 18th meeting of the SoINN steering Committee took place on the day preceding this 75<sup>th</sup> INN Consultation.

The website was now available in Arabic, in addition to English, French and Spanish.

Following changes in certain INN nomenclature schemes, some courses had been updated; this had been completed for vaccines and was almost complete for mAbs. A new course on ATC classification was well advanced. It was hoped that an update of these courses in the above four languages would be achieved by the end of the year.

The website's statistics show that few students had been connecting, with the majority of connections coming from the pharmaceutical industry. This underuse was partly explained by the fact that students, following distance learning during the pandemic, wanted physical meetings with their teachers. Also, for example, the pilot site of the University of Grenoble had set up a very interesting educational activity based on 'stems in pills', but this did not appear in the website statistics. It also had to be acknowledged that among health professionals and students, the SoINN was not sufficiently known and therefore promotional work was due to be implemented in the coming months.

A face-to-face meeting to set up and improve collaboration within pilot sites had long been envisaged but had been impeded by Covid pandemic travel restrictions. However, a first meeting would now take place in the spring of 2023. A pilot site had been approached to organise the meeting and preparation should begin in November 2022.

It was highlighted that the SoINN programme was not a restricted sub-committee of the INN and anyone who wished to participate could do so; new ideas were especially welcome.

*In discussion*, it was suggested that without students being examined on this or receiving credits, they would not be interested in the SoINN programme. It was also noted that, in the UK at least, some nurses are able to prescribe, and their training could be enhanced with the SoINN courses.

It was unfortunate that the covid pandemic had significantly impacted the SoINN expansion. It was underlined that the face-to-face meeting being planned would be important to enhance the profile of the SoINN, to welcome newcomers and generate new ideas. There were also plans to have a session at the next International Pharmaceutical Federation (FIP) meeting dedicated to the SoINN, and there were already some INN collaborators setting up working groups.

## **COLLABORATORS' UPDATES**

### **Brazilian Pharmaceutical Substances Nomenclature Committee (CTT DCB)**

The Brazilian Pharmaceutical Substances Nomenclature Committee (CTT DCB - Comitê Técnico Temático (Technic Thematic Committee) Denominações Comuns Brasileiras (Brazilian Nonproprietary Names) is one of the committees of the Brazilian Pharmacopeia, which is linked to Brazilian Health Regulatory Agency (ANVISA).

From April 2022 (the previous INN Consultation) to October, the CTT DCB had six meetings, almost once a month. At these meetings, 36 new names were approved, of which there were 19 chemicals, 12 biologicals, 4 excipients and 1 vaccine. All these substances were currently in the medicines registration process in ANVISA.

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

Last year, Dr Susanne Keitel retired after 14 years as the Director of the EDQM. The new Director is Dr Petra Dörr. After a number of years in industry, and then at Swissmedic (the Swiss Regulatory Agency), Dr Dörr's last role before joining the EDQM was at the WHO, as the Head of Unit for Regulation and Safety. Dr Dörr took over as Director of the EDQM in October 2021.

Following the publication of the 11th Edition of the European Pharmacopoeia in July 2022, the 11th Edition conference was held in Strasbourg in September. It was a hybrid meeting with almost 300 participants, including representatives from the WHO, national authorities, and sister pharmacopoeias including the JP, USP, and Indian Pharmacopoeia Commission, [which is joining the Pharmacopoeial Discussion Group \(PDG\) expansion pilot this month](#).

The PDG brings together the Japanese, US and European pharmacopoeias, with the WHO as an observer, so this pilot was another step towards increasing the harmonisation of international pharmacopoeias. The importance of increasing global pharmacopoeial harmonisation was one of the topics discussed during the conference. Other subjects included big data, further steps to reduce animal testing in the healthcare sector, and nanomedicines (including the COVID-19 mRNA vaccines).

Supplement 11.1 of the European Pharmacopoeia was published in October 2022, and the public forum Pharmeuropa 34.4 was open for comments until 31 December 2022.

Other recent publications included the [8th Edition of the Guide to the quality and safety of organs for transplantation](#), in July. The EDQM had been supporting the [European Day for Organ Donation and Transplantation](#), which was hosted by Poland on 8 October. This included a campaign to encourage people to consider becoming donors and, importantly, to discuss the issue with family and friends to make their wishes known. It was estimated that a single donor could save up to 8 lives through organ donation and save or improve over 100 more through tissue donation, therefore there was always a need for more donors.

Finally, there was an ongoing [call for experts](#) from the European Pharmacopoeia, which invited applicants from national authorities, industry or academia to join the wide range of expert

groups that contribute to developing and maintaining pharmacopoeial monographs. Experts were welcome not just from the Ph. Eur. Commission member states, but from all around the world. More details on this and all of the EDQM's activities were available on the EDQM website ([www.edqm.eu](http://www.edqm.eu)), as well as the Twitter feed (@edqm\_news).

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

Three new publications were highlighted:

- Glossary of terms used in physical organic chemistry (IUPAC Recommendations 2021), *Pure Appl. Chem.* 2022, **94**(4), pp. 353-534
- Terminology and the naming of conjugates based on polymers or other substrates (IUPAC Recommendations 2021), *Pure Appl. Chem.* 2022, **94**(5), pp. 559-571
- Standard atomic weights of the elements 2021 (IUPAC Technical Report), *Pure Appl. Chem.* 2022, **94**(5), pp. 573-600.

### **Pharmaceuticals and Medical Devices Agency (PMDA), Japan**

JAN (Japanese Accepted Names): from April 2022 to October 2022 the JAN Expert Committee took place virtually seven times, including an *ad hoc* meeting for COVID-19 related substances, and 32 names had been published.

JP (Japanese Pharmacopoeia): supplement 1 to the JP 18<sup>th</sup> edition would be implemented in December 2022. The main topic of interest was the revision of monographs related to the implementation of the ICH-Q3D guideline. The Pharmacopoeial Discussion Group (PDG), which brings together the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP), with the WHO as an observer, was delighted to welcome the Indian Pharmacopoeia Commission (IPC) as a participant in the PDG pilot for global expansion.

Link <https://www.pmda.go.jp/files/000248125.pdf>

### **Therapeutic Goods Administration (TGA), Australia**

In July 2022, the TGA completed its move into the new purpose-built, state-of-the-art building in Fairbairn Canberra. This has brought together all TGA's divisions and branches including the laboratories within the same building complex.

Provisional designations for COVID therapies continue at the TGA these included:

- a) April 2022: provisional determination for the Moderna bivalent COVID-19 vaccine "SPIKEVAX Bivalent Zero/Omicron"
- b) July 2022: provisional determination for two Pfizer vaccines - a monovalent COVID-19 vaccine, *riltozinameran* (COMIRNATY OMICRON), and a bivalent COVID-19 vaccine, *tozinameran & riltozinameran* (COMIRNATY BIVALENT)
- c) August 2022: provisional determination to *sabizabulin* for treatment of COVID-19

Provisional designation implied that sponsors could seek approval through the provisional pathway on the basis of preliminary clinical data where there was the potential for a substantial benefit to Australian patients. Additional information on all matters about COVID19 at the TGA could be obtained from <https://www.tga.gov.au/products/covid-19>

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

The 2022 summer USAN Council meeting took place virtually on June 9, 2022. Names for 42 drug substances were reviewed and discussed. Eleven new stems and infixes were approved and added to USAN's stem list. One stem definition was revised. Meeting topics discussed included: a negotiations update, USAN website metrics, the April 2022 INN Consultation, ISMP and FDA's medical error reports, and a COVID-19 drug substances update.

Twenty-three new INN applications and 6 revised INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 75th INN Consultation.

Through September 2022, USAN staff would have processed, researched, and made recommendations for, 221 USAN applications and forwarded this information to the USAN Council for their review and name selection. Also, through September 2022, 194 USAN would have been adopted and revenue realized for an additional 9 negotiations. Currently, there were approximately 187 active USAN negotiations.

The 2022 Winter meeting of the USAN Council would be a virtual meeting and was scheduled for December 2, 2022.

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

There were no significant updates on nomenclature to report.

A new commissioner, Dr Rob Califf, had been appointed to the FDA. The Center for Drugs Evaluation and Research (CDER) had a new director, Dr Patrizia Cavazzoni.

New bivalent COVID-19 vaccines had been authorised.

The no-travel policy for non-critical travel within FDA remained; this would hopefully change next year. The incumbent FDA representative at INN consultations would be retiring in 2024 and was currently training two replacements, one of whom would attend INN Consultations after this date.

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

USP reported transition to the GRSR platform for curation of chemical information. The presentation featured the USP Dictionary of USAN and International Drug Names, and also functionality of the GRSR public site hosted by NIH at <https://gsrs.ncats.nih.gov/ginas/app/beta/home>.

### **WHO Collaborating Centre for Drug Statistic Methodology**

Revision of the classification of immunosuppressants (ATC group L04) began in 2021 and the latest draft would be discussed at the meeting of the ATC/DDD Working Group in Geneva in October 2022. The current proposal included alternative subdivisions into new ATC 4th levels, either one for pharmacological subgroups only, or a hybrid alternative with some groups based on indication and some on pharmacologic sublevels. A new temporary classification would be published in November and included in the ATC index 2024.

There had been several quite extensive revisions in recent years, and it was hoped that there would be no further major reclassifications for some years to come, especially as the ATC/DDD classification was meant to be stable. The changes made in recent years ensured the system was more prepared for the inclusion of new drugs in the future.

The Centre was participating in the WHO-AMR-CC (WHO Antimicrobial Resistance Surveillance Collaborating Centre) Network in connection with the Global Antimicrobial Resistance Surveillance System (GLASS). At least 70 countries were enrolled in GLASS-AMC at present. They were able to collect national data based on the ATC/DDD methodology and more countries would be included in 2023.

### **World Intellectual Property Organization**

The WHO INN global data hub and the WIPO global brand database (GBD) had been connected since 2018, following the signing of a memorandum of understanding between WHO and WIPO to facilitate access and exchange of information on INN. Following the information exchange the WIPO database was updated with the INN only, in the six official

UN languages. The objective was to provide a means for trademark authorities to have accessible, up-to-date information on proposed and recommended INN in order for trademarks to be examined for potential conflict. An email alert was sent to WIPO members when new INN data was published on the WIPO GBD.

A new interface with the GBD had been created that could search through more than 52 million records from 71 data sources, including more than 11,000 INN up to and including rINN List 88. However, it should be noted that searches should not be done by Nice Class, for example, if a search was performed for INN in Nice class 5, no results would be returned; this was being addressed for the new interface, but currently both versions of the GBD remained available.

There remained a gap between some national authorities and the GBD as some trademarks were not listed until they were fully registered, which meant that it would be too late for a meaningful comparison with recommended INN. However, links between national TM offices and WIPO continued to improve.

The Chair noted that the interactions between INN and WIPO were to be highly commended, along with the new interface to the GBD.

There followed a brief demonstration of searching the GBD via the new interface.

### **CLOSE of MEETING**

The Chair congratulated all Experts and the INN Secretariat for the huge amount of work involved in assessing more than 250 requests, both before and during the meeting, and thanks were due to everyone for that.

Dr Balocco thanked the Chair for his efficient and competent leading of the meeting.

### **Next Meeting**

The 76<sup>th</sup> INN Consultation is scheduled to be held in Geneva on 28-31 March 2023.

## INN STAKEHOLDERS SESSION

### 75<sup>th</sup> Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

(a hybrid meeting with some participating virtually and some present at WHO HQ, Geneva)

Geneva, 18<sup>th</sup> October 2022

Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products welcomed all participants to this Stakeholders Session of the 75<sup>th</sup> INN Consultation on behalf of the ADG and Dr Clive Ondari, Director, Health Products policy and Standards. This was a hybrid meeting with many members of the INN Expert Group and the Secretariat present at WHO HQ in Geneva, and with all other participants including the Stakeholders attending virtually. The session provides a unique opportunity for stakeholders to discuss individual issues of interest. It was emphasised that any and all information discussed during the meeting must remain confidential until the meeting report is adopted and made public.

The meeting was chaired by Mr Adrian Evans who also welcomed the participants and highlighted that it gave the INN Expert Group an opportunity to understand how names are being used and the specific problems that arise from INN policies.

#### Heartseed

At the 72<sup>nd</sup> INN Consultation, Heartseed's allogeneic iPSC derived cardiomyocyte spheroids cell therapy substance was assigned the name *remumiocel* which was included in pINN List 126. In Feb 2022, the company requested an amendment to the Definition (the part of the INN that describes the substance in detail) and following some clarification queries, in May 2022 the company accepted the INN Experts' recommendation to postpone publication of *remumiocel* as a rINN. The company does not yet have any clinical data and attended this Stakeholders Session to share their thoughts on how the Definition should be modified.

The manufacturing process involves differentiating healthy donor-derived allogeneic iPSC's into cardiomyocytes followed by culturing in a unique medium that terminates undifferentiated iPSC and other cells. The highly purified cardiomyocytes are formed into spheroids that enhances engraftment following transplantation. The company anticipates that the manufacturing scale will evolve during the life cycle of the product from the initial plate culture through increasingly larger bioreactors. There will also be material changes, some of which will be major and some minor. Following such manufacturing changes, comparability of the final cell product will be required and significant discussion with regulatory authorities is anticipated.

With regard the INN Definition, the company explained that the removal of certain manufacturing features was requested as they saw these as minor, for example, a change of vectors expressing reprogramming factors from plasmids to Sendai virus or mRNA lipofection would not affect the final product. Also, while certain reprogramming factors such as OCT3/4, SOX2, and KLF4 are key to the process, others such as LMYC, LIN28, tumour suppressor p53 (Tp53), and Epstein Barr nuclear antigen 1 (EBNA1) are minor and may not be used in the future. Some other media supplements such as FBS would also be removed during scale-up. The company noted that the current INN Definition is not incorrect but that the minor

ingredients highlighted above should be removed from the Definition along with changing the method of assessing undifferentiated iPSC's, as none are likely to impact the final cell substance. Introduction of these changes to the Definition would obviate the need to assign a new INN when adjustments are made to the manufacturing process.

*In discussion*, the Experts felt that changing the expression vector may not be minor and that regulators may see some changes affecting not only efficacy but also safety. It was clarified that for new substances, a clear definition is required which should be based upon an optimised manufacturing process, and in retrospect this INN submission was probably made too early. Essentially, the company wished to know if the process gets changed after approval and if regulatory agencies accept such changes, can the INN Definition be changed.

The Chair confirmed that if regulators accept that process changes do not affect the final substance, then a change to the INN definition could be accepted, if necessary; this has happened in the past. Once the process is nailed down, the INN Experts can finalise the Definition.

### **ISA Therapeutics**

ISA Therapeutics attended the Stakeholders Session to propose harmonisation between USAN and INN for the non-proprietary naming of their HPV16 E6/E7 specifying, 12-peptide product ISA101b, administered in two shots.

The company had previously requested two INN for these two peptide mixtures but the request had been rejected as the substances were deemed to be mixtures and 12 separate INN would be required, one for each peptide. In their initial request for a USAN, two names were also sought, one for each mixture; however, as the product would fall under one IND, one name was considered to be sufficient and *peltopepimut-S* was assigned. This issue was also discussed at the EMA who agreed that 12 INN would not be workable for the label and that a single common name would suffice. Thus, the company approached the INN Experts to reconsider their stance.

The 12 peptides almost fully overlap the total sequence of HPV type 16 oncoproteins E6 and E7. The peptides are administered in two shots, one in each arm, with one portion containing seven E6 specifying peptides and the other containing two E6 and three E7 specifying peptides. The peptides are taken up by immature dendritic cells and induce strong and sustained antigen-specific T helper (Th1) and cytotoxic T lymphocyte (CTL) responses, which together gives a robust anti-tumour response.

Studies have shown that not every patient responds to every peptide due to differing HLA types; however, the 12 peptides provide sufficient epitopes for all frequent HLA types and no HLA typing is performed pre-treatment. Additional studies have shown that the 12-peptide combination gives superior activation of both CD4+ and CD8+ T cells compared to whole E6/E7 protein vaccines. Also, the response to the 12-peptides has been shown to be much higher after injection into two sites, potentially by avoiding competition at draining lymph nodes, whilst overloading of the peptides gave inferior results.

The company highlighted that having 1 USAN and 12 INN would not lead to a globally recognised unique name for their product. It would not lead to clear identification, communication and exchange of information amongst health care professionals, nor clear and

accurate dispensing. It would be highly impractical for labelling, product information, promotional material and the scientific literature. In conclusion, the company emphasised that ISA101b is one single product whose individual peptides are not considered to be efficacious on their own or in any other combination. Twelve INN would be impractical and confusing and harmonisation between USAN and INN on a single unique global name is required.

*In discussion*, the company acknowledged that individual peptides indeed can have activity but that the more epitopes an individual responds to, the greater the likelihood of a beneficial clinical response. Regarding dose, it was confirmed that there is a very broad dose optimum and experimentally it is striking that better responses have been obtained with lower doses, especially after administration at two sites, with all peptides present in the same final concentration.

The company was reassured that the INN Secretariat/Experts had been in discussion with USAN and CBER as the problem is not new and an optimal solution for peptide mixtures is currently being sought. The EMA representative attending the Consultation also acknowledged that the company had discussed naming with them and the EMA situation was to provide a simple common name as 12 INN would not be practicable, much as is done with multi-component vaccines.

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

The focus of the ASBM presentation was on the benefits of harmonizing biologic pharmacovigilance internationally by harmonising non-proprietary nomenclature.

The ASBM representative had recently chaired the pharmacovigilance track at a World Drug Safety conference in Boston. Several trends and discussion topics highlighted the continued importance of international harmonization and biologic traceability. One trend concerned a desire to increase the speed of bringing innovative drugs to market. This could involve reducing the need for unnecessary or duplicative clinical trials, or reliance on trials from other countries, without compromising patient safety. Indeed, the COVID-19 experience demonstrated that it is possible to accelerate development and approval of important medicines.

A second discussion point was for more diverse clinical trials, by greater inclusion of children, pregnant women, the elderly and ethnic groups, as clinical trials do not always focus on patient groups that are the intended targets. For example, an Alzheimer's drug trial is taking place across 16 countries with a broad diversity of participants and the benefits of such trials are beginning to be explored by companies. So the goal that emerged from the drug safety specialists was to increase access, reduce cost and build confidence, along with greater emphasis on post-market information, including benefit-risk management decisions.

One significant challenge to efficient global cooperation is the lack of harmonisation. Significantly for the INN group, a 2020 WHO report identified inconsistent nomenclature as a remaining challenge as it is clear that naming and labelling are both very important for pharmacovigilance and prescribing. Indeed, surveys show that there remains a clear need for harmonisation of distinguishable names with only two-thirds of ADR reports recording the brand name of the biologic, and even fewer recording the non-proprietary name. Other surveys show that only a small proportion of physicians record the non-proprietary name and extremely few use an officially recommended drug code number. Clearly, much greater use of INN would be beneficial.

As the number of approved biosimilars continues to grow, and prices reduce, the value that distinguishable nomenclature and international harmonization brings to the world increases. Biosimilars are also entering new therapeutic areas for example in ophthalmology and several of these may be automatically substituted at the pharmacy level. Consequently, ASBM is currently surveying Canadian ophthalmologists to gather their perspectives and whether AEs are associated with changing from one biosimilar to another.

In conclusion, the ASBM urged the WHO to make a voluntary distinct naming standard available to facilitate international cooperation and harmonization. This will help speed approval, increasing access to biosimilars while promoting safety and building confidence through strong post-market monitoring.

### **Redx Pharma PLC**

Redx attended the Stakeholders Session to request that their porcupine inhibitor RXC004 is assigned an INN distinct from the class of Wnt inhibitors having the *-vivint* stem.

Wnt comprises a diverse family of signalling glycoproteins whose secretion is activated by palmitoylation by the enzyme porcupine. Secreted Wnt ligands can then activate canonical ( $\beta$ -catenin-dependent) and non-canonical ( $\beta$ -catenin-independent) signalling pathways which have roles in driving both tumour growth and immune cell evasion in cancer. Porcupine inhibitors, such as RXC004, will block both canonical and non-canonical Wnt signalling pathways. In contrast, inhibitors of  $\beta$ -catenin interactions (like *tegavivint* and *foscenvivint*) will only block the canonical Wnt pathway.

Another group of inhibitors, represented for example by *lorezivivint*, are CLK/DYRK kinase inhibitors with multiple modes of action that have some effects on canonical Wnt gene expression in addition to multiple non-Wnt related mechanisms, including anti-inflammatory actions. Porcupine inhibitors in contrast are pro-inflammatory.

Wnt signalling induces osteoblast differentiation and proliferation and there is a large evidence base that reducing Wnt signalling would lead to decreased bone density. Wnt signalling is also required to maintain taste bud progenitor levels and the production of new taste cells, and evidence indicates that reducing Wnt signalling would lead to changes in taste. In clinical use, porcupine inhibitors alone demonstrate clear Wnt pathway linked side effects such as bone degeneration and changes in taste, and appropriate intervention is required to counteract bone density loss. These side effects are not reported with downstream Wnt pathway inhibitors with the *-vivint* stem. Consequently, Redx requested that their porcupine inhibitor RXC004 is assigned a suffix distinct from *-vivint*.

The Chair thanked the company for its clear presentation and that the Expert Group had been given much to consider.

### **Look-alike, sound-alike errors**

The final presentation was a discussion of look-alike, sound-alike (LASA) errors by Rachel Bryan, a linguistics doctoral student at Swansea University, Wales, UK.

The INN Experts were informed that LASA errors can result from similar names or similar packaging, can occur at various stages, may not cause harm or may cause serious harm. While errors are viewed as unavoidable, in reference to the Swiss Cheese Model of Error, the level of

harm can be reduced if there are multiple safeguards. Ms Bryan's study is to identify linguistic latent conditions in INN, i.e., intrinsic properties of names, that drive the risk of LASA errors. This is being achieved by analysis of error reports involving 1,162 INN whose substances are currently authorised medicines in the UK. The analysis involves orthographic measures, e.g. the number of words, letters and syllables; morphosemantics, e.g. the presence of stems and substems and their variations; and relational aspects, e.g. similarity of letter strings and alignment with the ATC coding system.

There were three initial tentative findings. First, the average name has 10.6 letters and 4.2 syllables, and the longer the name, or names with more than one word, the more likely there would be a LASA error. Thus, INN should be kept short with <12 letters and <5 syllables. Second, common start or end strings in INN increases the risk of LASA error. In this study, 7% of endings appear in 57% of INN, for example, *-mab* as in *infliximab*, and *-ole* as in *fluconazole*, whilst 2% of beginnings appear in 12% of INN. Thus, newly created stems should employ novel endings whilst the random prefix at the beginning of the INN should avoid commonly used strings. Third, stems of high frequency and non-meaningful stems are more likely to be in a LASA error. For example, stems ending *-ine* are highly common and it is recommended that when proposing a suffix for a new INN, there should be a check that it does not contain part of an existing pharmacological stem for a group that the new substance does not belong to.

Ms Bryan would appreciate the views of the Experts on this study and suggestions as to where the research should go in the future.

*In discussion*, the Experts expressed considerable interest in this study. They agreed that there were huge problems with the *-mab* stem but because of that it had been discontinued and replaced with several new stems. It was also noted that only 10% of names were included in the study and that there was an underrepresentation of advanced therapy names, many of which were two-word names. Ms Bryan agreed that it would be beneficial to broaden the database. She further added that her greatest source of error reports was the ISMP (Institute for Safe Medication Practices) but that other sources including literature had been used. The value of Tall Man Lettering, the practice of writing part of a drug's name in upper case letters to help distinguish LASA drugs from one another to avoid medication errors, was discussed. Ms Bryan had published on this but her studies were not particularly conclusive and probably the best solution to minimise LASA errors is to adopt a variety of approaches.

The Chair thanked the speaker for an interesting presentation and expressed interest in further cooperation with Ms Bryan.

### **Close of meeting**

The Chair thanked all speakers for their contributions which gave the Experts much to consider, and with that he closed the meeting.