

**71st Consultation on  
International Nonproprietary Names for Pharmaceutical Substances  
Geneva, 20-23 October 2020 (virtual meeting)**

***Executive Summary***

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

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# **71<sup>st</sup> Consultation on International Nonproprietary Names for Pharmaceutical Substances**

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## **EXECUTIVE SUMMARY**

### **OPENING OF MEETING**

The 71<sup>st</sup> INN Consultation, a virtual meeting, was opened by *Dr Clive Ondari*, acting Director, Health Products policy and Standards (HPS). He welcomed the INN Experts and Advisors and thanked them for their exceptional efforts in August (2020) in naming substances being developed to address the Covid-19 pandemic. With regard to the pandemic, Dr Ondari informed the meeting of a worldwide collaboration called Access to Covid-19 Tools (ACT) Accelerator, involving WHO and a number of other global health organisations and some private sector partners, and whose aim is to accelerate the development, production and equitable access to new Covid-19 diagnostics, therapeutics and vaccines. Within this collaboration, WHO is working on many fronts at global, subregional and country level to ensure readiness for uptake and delivery of ensuing tools and products.

*Dr Raffaella Balocco*, Unit Head, INN Programme and Classification of Medical Products, thanked Dr Ondari for his remarks and also the Experts for the work performed between consultations and their extra work for the August Consultation on Covid-19 substances. At this Consultation, 239 requests are to be discussed comprising 201 new requests and 38 outstanding requests and objections, with a slight majority of biological substances. She highlighted the increasing number and complexity of biological substances. Much of the work of the Group goes unnoticed and the Experts should take satisfaction that some of the Covid-19 vaccines that may soon appear on the market have been named by the Group. The INN Team itself has been very busy, supported by the Experts. Dr Balocco welcomed all to the Consultation and was grateful for the good collaboration with USAN.

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

*Dr Ondari* led the election of the chair, vice-chairs and rapporteur. Prof Sarel Malan was elected as Chair of the meeting; Prof Menico Rizzi was elected as the vice-chair for biologics and Dr Adrian Evans was elected as the vice-chair for chemicals. Dr James S Robertson was elected rapporteur.

### **INTRODUCTORY REMARKS**

Dr Ondari continued the meeting by thanking again the Experts and Advisors for their contributions to public health across the world. He also had a special word of thanks for Dr Balocco and all members of the INN Unit. He highlighted that the INN Programme is an unsung hero of WHO and on behalf of ADG wished all a fruitful consultation.

The Chair, *Prof. Sarel Malan*, thanked Dr Ondari and commented that he was glad for the opportunity to contribute to public health; he added that all experts enjoy the work and valued making even a small difference. He appreciated the support he gets from the Expert Group and the excellent backing of the INN Unit members.

Dr Balocco briefly ran through procedural aspects of holding the meeting by video conferencing.

Given the presence of several new members, the Chair called for a *tour de table* of introductions.

## **70<sup>th</sup> NOTES OF CONSULTATION**

The Notes of Consultation of the 70<sup>th</sup> INN Consultation including the addendum Consultation on Covid-19 Medicinal Substances held on 20-21 August 2020, was tabled and adopted, with thanks to the Rapporteur.

## **NOMENCLATURE of INN**

During the 71<sup>st</sup> INN Consultation, a total of 239 INN requests was discussed, including:

- 207 new INN requests, including 110 for biological substances
- 28 outstanding requests
- 4 previously selected proposed/recommended INN, against which a formal objection or a request of substitution had been raised.

As a result of these discussions, 225 names were selected, which are planned to be published in List 125 of proposed INN (p.INN), while 7 requests were deferred for future discussion. Three requests were rejected by the INN Expert Group, as the substance did not conform to the criteria for INN selection. Three amendments were planned to be published in a forthcoming List of p.INN; one request of substitution could not be retained as it did not conform to the criteria.

Three new stems/substems were selected, seven suffixes were promoted to the pre-stem list and it was decided to review the descriptions of two stems/pre-stems.

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

The 14th meeting of the SoINN steering committee took place on Monday, 19 October 2020. Despite the pandemic, the SoINN is very much alive as it is a virtual school, and from the start the committee has practiced teleworking. SoINN courses have now been translated into Spanish and French, and a computer scientist is being recruited to assist the INN IT expert in enhancing the SoINN platform, uploading the translated material and developing the plug-in for the platform.

The ‘Stems in Pills’ project involves creating a course in clinical pharmacology in which sections are based upon stems, with each stem corresponding to a pharmacology class. About fifteen chapters corresponding to widely used stems have already been drafted and important help by a Spanish colleague is acknowledged. Various comments received will be included in a final version which is planned to be posted on the SoINN website before the end of the year after validation by the steering committee.

Physical meetings with the various pilot sites are on hold, but virtual meetings are scheduled to maintain contact and stimulate their work. To ensure continued promotion of the SoINN, an article on SoINN will soon be submitted to a pharmacy journal and contacts with academic societies will continue to be pursued. Finally, as part of the cooperation between the INN

Programme and the ATC-DDD Committee, a course on ATC classification is planned for the SoINN website.

## **COLLABORATORS' UPDATES**

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

The JAN (Japanese Accepted Name) Expert Committee met five times via a web conferencing system. Since April 2020, 21 new names have been published, including *remdesivir*(116)(78).

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

The TGA has granted a provisional determination to AstraZeneca Pty Ltd in relation to its COVID-19 Vaccine, ChAdOx1-S [recombinant] and Pfizer Australia Pty Ltd in relation to its COVID-19 Vaccine, BNT162b2<sup>1</sup> [mRNA]. The granting of a provisional determination means that the TGA has made a decision that AstraZeneca is now eligible to apply for provisional registration for the vaccine in the Australian Register of Therapeutic Goods (ARTG). Provisional determination is the first step in the process and does not mean that an application has or will be made, or that the vaccine will be provisionally approved for inclusion in the ARTG.

The heads of the Australia-Canada-Singapore-Switzerland (ACSS) Consortium have announced that the United Kingdom (UK) therapeutic products regulator, the Medicines and Healthcare products Regulatory Authority (MHRA), is joining as a new member. The group, now known as the Access Consortium, aims to provide patients with timely access to high-quality, safe and effective therapeutic products in the five countries.

In order to enhance transparency for prescription medicines, the TGA now has approval to publish, on the TGA website, a description of major innovator medicine applications that are under evaluation by the TGA from January 2021. The change is to allow health practitioners and their patients to discuss potential new treatment options.

The TGA also now has approval to introduce an earlier patent notification scheme for first generic and biosimilar medicines through legislative change planned to be introduced to Parliament in late 2020. The proposed changes would require applicants for the first generic and biosimilar form of an originator product to notify the patent holder when their application is accepted for evaluation by the TGA.

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

The 2020 summer USAN Council meeting took place virtually on June 12, 2020. Names for 45 drug substances were reviewed and discussed. Seven new stems and infixes were approved and added to USAN's stem list. One stem definition was revised. Forty-nine new INN applications and 4 revised INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 71st INN Consultation.

Through October 2020, USAN staff will have processed, researched and made recommendations for 85 USAN applications and forwarded this information to the USAN Council for their review and selection. Also, through October 2020, 168 USAN will have been adopted for 2020. Revenue was realized for an additional negotiation. Currently, there are approximately 210 active USAN negotiations.

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<sup>1</sup> This was assigned the INN *tozinameran* (124) at the 70<sup>th</sup> INN Consultation: Addendum

The 2020 Winter meeting of the USAN Council is scheduled to occur on December 4, 2020. It will be a virtual meeting.

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

Many Covid-19 vaccines are being evaluated, but from a nomenclature point of view, the policy of CBER is not to adopt names for prophylactic vaccines and internationally they will have separate names. Very recently, the FDA granted an approval for Veklury® (*remdesivir* (116)(78)), the first US drug for treating Covid-19.

Most FDA staff remain working from home and this will probably continue as a large spike of infection continues around the US and only those in laboratories are allowed to go into work.

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

The USP is playing a critical role in the public health response to COVID-19 including helping to accelerate the work of scientists involved in the development, manufacturing, and quality testing of COVID-19 vaccines and treatments, supporting front line workers impacted by shortages of critical drugs and personal protection equipment and helping to build a more resilient global medicines supply chain. USP has developed several informational resources including the hand sanitizer toolkit to help address the shortage of hand sanitizers. Additionally, USP has modified its operations to protect the health, safety and security of the staff and volunteers. 80% of the USP personnel is working remotely. The USP published a newly redesigned website and recently celebrated its 200-year anniversary.

The USP is committed to using the Global Substance Registration System (G-SRS) as the central repository of the chemical information. The 2021 edition of the USP Dictionary of USAN and International Drug Names was produced from GSRS data. More and more agencies are subscribing to this system, including the European Medicines Agency.

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

The WCO receives a list of new INN twice per year from WHO and the continued collaboration between WCO and the INN Programme especially during this pandemic is very important to monitor, control and facilitate trade in such substances. The lists are relied upon by customs agencies and serve as a basis of the movement of medicines, and especially during the pandemic for non-tariff release of products.

A recent operation involving 99 customs members across world over 45 days, revealed an alarming level of illegal trafficking of medicines with 1700 seizures and detentions, and 300 million items of illicit medicines including 15 million medical supplies, such as masks, and almost 3 million litres of sanitising gel. The WCO representative looked forward to discussing the latest INN lists at their November meeting with the cooperation of Dr Sophie Lasseur of the INN Team. The WCO would be grateful to receive any further lists of Covid-19 related INN so that the substances can be classified to prevent trade in illicit medicines.

Dr Balocco, Unit Head, INN Programme and Classification of Medical Products, requested the WCO representative to provide feedback on the use of INN lists to share with WHO management. The WCO representative agreed to share more information of this recent operation into illicit trafficking of Covid-19 related substances with WHO.

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

During 2020, 120 new ATC (Anatomical Therapeutic Chemical) codes were assigned plus 100 new Defined Daily Doses (DDDs), many for protein kinase inhibitors for cancer treatment. A new ATC code has also been assigned for *remdesivir* (116)(78), an antiviral compound being used for treating Covid-19 patients.

There was a meeting recently with members of the INN Team and the INN Expert Group; a good collaboration with WHO HQ is appreciated.

### **WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, Sweden (UMC)**

The Uppsala Monitoring Centre (UMC) was the first WHO Collaborating Centre to be established for pharmacovigilance when, in 1978, the scientific and technical responsibility of the WHO Programme for International Drug Monitoring was transferred to Sweden. The work of the INN Programme is very important for the UMC and pharmacovigilance reporting and the INN themselves are crucial for those not familiar with brand names. The recently assigned INN for Covid-19 vaccines and treatments will be very useful for monitoring their use.

### **CLOSE OF MEETING**

At the close of the meeting, the Chair thanked the INN Team for their pre-prepared presentations of each application which greatly simplified the work of the experts, and without which it would have been difficult to get through in timely manner. He also thanked the Experts and Advisors for their input and responses during this virtual meeting.

Dr Balocco thanked the Chair for guiding the meeting, the Experts and her team for their work, noting that it all contributes to the health of the world.

### **Next meeting**

The 72<sup>nd</sup> INN Consultation will take place on 12-16 April 2021.

## SESSION for INN STAKEHOLDERS

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

(a virtual meeting)

Geneva, 20 October 2020

#### OPENING REMARKS

The Open Session adjoining the 71<sup>st</sup> INN Consultation was opened by *Dr Raffaella Balocco*, Unit Head, INN Programme and Classification of Medical Products. She expressed her gratitude to IT for organising the virtual meeting. She welcomed the stakeholders, and the INN Experts and advisors, and passed the floor to *Dr Clive Ondari*, acting Director, Health Products Policy and Standards (HPS), to chair the meeting.

Dr Ondari echoed Dr Balocco's warm welcome to stakeholders to this 71<sup>st</sup> INN Open Session. He expressed his appreciation for the continued strong and excellent collaboration with stakeholders and reminded them of the confidentiality nature of the meeting until the official report is approved and published. Without further ado, he requested the first of the four stakeholders online, to begin their presentation.

#### H. Lundbeck A/S

H. Lundbeck A/S proposed a novel suffix stem and candidate INN for its compound Lu AG06466, a first-in-class, orally-bioavailable, brain-penetrant compound that selectively modulates both endocannabinoid and eicosanoid lipid signalling pathways and which is being developed for the treatment of several neurological and psychiatric conditions

Lu AG06466 selectively reduces the activity of monoacylglycerol lipase activity, thus controlling the degradation of 2-arachidonoylglycerol (2-AG) to arachidonic acid (AA). 2-AG is the most abundant endocannabinoid in the brain, whose primary function is to regulate excitability and inflammation whilst AA is an important precursor of eicosanoids such as prostaglandins that primarily regulate inflammation. Therefore, modulation of inflammation and excitability is achieved by Lu AG06466 modulating the endogenous levels of both endocannabinoids and eicosanoids.

Endocannabinoids and eicosanoids are two of the most prominent lipid signalling pathways, and lipid messengers are involved in regulation of several cellular functions, including those involved in multiple pathological conditions. With Lu AG06466 at the crossroads of two major lipid signalling pathways, it provides an attractive approach for the treatment of several brain disorders.

The INN Expert group has not yet assigned a stem for lipid-signalling modulation and so H. Lundbeck A/S proposed the novel suffix *-lisor*, with accompanying six INN proposals with this suffix. It was also highlighted that the company is developing three other molecules focused on the modulation of lipid signalling and that other companies are developing compounds that would fit in the same stem category.

*In discussion*, the company was quizzed as to why a novel suffix should be given to modulators of this specific enzyme. In response it was highlighted that the enzyme is a key regulator of AA and by reducing enzyme activity there would be an increase in 2AG and a reduction in AA, and thus a reduction in inflammation. So, this enzyme is at the core of two lipid pathways concerning excitability and reducing inflammation. If such a pathway is interrupted later in the cycle, these two components cannot be modulated.

## Servier

Earlier in 2020, Servier requested the WHO Collaborating Centre for Drug Statistics Methodology in Norway for a new ATC (Anatomical Therapeutic Chemical) code for its *irinotecan sucrosofate* liposomal formulation; however, the Centre replied that an INN for this substance would be required in order to assign a separate ATC 5th level code. Consequently, an application was submitted to the INN Programme for an INN such as *pegliposomal irinotecan sucrosofate*. The company is aware from discussion of liposomal substances at the 69<sup>th</sup> INN Consultation, that INN are assigned only to well defined substances and not mixtures, that formulation is not a part of INN and that there could be deviation from these rules only under exceptional circumstances. The company however claimed that this situation is exceptional in that the posology for its pegylated liposomal irinotecan substance is 5-fold lower than conventional irinotecan formulations giving it improved safety. Furthermore, the combination of irinotecan with sucrose octasulfate constitutes a new chemical structure that provides different pharmacokinetic behaviour compared to conventional irinotecan, and this is the reason *irinotecan sucrosofate* was allocated a USAN in 2013.

The company also emphasised that the substance is not a salt as indicated by having several sucrosulfate moieties per irinotecan, plus if it were a salt, it would rapidly dissociate upon dissolution, which it does not and in contrast provides sustained release over 16 hours.

*In discussion*, it was queried if the active moiety was a prodrug to which the company responded that it indeed behaves like a prodrug, but that it not a typical prodrug whereby the active moiety is released by metabolism; in this case the slow release of irinotecan is due to its complex with sucrosulfate..

The company was also further questioned on evidence that it is not a salt. The company outlined the history of the substance prior to its acquisition by Servier and that Servier does not have its full research background. However, its own research indicates that precipitates of the substance are not crystalline, that the chemical structure of irinotecan does not lend itself to readily form a salt and the lack of ease dissociation of the moieties upon dissolution all point to it not being a salt.

## Kite Pharma

*Axicabtagene ciloleucel* (marketed by Kite Pharma under the tradename Yescarta®) is a CD19-directed, genetically modified, autologous T-cell immunotherapy for the treatment of relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL). KTE-X19, also marketed by Kite Pharma, is a CD19-directed autologous T-cell immunotherapy that is genetically modified with the identical vector as in *axicabtagene ciloleucel*, but in this case for the treatment of patients with r/r mantle cell lymphoma (MCL). The company is requesting a new INN for KTE-X19 on the basis that the starting materials and the manufacturing process, and thus the final product characteristics, are different from *axicabtagene ciloleucel*.

Both cell substances use cells derived from patient apheresis; however, the presence of circulating tumour cells and B Blasts in the MCL patient apheresis, unlike DLBCL patient apheresis, necessitate the inclusion of a positive selection step for CD4+/CD8+ T cells in the MCL manufacturing process. This T cell selection step for KTE-X19 is required to remove blasts and circulating tumour cells to ensure a safe substance and results in distinct potency markers for KTE-X19.

Both the FDA and the EMA recognise KTE-X19 and *axicabtagene ciloleucel* to be distinct cellular substances requiring separate regulatory review and the company respectfully requested a new distinct INN for KTE-X19.

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

The ASBM offered its continued support for the INN's biological qualifier (BQ) proposals. It highlighted how the Covid-19 pandemic has demonstrated how the world looks to the WHO for public health support and that biological naming remains an important issue. One argument against distinguishable names was that biosimilars may be seen as inferior and that this would hamper their use. But that has not happened in the USA, and in 5 years of use, two biosimilars of *filgrastim* have achieved a 72% share of the market; good uptake has also been seen *bevacizumab*, *trastuzumab* and *pegfilgrastim* biosimilars. So, distinguishable names are not an impediment to uptake. Another argument against the BQ is the presence of existing ways of distinguishing biologics, particularly in pharmacovigilance (PV) programmes. Efforts have been made to improve PV programmes through regulation but in a study of the UK adverse drug reaction (ADR) reporting program, no one reporting system is consistently used. Ideally, all methods of identification should be used but in the UK study, only 38% of reports included an identifiable brand name and only 15% had batch numbers. These findings prompted the authors to conclude that the system needs to be improved. These data are consistent with ASBM's survey findings that show inconsistent information being included in ADR reports with brand name, batch number and the name of the manufacturer not always being specified. The BQ is a means of having strong pharmacovigilance programmes, and this is especially important during the pandemic with many biologics, both originator and biosimilar, being investigated for treatment of Covid-19.

The ASBM sees a need for WHO leadership as more important than ever. As biologics and biosimilars continue to increase, with distinguishable non-proprietary names not having a negative impact on the uptake of biosimilars, and with PV programmes needing to be improved, the lack of a consistent approach points to a need for WHO leadership, just like is happening for the pandemic.

Several early supporters of the BQ have reversed their views, explicitly citing lack of WHO action on naming. Yet they remain willing to harmonise with a global standard should one be made available by the WHO. At the April INN Consultation, the ASBM offered to draft a letter to gauge the level of support for BQ among regulators, and the ASBM repeated this offer.

*The Chair* thanked the ASBM for its offer of help in gathering information and welcomed the sharing of any data from ASBM surveys.

## **CLOSE of MEETING**

In bringing the meeting to a close the Chair thanked the partners for their presentations and also the INN Experts and other representatives for their support.