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72nd Consultation on

International Nonproprietary Names for Pharmaceutical Substances

Geneva, 13-16 April 2021 (virtual meeting)

Executive Summary

Programme on International Nonproprietary Names (INN)

INN Programme and Classification of Medical Products Unit
Health Products Policy and Standards Department (HPS)
Access to Medicines and Health Products Division (MHP)
World Health Organization, Geneva

72nd Consultation on International Nonproprietary Names for Pharmaceutical Substances

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EXECUTIVE SUMMARY

OPENING REMARKS

The 72nd INN Consultation was held virtually and was opened by Dr Clive Ondari, Director, Health Products policy and Standards (HPS). On behalf of the Assistant Director-General, he welcomed the INN Experts and the various collaborating organisations to the meeting and thanked them for the time they spend supporting the INN Programme. He also appreciated the input of working groups and the huge amount of work done on monoclonal antibodies, cell therapy substances and on naming vaccines in response to the COVID-19 crisis. The INN Unit itself has done an extraordinary amount of work, processing a record 268 requests, and he was highly appreciative of that. Clearly product development is very active and he welcomed feedback on how WHO might expand the capacity of the Unit, maintain expertise, and keep up with the pace of expertise required.

Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products, also expressed her gratitude to all experts and advisors for their work prior to the Consultation in commenting upon requests. These comments are essential and part of the mandate of Experts, but nonetheless, the INN Unit is extremely grateful for all the input.

ELECTION of CHAIR, VICE-CHAIRS and RAPPORTEUR

Dr Balocco led the election of office bearers. Prof. Sarel Malan was proposed and elected Chair of the meeting, Prof. Menico Rizzi was proposed and elected Vice-Chair for Biologicals, Dr Adrian Evans was proposed and elected Vice-Chair for Chemicals, and Dr James S Robertson was proposed and elected Rapporteur.

The Chair thanked Dr Ondari and the WHO for supporting and directing the Programme. He also expressed his appreciation of the work of Dr Balocco and her team, for being so organised and working so hard.

72nd NOTES of CONSULTATION

The Notes of Consultation of the 71st INN Consultation held as a virtual meeting on 20-23 October 2020 was tabled and adopted as a true reflection of the meeting.

NOMENCLATURE of INN

During the 72nd INN Consultation, a total of 263 INN requests was discussed, including:

- 226 new INN requests, including 118 for biological substances
- 33 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, 249 names were selected, which are planned to be published in Lists 125 (COVID-19-related requests only) and 126 of proposed INN (p.INN), while 6 requests were withdrawn by the applicants themselves, 2 requests were INNM (INN modified) and 2 requests were deferred for future discussion.

One amendment was planned to be published in a forthcoming List of p.INN; two objections were withdrawn by the originators; one request of substitution could not be retained as it did

not conform to the criteria; one request was closed as required additional information failed to be submitted.

Nine new stems/substems were selected, 10 suffixes were promoted to the pre-stem list and it was decided to review the descriptions of 4 stems/pre-stems.

WORKING GROUP on MONOCLONAL ANTIBODIES

The INN working group on monoclonal antibodies (mAb) met virtually on two occasions to discuss the problem of creating unique INN for mAbs; the meetings comprised INN Experts, INN biologicals advisors and a mAb expert from CBER, USA.

The stem *-mab* is used for any substance that contains at least an immunoglobulin variable domain. The stem is well known, easily recognised and is the largest class of INN with 744 *-mab* substances (up to and including PL124). However, this has resulted in exceptional overcrowding and difficulty in creating unique *-mab* INN that are not overly long. Thus, there is a need to consider alternative approaches and sub-dividing mAbs into four groups was proposed.

Group 1: would retain the stem *-mab*, but would apply only to monospecific full length and Fc unmodified immunoglobulins of any class; mAbs with differences in glycosylation would also fall into this group.

Group 2: for monospecific full-length immunoglobulins with engineered constant domains (CH1/2/3), a new suffix *-keng* (or *-meng*) for 'constant engineered' was proposed; this group would include for example mutations to enhance or delete Fc function or glycosylation.

Group 3: for bi- and multi-specific immunoglobulins regardless of the format, type or shape, including full length, full length plus or fragments, the suffix *-mig* for multi-immunoglobulin was proposed.

Group 4: for all monospecific constructs that do not contain an Fc domain, or fragments of any kind derived from an immunoglobulin variable domain, the suffix *-frag* or *-ment* for fragment, was proposed.

Applying this scheme to the 36 mAbs named in PL124, 10 would have remained as *-mab*, 18 would have been named *-keng*/*-meng*, 7 would have been named *-mig* and 1 would have been named *-frag*/*-ment*. However, allocating substances to individual groups may not necessarily be clear cut and distinguishing between groups 1 and 2 especially may be difficult. In the case of PL124, half of the mAb substances would fall into group 2, and it may not be easy to convey why these 18 should receive a *-keng*/*-meng* suffix rather than *-mab*.

A separate proposal from the working group concerned infixes. There has been concern at the huge application of two specific infixes *-li-* (for immunomodulating; currently 261 INN) and *-ta-* (for tumour; currently 292 INN). It was appreciated that during development the mechanism of action of a mAb may not be fully understood and may differ for different indications, but to reduce the overcrowding of mAbs with a *-li-* and *-ta-* infix, the following was proposed.

The *-li-* infix would be retained for mAbs that appear to be immunomodulating; but where it can be shown that a mAb is an immunostimulant or an immunosuppressive, new infixes *-sti-* and *-pru-*, respectively, would apply. In addition, a new infix *-cito-* would apply for mAbs that are immunosuppressive by killing malignant or normal immune cells (for haematologic cancers, autoimmune and inflammatory diseases).

The *-ta-* infix would be retained for mAbs targeting solid tumours only.

The use of another highly used infix, *-ci-* for cardiovascular, would be discontinued and replaced with more treatment specific infixes such as *-angi-* for angiogenesis inhibitors, *-col-* for coagulation disorders (pro- as well as anticoagulant activity) and *-lipo-* for dyslipidaemia.

Another topic discussed by the working group was the naming of antibody drug conjugates (ADCs). These are named with two words, the first being the INN for the mAb and the second referring to the drug conjugate. For most but not all ADCs, the standalone mAb is not in clinical development. The concern with INN for ADCs is that prescribers may fail to notice the second word and confuse the standalone mAb with the conjugated mAb, potentially resulting in inappropriate prescribing and/or incorrect dosing of the drug substance. Modifying INN for ADCs by for example the addition of *-con-* as a prefix or suffix to the word for the mAb was not considered of value. The problem is possibly limited to a particular database in the USA, which does not recognize second words in names and the US FDA has instigated its own solution for drug product labelling of ADCs by adding a prefix to the drug product label. The working group concluded that no change for ADC nomenclature was required at this time.

In discussion, a concern voiced was what would happen where the Fc is mutated in a mAb with a pre-existing *-mab* stem INN and the applicant wished to retain connection to the original mAb by having a *-mab* stem rather than a *-keng* stem. It was felt that this should not be done and that the *-keng* suffix should not be seen as inferior. Since the *-mab* stem is so well known and popular, it was queried whether it could be included in some way in groups 2-4. However, having for example two suffixes would make for more complex INN which would defeat the purpose of the exercise in making mAb INN simpler. It was felt unfortunate to lose the *-mab* stem from many new substances but in response to the Chair requesting a recommendation, the INN Expert Group gave its support to the new scheme. The meeting was informed that the representative from CBER was also supportive of the new scheme. The working group will finalise the scheme and publish it as soon as possible after the meeting.

The working group was thanked for its work on this topic.

COVID-19 VACCINES INN

Several COVID-19 vaccine manufacturers are updating their vaccine in order to tackle SARS-CoV-2 variants of concern (VOC). Changes to a vaccine substance that already has an INN will require the assignment of a new INN. The INN Experts were given a presentation on how this could be approached. Various options were tabled including a totally unique standalone INN, attaching a short random prefix to the original INN, the addition of a Greek letter suffix to the original INN, and several options of an extra suffix such as a qualifier containing 3 or 4 random letters, an abbreviation of the geographical name of the VOC, the numerical designation of the VOC, or various formats of a suffix that indicates version number. Most of these were discounted as not being practical or not complying with rules of INN nomenclature. To create a totally new unique INN was felt to be not useful. The modification of the pre-existing INN with a single syllable prefix would maintain the link to the original INN and would be in line with INN rules and was presented as the preferred option. In addition, the process would have to be accelerated and a timetable was proposed.

The recommendation put to the Experts was that where a COVID-19 vaccine already has an INN, the INN for a VOC would be the addition of a short syllable to the pre-existing INN. It was emphasised that only where a vaccine substance in which the nucleic acid or protein structure had been modified by the substitution of a small number of codons or amino acids to address a VOC would a link be made to an original INN; any other change to the substance

would trigger the need for a totally new INN. Finally, it was mooted for the future that a vaccine identifier that would include data such as the manufacturing site, maybe have value.

The EMA representative informed the meeting that for regulatory authorisation the agency was aiming for a flexible approach and could consider VOCs being included in pre-existing COVID-19 vaccine marketing authorisations. The EMA is trying to accommodate all possible scenarios such as multi-valent vaccines and it will be important to assess any changes in as short a timeframe as possible. With respect to naming, some vaccines with no INN have been given a common name, which is not expected to change for the variants. Therefore, distinction is needed at the level of the invented name and use of a qualifier or code is being considered. With regard to INN, early availability was emphasised, as naming and labelling has to be agreed early in the process, well before the approval of the vaccine. For COVID-19 vaccines that were approved with a common name and where a recommended INN has subsequently been assigned by WHO, the INN would be introduced on the labelling in the near future. The EMA representative expressed agreement with the short prefix approach for VOC INN and an accelerated process for its assignment.

In discussion, it was queried that if a short prefix is added to a pre-existing INN, would the same prefix be used where the same changes were introduced to adapt the vaccine to the same VOC. It was felt that this would not be a useful approach. The importance of taking an immediate decision on this was emphasised to the experts and that the option of a short prefix was in keeping with INN rules of nomenclature.

The Chair called for a decision on this and there was good consensus agreement on adopting the proposed short syllable prefix approach. It was also agreed that the process should be accelerated, including the preparation of a new definition that would accompany a new name. The decision should be made available after the Consultation without waiting for the official meeting report, following approval of a written statement by the experts.

INN and TRADE MARK CONFLICTS

In assessing the potential conflict of a new INN with a pre-existing trade mark, the INN Experts have increasingly relied upon comparing the first 5 letters of the INN with the first 5 letters of a trade mark, and if they are identical then the new INN is rejected. The USAN representative voiced concern over the number of potential names being rejected because of this approach; potential INN should be compared to trade marks as a whole and not broken down in this way for comparison. There is frustration within the USAN Council that names already vetted by the Council and the applicant are getting rejected by the INN Experts for this reason. The MHRA (UK) representative expressed sympathy with this adding that what is applied at the INN stage is more stringent than what the MHRA applies at the national level. The MHRA takes into consideration legal issues and the nature of the substance; limiting comparison to 5 letters in a row makes it very difficult to get a new name accepted.

Dr Balocco highlighted that comparison of 5 letters is not a written rule of INN nomenclature, the official rule being that Member States are recommended not to have trade marks derived from the INN. When the programme was established, there was agreement between WHO and industry that INN and trade marks should not conflict but with no information as to what defined a conflict. She agreed with the USAN representative that it should not simply be the number of letters, and other aspects such as what the drugs are intended for, should be considered.

The WIPO representative added that there are several notions to consider. A trademark is a proprietary right and it follows the principle of speciality, i.e., what the trademark is applied for. It was explained that a trademark followed by ® means that it is registered while a

trademark followed by ™ means that the application is still being processed by the Trademark Authority. A trade name is a broader notion, being the name of a company. WHO Resolution 46.19 states that stems and names derived from INN should not be used as a trade mark, which is a private right of the company. When processing trade mark applications, national systems apply the confusion test, and assess the list of products concerned, e.g., Class 5 pharmaceutical substances. For assessing a conflict, many countries look at the overall impression of the mark, the overall pronunciation, and not simply a few syllables.

It was agreed that this should be discussed in greater depth at the next monthly INN Open Club meeting.

SoINN

The 15th meeting of the SoINN Steering Committee took place on the day before the start of the 72nd Consultation.

The SoINN website has undergone a major evolution since the last meeting. It now integrates the services of MedNet and the 'stem in pills' section for studying clinical pharmacology stem by stem. In addition, almost the entire site is now available in both English and French. Evolution of the website will continue in the coming months with the implementation of a Spanish version and with versions in Arabic and Chinese being explored. Also, the potential amendment of nomenclature rules for monoclonal antibodies and advanced therapy substances would require an update of relevant courses. New documents will be added when available including one under development on isomers.

Publications on studies on the knowledge and use of INN, and on the science of nomenclature, are in progress and essential for the visibility of the SoINN. In all, five publications are at various stages of development.

For its continued development, the SoINN relies on university centres making use of it in teaching and research, and the committee is currently collaborating with universities in South Africa, Italy, Spain and France. A face-to-face meeting with these centres had been planned but delayed due to the Covid-19 pandemic; a meeting in spring 2022 is anticipated.

The Consultation was also informed that the SoINN website is the most visited site in WHO, currently experiencing a 20% increase in visits per month, and which is likely to increase further when content appears in additional languages.

SoINN has been a formidable activity and all those involved were thanked for their contribution. New input was welcomed and volunteers to join the steering committee were encouraged to contribute to its evolution.

International Nonproprietary Names Modified (INNM)

The most recent document on INNM was published in 2006. A corrected and improved version has been submitted but remains to be published. Improved features of the revised INNM document include:

- the addition of structural formula to all examples of INNM,
- examples that were listed in an incorrect paragraph have been shifted to the proper paragraph,
- discussion of previously underlying ambiguities and possible solutions has been added,
- a paragraph on the special policy for naming complexes of radio-isotopic metal ions has been added,

- a paragraph on co-crystals and molecular complexes has been added.

International Nonproprietary Names for Stereoisomers

An internal document on INN for stereochemistry dates from 1999. It contains several errors and inconsistencies which were never resolved, hence remained unpublished. A new document entitled 'Prefixes for Indication of Stereoisomerism in INN' has been prepared and is intended to be used as a module within the School of INN.

At the start of the INN Programme in 1953, only *dex(tro)-* or *lev(o)-*, and *ci(s)-* or *tra(ns)-* were available to indicate stereoisomers; however, they were often ambiguous and sometimes erroneous. In 1966 the unambiguous Cahn-Ingold-Prelog (CIP) stereo symbols (*R*)/(*S*) and (*E*)/(*Z*) became available, resulting in the preferable shorter prefixes *ar-/es-* and *en-/zu-* for INN. Later the original system of assigning suffixes to characteristic chemical groups of drug molecules was changed to the current, more appropriate system of stems with pharmacological definitions. Where stereoisomers have very different pharmacological activities, the INN of a new stereoisomer must not be created by simply adding a stereo prefix to an existing INN.

The explanatory document also has five annexes listing INN with specific stereochemical features, including lists of various prefixes used in the past for stereo-isomers.

COLLABORATORS' UPDATES

European Directorate for the Quality of Medicines (EDQM)

The EDQM representative expressed appreciation that an update of the INNM document was being prepared, which would be very helpful for pharmacopoeias.

The work of EDQM itself continues as normal with Ph. Eur. Supplement 10.6 finalised for publication at the end of June, while Pharmeuropa 33.2 is out for comment with a deadline of June 30. Several changes have taken place including considerable focus on Covid-19 with a number of different resources related to vaccine development being made available free of charge, including guidelines critical for co-ordinated independent batch control by EU OMCLs, the support of COVID-19 vaccine developers by providing selected training materials, and facilitation of processing of certificates of suitability. In other areas, there have been a number of webinars on a wide range of topics, such as responsibilities of data protection, and a drive to find alternatives to animal testing with a virtual workshop focusing on the replacement of *in vivo* mouse testing with cell culture systems, using *Clostridium septicum* vaccine as a proof of concept for testing toxins, being held in March 2021. Much of this is advertised on the EDQM Twitter feed (@edqm_news), with several tweets a week, covering a range of items such as news, recent publications, webinars, free training sessions and job vacancies.

International Union of Pure and Applied Chemistry (IUPAC)

When there is a long chemical name that cannot fit into one line, IUPAC has published recommendations as to where to insert breaks or hyphens in the name: "End-of-line hyphenation of chemical names (IUPAC Recommendations 2020) Pure Appl. Chem. 2021, 93(1) 47-68. It is free to download. https://www.degruyter.com/document/doi/10.1515/pac-2019-1005/html

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Since November 2020, the JAN (Japanese Accepted Names) expert committee met virtually on two occasions. Since November 2020, 32 names have been published including *tozinameran* (123) (85) and the JP (Japanese Pharmacopoeia) 18th edition will be

implemented in June 2021. The critical importance of quality for pharmaceutical medicines has never been more evident than it has been as the result of the COVID-19 public health crisis and a joint MHLW/PMDA-USP Workshop on the Role of Quality in Pharmaceuticals, will be held on June 16-17, 2021 (JST). https://www.pmda.go.jp/english/symposia/0196.html

Therapeutic Goods Administration (TGA), Australia

The Therapeutic Goods Administration (TGA) has introduced a new standard for serialisation of medicines and use of data matrix codes. Therapeutic Goods (Medicines - Standard for Serialisation and Data Matrix Codes) (TGO 106) Order 2021, commences on 1 January 2023 and provides clarity for adopters of serialisation and data matrix codes on medicines supplied in Australia. The standard aligns with global standards to provide consistency for sponsors and manufacturers operating in multiple jurisdictions and to ensure global interoperability. The standard does not mandate the use of data matrix codes or serialisation of medicines but sets out requirements if medicine sponsors choose to do either of these.

The TGA now has a searchable database that provides information on medicines not on the Australian Register of Therapeutic Goods (ARTG) that are approved for import and supply in Australia because:
-there is a shortage of a medicine registered in Australia; and
-the medicine is needed in the interest of public health.
The database holds information on approvals current on or after 21 February 2018.

From January 2021, prescription medicines under evaluation by the TGA can now be searched by anyone at https://www.tga.gov.au/prescription-medicines-applications-under-evaluation. This list excludes generics and biosimilars. Entries are removed from the list as part of the monthly update, if the medicine application has been decided (approved or rejected for registration), or when the applicant has withdrawn the application.

TGA has adopted guidance (https://www.tga.gov.au/points-consider-strain-changes-authorised-covid-19-vaccines-ongoing-sars-cov-2-pandemic) developed by the Access Consortium - a coalition of regulatory authorities from Australia, Canada, Singapore, Switzerland and the United Kingdom. The guidance lays out what information the medicines regulators would need in order to approve any modifications to authorised COVID-19 vaccines, should virus mutations make them less effective at preventing the disease.

United States Adopted Names (USAN)

The 2020 winter USAN Council meeting took place virtually on December 4, 2020. Names for 38 drug substances were reviewed and discussed. Eighteen new stems and infixes were approved and added to USAN's stem list. One stem, '-xertinib' was revised to '-terkib'. Forty-three new INN applications and 2 revised INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 72nd INN Consultation.

Through March 2021, USAN staff will have processed, researched, and made recommendations for 75 USAN applications and forwarded this information to the USAN Council for their review and selection. During the same time frame in 2020, 47 applications were processed.

Through March 2021, 55 USAN will have been adopted for 2021. Revenue was realized for an additional 2 negotiations. Currently, there are approximately 197 active USAN negotiations.

The 2021 Summer meeting of the USAN Council is scheduled to occur on June 4, 2021. It will be a virtual meeting.

United States Food and Drug Administration (FDA)

The FDA representative had nothing to report on nomenclature but noted that the FDA had issued three Emergency Use Authorizations for vaccines and several for therapies; one vaccine is by J&J, which is on hold for the assessment of the occurrence of rare blood clots. The FDA has a new acting commissioner, who used to be director of CDER, which now needs a commissioner. With no USAN for prophylactic vaccines, they will have a different name at FDA and the only group involved in naming is the FDA naming group. The FDA has been working virtually for over a year now, and there is a moratorium on all non-critical travel.

United States Pharmacopoeia (USP)

Since the beginning of the COVID-19 pandemic, USP's three-part response has centered on:

1) Ensuring the safety and security of staff and expert volunteers
2) Adapting its operations, and
3) Delivering on its public health mission

The majority of the USP staff continue to work remotely with its laboratory and distribution staff utilizing a rotating onsite schedule. USP continues to focus on building the public's trust in COVID-19 vaccines, treatments and preventatives. USP has published and developed several resources including the *USP Hand Sanitizer Toolkit* to address shortages and quality issues, the *COVID-19 Vaccine Handling Toolkit* to help vaccine administrators address operational efficiency gaps while maintaining quality and safety, and developed or partnered on resources to help reduce the risks from substandard and falsified COVID-19 treatments.

World Customs Organisation (WCO)

The WCO representative highlighted the close cooperation between the INN and WCO, with the Harmonized System Committee agreeing to classify INN substances contained in INN Lists 122 and 123.

The Scientific Sub-Committee came to a general consensus that products in which sequences encoding patient specific antigen had already been inserted were to be classified as vaccines since they had the properties of a complete vaccine, while products to which sequences encoding patient specific antigen had not yet been inserted, were to be classified based on their structure as mRNA, since they were incomplete and, therefore, did not have a property as a complete vaccine.

Due to the pandemic situation, the WCO also classified the substances on the proposed INN List 124 –COVID-19 special edition, created following the 71st INN special consultation on COVID-19 substances. The HSC has discussed updating the definition of vaccines in the Explanatory Notes by including the new mRNA vaccines.

In close cooperation with the WHO, the WCO has prepared a new HS classification reference for vaccines and their medical consumables normally used during the vaccination process, including the equipment used for their storage and transportation.

The WCO looked forward to work more with the INN Programme and was grateful for the excellent guidance provided to the Scientific Committee by the INN Team.

WHO Collaborating Centre for Drug Statistics Methodology, Norway

At its biannual March 2021 meeting, the Centre decided to reclass monoclonal antibodies (mAbs) and mAb conjugates that are used in cancer treatment due to their increasing numbers. A new 3rd level ATC was established and subdivided according to the target into 8 new ATC 4th levels. Forty-five substances were reclassified in these new groups, including

one “Other group” (X-group) where substances can be moved later to a specific level when there are enough substances with the same molecular action. Forty-four new codes were created and 4 substances were classified in existing codes.

The classification of anti-viral and anti-bacterial monoclonal antibodies has been changed with two separate ATC 4th levels created for them. A new 4th level has been created for FGFR tyrosine kinase inhibitors and includes 4 different substances. The Centre also established 17 new DDDs (defined daily dose). The new classification of mAbs is to be published on the web for comment. Depending on comments received, the changes will go into the next index (2022) or will wait until 2023.

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

The UMC representative was pleased to attend the Consultation for the first time. The UMC is a WHO collaborating centre working with drug monitoring worldwide and part of its work is to assign individual case safety reports (ICSRs) to the right substance. With the rapid appearance of Covid-19 vaccines, the Centre has worked hard to establish mapping the ICSRs to the correct COVID-19 vaccine. Having INN for mRNAs is appreciated and has made the mapping more reliable. It would be good to have INN for all types of vaccines, like the inactivated vaccines, as this would help in the mapping between ICSRs and substances.

CLOSE of MEETING

With no other points to raise, the Chair closed the 72nd Consultation, thanking the entire INN Team for all their work in preparing for this meeting, the individual technical officers who presented the requests and the support of the admin staff. He thanked the Experts and Advisors for their open communication involving both agreement and disagreement all of which is informative.

Dr Balocco thanked the Chair for his excellent leadership of this virtual meeting.

Next meeting: 73rd INN Consultation, 19-22 October 2021

OPEN SESSION for INN STAKEHOLDERS

72nd Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

(a virtual meeting)

Geneva, 13 April 2021

OPENING REMARKS

The Open session was opened by Dr Raffaella Balocco, Unit Head, INN Programme and Classification of Medical Products, on behalf of Dr Clive Ondari, Director Health Products and Standards, and the ADG Dr Mariângela Batista Galvão Simão. She welcomed all participants to the Open Session and highlighted that these sessions had been established to have direct dialogue with stakeholders, during which individual cases can be presented and issues discussed. It was highlighted that the Open Session is open only to those present in the meeting and all information disclosed and discussed was to be kept confidential until the meeting report is agreed and published.

The Chair of the meeting, Prof. Sarel Malan, welcomed the stakeholders to these twice a year session and looked forward to hearing their opinions and comments which will be taken into consideration by the Experts in the closed plenary session.

STAKEHOLDER PRESENTATIONS

Cend Therapeutics

A major problem in tackling solid tumours is for anti-cancer drugs to penetrate the physical barrier surrounding the tumour. Cend Therapeutics is developing a cyclic peptide (Cend-1) that will bind to specific receptors on the tumour surface. The peptide then undergoes a proteolytic cleavage from a furin-like protease, linearising the peptide and in conjunction with the receptor, opening up the microenvironment of the tumour to blood borne anti-cancer drugs.

In animal models less than 1% of drugs can reach a solid tumour; however, in the presence of Cend-1, imaging demonstrates how the tumour environment gets opened up within 30 mins of application and is long lasting. Concomitant treatment with Cend-1 and Abraxane®, shows 10-30 times more drug within the tumour compared to without Cend-1. The same process operates with mAb therapy and for example 40X more *trastuzumab* will penetrate a solid tumour in the presence of Cend-1 than without. This allows for lower doses of anti-cancer agents with consequent lower side effects and improved treatment of solid tumours.

Cend-1 entered first-in-man trials in 2018, is well tolerated and in solid tumour pancreatic cancer patients there are encouraging signs of anti-tumour activity using Cend-1 + nab-paclitaxel + *gemcitabine*. In applying for an INN for Cend-1, the name *argiditide* was proposed.

In discussion, it was added that 90% of metastatic stage 4 tumours express the appropriate receptors, but at very early stages, the tumour may not be growing quickly enough to do so.

Syndax Pharma

Syndax is developing a novel protein-protein interaction (PPI) inhibitor, SNDX-5613, that targets the nuclear scaffold protein, menin. The company presented at the Open Session to petition for a unique stem *-menib*, for their INN request for SNDX-5613.

Spontaneous rearrangements at the mixed-lineage leukaemia protein 1 (MLL1) locus create fusion proteins that lack methyl transferase activity. MLL1 fusions bind to the chromatin scaffolding protein menin via a conserved 5-amino acid motif (-FPARP-) near the amino terminus of the fusion protein; this results in the activation of transcription of leukaemia causing genes. SNDX-5613 was designed to bind with high affinity (pM) in the highly conserved menin binding pocket of MLL1, thus blocking the MLL1 fusion-menin interaction. Indeed, studies show that SNDX-5613 treatment of MV4;11 leukemic cells results in a rapid loss of the leukemic gene, MEIS1, and induction of the differentiation program (CD11b) in MV4;11 cells.

Menin inhibitors are a pharmacologically distinct class of protein-protein interaction (PPI) inhibitors. There is no precedent for this mechanism of action and assignment of a unique stem (-menib) to SNDX-5613 would parallel the approach taken with other PPI inhibitor classes such as *-bresib* for inhibitors of BET family of proteins or *-nutlin* for inhibiting the interaction of MDM2 with p53. Menin inhibitors are mechanistically distinct from inhibitors of enzymes that epigenetically modify chromatin and so the stem *-metostat* would also not be appropriate. Thus, the request for a unique stem -menib for SNDX-5613 with six possible random prefixes suggested by the company. Other companies are also developing menin PPI inhibitors which they characterise as a new emerging class of inhibitor that would benefit from a new unique stem.

Kodiak Science

Kodiak's focus is on the development of a new generation of medicine in ophthalmology involving monoclonal antibodies (mAb) conjugated with biopolymers that increase half-life and improves bioavailability, biocompatibility and stability. Intravitreal anti-VEGF agents can improve and maintain vision when dosed per label, yet in the real word, visual gains are minimal and not maintained as patients cannot be treated frequently enough and are over-extended between doses. Kodiak's lead candidate KSI-301 may change clinical and real-world outcomes by reducing the number of treatments required per year.

An INN was requested for the mAb-biopolymer KSI-301; however, the second word for the polymer was rejected by the company due to the insertion of a *-dri-* infix, indicating a dendrimer, in front of the *-mer* stem. The company argued that the structure of a dendrimer polymer repeatedly branches and grows, whereas in contrast, the polymer of KSI-301 although having some comparison to a dendrimer, does not have a repeating branch unit and is more linear. In polymerisation, it initially establishes 9 branches but then proceeds in linear fashion, with each branch not having the same number of units; this also results in the molecular weight increasing linearly plus it is not spherical. Consequently, the company has proposed three alternative infixes, -clip- or -cli- for controlled living polymerization (manufacturing process) or -dro- for its highly hydrophilic properties.

In discussion, the company agreed that an alternative could be based upon the linearity of their polymer. In addition, when challenged as to why its polymer should have a specific infix, the company acknowledged that it would accept *-mer* alone with no specific infix, the main point being not to have the misleading *-dri-* infix.

Rakuten Medical

Rakiten petitioned the INN Expert Group for a substitution of the previously Recommended INN, *cetuximab sarotalocan*, to avoid patient errors and suggested reversing the order of the words to *sarotalocan cetuximab*. Rakuten Medical's investigational treatment platform Illuminox™ is based upon photoimmunotherapy consisting of *cetuximab*, a mAb targeting epidermal growth factor receptors (EGFRs) on tumour cells, conjugated with a

light-activatable dye (IRDye® 700DX) (*sarotalocan*) and a laser device system. Activated, the dye causes tumour cell necrosis with minimal effects on healthy tissue. Both drug and device are necessary for the therapeutic activity.

The rINN was published in 2018 but many healthcare workers confuse the drug-conjugate *cetuximab sarotalocan* with *cetuximab*, which is no longer a favourable treatment, and so there is hesitation in the use of the mAb conjugate. The company has concern that the INN confusion may potentially lead to improper use, inappropriate substitution, or medication errors. It was pointed out that this situation is not unique and for example there has been misuse of the mAb conjugate *trastuzumab emtansine* instead of the stand-alone mAb *trastuzumab* (Herceptin) during clinical trials such that the US FDA has modified the conjugate name to *ado-trastuzumab emtansine* for greater clarity.

In discussion it was highlighted that *cetuximab sarotalocan* was named according to INN rules and that a request for substitution of a recommended INN has to be accepted first by the INN Expert Group and then WHO has to inform each of the 194 Member States, and if one rejects the request, the substitution cannot take place. The INN experts have studied these situations and published a commentary in WHO Drug Information[1] which notes that conjugates are named according to convention and this will continue until it changes. It further notes that biological medicines are typically prescribed as INN plus trade name and whilst the INN experts wish to ensure patient safety, issues of dosing and safe prescribing remain when the conjugate word is placed before the mAb word. In Rakuten's case, the conjugate is more important, but in others the mAb is more important. It is difficult to find a good solution and the naming rule cannot be changed without other problems.

Alliance for Safe Biologic Medicines (ASBM)

The ASBM emphasised that the WHO plays a major role in building public confidence in COVID-19 vaccines and this reflects the importance the WHO plays in promoting public confidence in other medicines, including biologics, through providing strong global pharmacovigilance (PV). The ASBM has made representation to the INN Expert Group many times since the original biological qualifier (BQ) proposal and this continued effort demonstrates its determination and resolve to support the INN Programme's efforts and effect change on this issue.

To reflect the ongoing interest of the ASBM in this, the association will present a poster at the annual (virtual) DIA meeting in June 2021 which examines the literature on PV programs and emphasis on identifiability in adverse drug reaction (ADR) reporting. It has observed that pharmacovigilance of biologics and biosimilars is very important and more challenging than for non-biologics or generic small molecules. Surveys note a lack of batch number recording and an emphasis on brand name reporting; however, recording of brand names varies widely and as the number of biosimilars proliferate, there is decreasing identification by brand name in ADR reports.

Many published reports, including ASBM's own surveys of prescribers over several years, show a clear lack of identification of the brand name in ADR reports, especially in the EU in which brand name reporting became a mandatory requirement in 2012. Indeed, a 2020 WHO

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Sally Pepper, Sarel Malan, Gilles Mignot, Raffaella Balocco: Look-alike sound-alike drug name confusion: trastuzumab emtansine, WHO Drug Information Vol. 30, No. 1, 2016

study identified a lack of consensus on naming as one of four "remaining regulatory challenges" facing biosimilars globally.

In discussing Canadian data, the ASBM reminded the INN experts, that in 2019 Health Canada, after long supporting distinct naming and the BQ, shifted to use of brand names and country-specific identifiers, citing lack of WHO action in establishing international consistency.

In conclusion, the ASBM highlighted that reporting on brand names in ADR reports continues to be inadequate despite widespread recognition of its importance. WHO has identified a lack of a naming standard as a regulatory challenge that undermines the strong pharmacovigilance needed for biologics and biosimilars, and ASBM underlined that the WHO has the ability and the duty to make a global standard available to address this global pharmacovigilance need.

ASBM also reiterated its offer to draft a petition on behalf of INN to address this global regulatory challenge.

In discussion, it was highlighted that legislating for brand name but not batch number will not help and that as no system will be perfect, it is education that is important. In response to a question about PV data for small molecule drugs, ASBM replied that it had not analysed the situation for small molecules as generally they are interchangeable and much less of an issue. In discussing to what extent adoption of a BQ would facilitate PV, ASBM noted that the US FDA had taken this approach but it was not clear yet if any data are available on identification of the medicine in this way. It appeared that the FDA intends to keep the 4-letter extension to product names despite companies complaining that it is cumbersome as the FDA is confident that it has the right approach.

CLOSE OF MEETING

The Chair thanked all presenters noting that these presentations are always interesting and informative, and that the information will be taken onboard in the discussions of the Expert Group.