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56th MEETING OF THE WHO INTERNATIONAL WORKING GROUP FOR DRUG STATISTICS METHODOLOGY

Geneva, 28-29 October 2024

Executive Summary

International Nonproprietary Names (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

56th MEETING OF THE WHO INTERNATIONAL WORKING GROUP FOR DRUG STATISTICS METHODOLOGY

Geneva, 28-29 October 2024 (hybrid meeting)

EXECUTIVE SUMMARY

Welcome and opening remarks

Dr Raffaella Balocco, Unit Head, International Nonproprietary Names (INN) Programme and Classification of Medical Products, welcomed all participants to the 56th meeting.

The Assistant Director-General for Access to Medicines and Health Products, Dr Yukiko Nakatani, noted that achieving effective drug utilization was crucial for advancing global health. Dr Nakatani emphasized the importance of the Anatomical Therapeutic Chemical (ATC) classification system and Defined Daily Doses (DDD) as tools for standardizing the measurement of drug consumption to assess that drugs are prescribed appropriately and utilized effectively to maximize therapeutic benefits while minimizing risks. Dr Nakatani noted that many countries had adopted the ATC classification and DDD methodology, demonstrating their importance and relevance in healthcare systems worldwide. Dr Nakatani acknowledged the instrumental role of the WHO Collaborating Centre for Drug Statistics Methodology (the 'ATC/DDD Centre') in establishing this methodology and commented that WHO was committed to working closely with the ATC/DDD Centre to ensure that the benefits of the methodology are realized worldwide. Dr Nakatani noted several successful collaborations, in particular work addressing the application of DDDs for cancer drugs and the conduct of a survey to evaluate the use of the ATC classification and DDDs across different countries. Dr Nakatani noted that the International Nonproprietary Names (INN) and ATC and DDD tools, and their link to the Essential Medicines List (EML), are fundamental components to the WHO's mission to ensure both access to medicines and their rational use so that patients receive safe and effective treatments when needed. Dr Nakatani thanked the experts from the WHO International Working Group for Drug Statistics Methodology (the "Working Group"), the ATC/DDD Centre, the liaison experts from INN Expert Group, distinguished observers and the WHO Secretariat for their dedication and collaboration.

Election of Chair and rapporteur

Professor Vera Vlahović-Palčevski was elected as the Chair and Professor Morten Andersen was elected as the Vice-Chair of the meeting. Dr Kerry Atkins was elected as Rapporteur to draft the executive summary of the meeting.

Minutes of the 55th meeting

The minutes of the 55th meeting were adopted without objection.

Report from the WHO Collaborating Centre for Drug Statistics Methodology

Dr Mohammad Nouri Sharikabad, Director, provided an update from the ATC/DDD Centre, including:

- A global questionnaire on the ATC/DDD methodology was being conducted with over 10,000 invitations for input sent via email;
- Promotion of the ATC/DDD system alongside the Identification of Medicinal Products (IDMP) standards through the UNICOM project;
- Developing ATC/DDD methodology online course for the School of INN;
- Provision of the annual ATC/DDD course and training workshops held in Canberra, Australia and Mombasa, Kenya;
- Development of an Application Programming Interface (API), a digital solution designed for direct, user-friendly access to the ATC/DDD index;
- Participation in the *ad hoc* Working Group for DDDs on Cancer Drugs;
- Introduction of a new statistic bank for Norwegian prescribed drug registry to expand the use of ATC/DDD; and
- Publication of the 2024 indexes and guidelines.

Further details about these initiatives are discussed below.

The Working Group reflected on the passing of Ms Irene Litleskare in July and acknowledged the significant contribution that Ms Litleskare had made to the work of the Norwegian Institute of Public Health, the ATC/DDD Centre and the WHO International Working Group for Drug Statistics Methodology.

Points for discussion from the WHO Headquarters

Dr Balocco discussed the need to further strengthen the collaboration between the Working Group, the ATC/DDD Centre, the INN Expert Group, and the EML group to promote the ATC/DDD more globally. It was noted that the Working Group, together with the ATC/DDD Centre and in collaboration with the INN Expert Group and EML group, was in a unique position in setting standards in the field of nomenclature and drugs classification. Dr Balocco noted that with the rapid innovation in health technologies and more substances reaching the INN Expert Group for classification, there is a need to work more closely to assign appropriate INN names and ATC classifications for these new substances. In particular to consider new nomenclature schemes for biologicals such as cell therapies and gene therapies.

Dr Balocco reported that there had been a large number of visitors to the WHO INN website and that the School of INN platform was available in four UN languages. Further updates to the INN website were planned to provide more visibility to the ATC/DDD methodology.

ATC classification items

The Working Group discussed two challenges and two proposed alterations for ATC codes and made the following decisions:

- To establish a new ATC 4th level L01EP *Cellular-Mesenchymal-Epithelial Transition factor (c-MET) inhibitors.* The Working Group recommended to include savolitinib and

to move capmatinib (with current ATC code L01EX17) and tepotinib (with current ATC code L01EX21) to the new level L01EP.

- To establish a new ATC 4th level L04AL *Neonatal fragment crystallisable receptor (FcRn) inhibitors*. The Working Group recommended to include nipocalimab and to move efgartigimod alfa (with current ATC code L04AA58) and rozanolixizumab (with current ATC code L04AG16) to the new level L04AL.
- The Working Group considered whether to classify bispecific antibodies together with the monoclonal antibodies by main antigen target, as an alternative to establishing a new 4th level that includes all bispecific antibodies. The Working Group had previously considered this option at its 53rd meeting and decided that more bispecific antibodies should be included in the ATC/DDD system before making a decision. The Working Group noted that since its previous consideration only four substances had been classified and all were "T-cell engaging bispecific antibodies". As such, the Working Group considered it was still premature to decide on a reclassification of the bispecific antibodies.
- To modify the name of the ATC code J07BX01 from "smallpox and monkeypox vaccines" to "smallpox and mpox vaccines". Considering recent recommendations from the WHO, the Working Group concluded that this was an appropriate descriptor for this code to align with WHO recommendations.

A total of 62 new ATC 5th level codes proposed by the ATC/DDD Centre were considered including the following Working Group decisions:

- An ATC 5th level was not assigned to fecal microbiota as the Working Group was uncertain about whether fecal transplantation products should be regarded as a drug and the standardisation of these products. It was noted that no INN had been assigned for these products. It was suggested that relevant regulatory authorities and stakeholders are invited by WHO to an open session to clarify these questions.
- To establish a new ATC 5th level codes for:
  - Chikungunya vaccines in J07BX *Other viral vaccines.*
  - Doxecitine and doxribtimine in A16AX *Various alimentary tract and metabolism products*.
  - Insulin icodec and semaglutide in the 50-series in A10AE *Insulins and analogues for injection, long-acting*. The Working Group requested that the ATC/DDD Centre consider evaluating an ATC 4th level for combinations of insulin and GLP-analogues when more data regarding use is available.
  - Nogapendekin alfa and inbakicept in L03AC *Interleukins*.
  - Piracetam and cinnarizine in the 50 – series in N06BX *Other psychostimulants and nootropics.* Classification under the existing code for cinnarizine, combinations (N07CA52) was considered, however the substances classified in this code were primarily indicated for antivertigo indications whereas piracetam and cinnarizine could be used to treat multiple indications. The Working Group also noted that the DDD assigned to the existing combination code referred to cinnarizine only. The addition of a comment in the Guidelines at N07CA was recommended to note the classification of piracetam and cinnarizine in N06BX.
  - Pridopidine in N07XX *Other nervous system drugs.*
  - Rivoceranib in L01EK *Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors.*
  - Zongertinib in L01EH *Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors.* The Working Group agreed with the ATC/DDD Centre's proposal to revise the Guidelines (L01EH and L01EB) to clarify that all HER2-targeting

substances, not restricted to those targeting HER2 and EGFR, are classified in L01EH.

- To classify the following products into existing ATC 5th level codes:
  - Combination of ticagrelor and acetylsalicylic acid in the existing code (B01AC30) in B01AC *Platelet aggregation inhibitors excl. heparin*.
  - Diflunisal in the existing code (N02BA11) in *N02BA Salicylic acid and derivatives.*

Defined Daily Dose Items

The Working Group agreed with the proposed DDDs and approved the dose protocol presented by the ATC/DDD Centre. DDDs for 14 new single substances and 2 DDDs for combination products were assigned. The Working Group commented that:

- While basing the DDD for nogapendekin alfa and inbakicept (L03AC03) on the maintenance dose was appropriate, it was noted that the DDD for the intravesical administered BCG vaccine (L03AX03), which is used in combination with nogapendekin alfa and inbakicept, was based on the induction dose.
- Solriamfetol (N06BA14) had two main indications for obstructive sleep apnoea (OSA) and narcolepsy. It was decided to assign a DDD of 100 mg (O) being approximately in the middle of the average doses for the two indications.

Two DDD alteration requests were considered:

- A request to increase the DDD for tobramycin inhalation solution (J01GB01) from 0.3 g to 0.6 g. The Working Group considered the argument that tobramycin may be used more frequently for bronchiectasis in a continuous dosing regimen for up to three months, and therefore, the medication-free days should be excluded from the DDD calculation. However, DDDs are typically based on approved product information, which, in this case, included the medication-free period across all product information documents. The Working Group considered that there was insufficient documentation on the global usage patterns of tobramycin inhalation solution to justify a change in the DDD. It was decided not to alter the DDD for tobramycin inhalation solution but to keep the DDD on 0.3 g based on intermittent dosing.
- The Working Group decided not to alter the DDDs for oral azithromycin, parenteral cloxacillin, and conventional amphotericin B. As antibiotic consumption was a critical area in drug utilisation research, any changes to the DDDs for antibiotics needed to be carefully considered. The Working Group considered that it would be appropriate to reconsider the DDDs for azithromycin and cloxacillin as part of a more comprehensive revision of antibiotics undertaken in the future.

Ad hoc Working Group on DDDs for cancer drugs

Dr Atkins provided an update on the work of the *ad hoc* Working Group on DDD for Cancer Drugs (*ad hoc* WG) which was established at M54 based on a request from the Italian Society of Pharmacology and the Italian Association of Epidemiology ("the Italian DDD Working Group"). It was noted that six meetings had been held during 2024 over the period February to July including representatives from the Working Group, the ATC/DDD Centre, INN Programme, WHO EML group, European Society for Medical Oncology (ESMO), International Society of Oncology Pharmacy Practitioners (ISOPP), and the Italian DDD Working Group. The Working Group noted that a total of 38 antineoplastic agents were

reviewed. Thisincluded substances proposed by the Italian DDD WG, along with substances on the EML, where the DDD was based on standard dosing or recommended dosing based on body weight.

The Working Group considered important implications in assigning DDDs for these substances. It was discussed that while the use of DDDs for reimbursement purposes is not an appropriate use of the ATC/DDD system, decisions needed to be mindful that there were countries where the DDD is one of the metrics considered for the reimbursement of patients for cancer therapies. Dr Sharikabad presented other considerations including: cases where grams of the active substance would be a more appropriate measure of therapeutic intensity; difficulties in assigning a meaningful DDD for substances where there is individual variation in dosage; addressing uncertainty in identifying the main indication and best dosage as a basis for the DDD assignment; potential for pharmaceutical companies to propose DDDs to increase their revenues for cancer treatments rather than meaningful DDDs for drug research; managing additional complexity for Guidelines text; and that the ability to aggregate data upwards to the ATC 4th level needed to be thoughtfully considered where DDDs are not assigned for all substances within an ATC 4th level. A suggested approach was to start with one ATC 4th level and look at the corresponding ATC 5th levels which may facilitate the identification of a main indication and appropriate Guidelines text.

In selecting a main indication for a substance, the *ad hoc* WG considered this should align with the EML, or if a substance was not listed in the EML, the indication should be based on the most prevalent disease or utilisation data. The Working Group discussed whether the indication for a substance from the EML would reflect the main indication of use globally. It was argued that the EML, as a resource developed by WHO, was an appropriate reference where the main dosages had been investigated by cancer experts.

A total of 30 new DDDs proposed by the *ad hoc* WG were recommended by the Working Group out of the 38 antineoplastic agents that were reviewed. It was agreed that the DDDs would be published as temporary codes in the WHO Drug Information and on the ATC/DDD Centre's website following the March 2025 meeting. The Working Group decided to prepare an explanatory letter for its stakeholders detailing the rationale behind the assignment of DDDs for anticancer drugs. For the substances where a decision to assign a DDD was not made, the Working Group requested that the ad hoc WG provide further advice, including undertaking data collection and analysis on the indications of use and doses supplied in practice, to inform its decision making.

Initiatives to promote the application and uptake of the ATC/DDD methodology

ATC DDD Questionnaire

The ATC/DDD Centre presented on a global questionnaire that it was prepared in collaboration with WHO/INN, conducting to assess how the ATC/DDD system is implemented and utilised by its users. The Working Group appreciated the value of this activity in understanding how the ATC/DDD methodology can be applied within the resources available in each country, region, or institution, thus maximising its benefits for public health. The Working Group noted that the questionnaire was raising awareness about

the ATC/DDD system, the availability of guidelines and training courses, and opportunities for users to request an ATC code or a DDD when needed.

Italian Working Group on DDD and EMMA Initiative

Dr Giuseppe Roberto gave an update on the work of the Italian Working Group on DDDs which has focussing on the assignment of DDDs for antineoplastic agents, ophthalmological medications and otological drugs. The Exposure to Medications Measured using the ATC/DDD Classification System (EMMA) initiative was also discussed which was examining variations of the ATC/DDD system used in different countries and how the methodology was reported in the literature. The Working Group noted that the outcomes of EMMA would complement the questionnaire being undertaken by the ATC/DDD Centre.

DURU – South Africa

Prof Truter provided a presentation on the Drug Utilisation Research Unit (DURU) at Nelson Mandela University in South Africa and described how this group was using the ATC/DDD methodology in its research and educational activities. The Working Group noted that DURU had established a wide network of collaborations within Africa and internationally with scientific associations and other research groups. It was further noted that the Government of the Republic of South Africa was implementing the Health Terminological Systems which would formally incorporate the ATC/DDD classification system into the healthcare coding framework in South Africa.

Capacity building and trainings

INN/ATC course for the WHO Academy

Prof Albert Figueras gave a presentation on the development of an introductory course through the WHO Academy which aimed to familiarise users with the INN and the ATC classifications and how they can be applied to support appropriate prescribing practices, investigate drug safety, drug research, and policy making.

Course on the ATC DDD methodology for the SoINN

At its M54 the Working Group decided to establish a project to develop an online course for the School of INN on the ATC/DDD methodology. The Working Group noted that a team had been formed to progress this work including Dr Houda Sefiani, Prof Truter and Dr Ioakeim Skoufa. Dr Sefiani provided an update on the project and it was noted that the English version of the course was expected to be ready in March 2025.

Other Training courses

The ATC/DDD Centre also advised that in addition to its annual course, tailored courses were also being made available. The Working Group noted the successful workshop on ATC/DDD that was held in Australia in June 2024 presented by Professor Ilse Truter and Dr Ignatios Ioakeim Skoufa with participants attending from the Department of Health and Aged Care, Australian Bureau of Statistics, Australian Institute of Health and Welfare, Therapeutic Goods Administration and drug researchers.

Other items

ATC and INN Classification

Prof Sarel Malan shared reflections on future challenges regarding the classification of novel substances and the potential need to explore harmonisation between the INN and the ATC/DDD system.

Development of an online platform for ATC/DDD submissions

Dr Antonio Romeo noted that work on the implementation of an online platform to support communications between WHO, the ATC/DDD Centre and the Working Group was ongoing. It was noted that Dr Romeo was working with Dr Ioakeim Skoufa to adapt the INN Integrated Data Management Information System (IDMIS) platform to align with the workflow, specific requirements, and characteristics of the ATC/DDD methodology.

Next meeting

An invitation was received from the Public Health Institute of Chile to hold the next meeting of the WHO International Working Group for Drug Statistics Methodology, in Spring 2025 in Santiago, Chile.