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57th MEETING OF THE WHO ADVISORY GROUP FOR DRUG STATISTICS METHODOLOGY

Instituto de Salud Pública de Chile, Santiago, Chile/via Zoom
1-2 April 2025

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

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EXECUTIVE SUMMARY

Welcome and opening remarks

Dr Catterina Ferreccio, Director of Instituto de Salud Pública (ISP), extended a warm welcome to all the meeting participants.

Dr Raffaella Balocco, Unit Head, International Nonproprietary Names (INN) Programme and Classification of Medical Products, also welcomed all participants to the 57th meeting.

Mr Deus Mubangizi warmly welcomed participants to the 57th Meeting of the WHO Advisory Group for Drug Statistics Methodology, held in Santiago, Chile, expressing gratitude to the Chilean authorities and the Instituto de Salud Pública de Chile for their generous hospitality. He acknowledged the critical expertise of the Advisory Group (AG), whose recommendations ensure the scientific rigor and global relevance of the ATC/DDD methodologies, supporting WHO's mission to enhance access to quality medicines. Mr Mubangizi praised the WHO Collaborating Centre for Drug Statistics Methodology for its technical preparations, while noting that WHO retains decision-making authority guided by the Group's advice.

Mr Mubangizi highlighted the meeting's focus on reviewing ATC classifications and DDD assignments, emphasizing their practical impact on rational prescribing, pharmacovigilance, and access to essential medicines worldwide. Mr Mubangizi underscored the interconnectedness of WHO's INN, EML, and ATC/DDD programs, which collectively ensure universal medicine identification, prioritize essential medicines, and monitor their rational use. Amid global challenges, he stressed the need for strengthened collaboration to serve vulnerable populations.

Mr Mubangizi also thanked WHO's INN Unit, Juan Roldan, and the Chilean team for their efforts in organizing the meeting and a subsequent training session, which will reinforce the integration of WHO's medicines programs. He concluded by wishing participants a productive meeting and encouraging them to enjoy Chile's cultural and natural beauty.

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 Nitin Bagul was elected as Rapporteur to draft the executive summary of the meeting.

Minutes of the 56th meeting

The minutes of the 56th meeting were adopted without objection.

Points for discussion from the WHO Headquarters

Dr Balocco welcomed participants to the meeting themed *Working Together for a Stronger Future*, emphasizing the shared commitment to ensuring accessible, rational, and safe use of medicines. The International Non-proprietary Names (INN), Essential Medicines List (EML), and Anatomical Therapeutic Chemical (ATC) classification systems were highlighted as interconnected pillars critical to public health. Their synergy supports clear medicine identification, appropriate selection, and effective monitoring, fostering trust among healthcare professionals, regulators, and patients.
The remarks underscored ongoing challenges in harmonization, implementation, and adaptation to new medical technologies, urging collaborative discussions to address these issues. The meeting was framed as an opportunity to exchange insights, align strategies, and innovate for equitable medicine access globally.

Key WHO Insights:

1. **Global Access**: Over 2 billion people lack access to essential medicines, necessitating stronger INN, EML, and ATC alignment to prioritize delivery to underserved populations.
2. **Rational Use**: Up to 50% of medicines are used inappropriately, with INN, EML, and ATC integration critical to promoting rational prescribing and dispensing.
3. **Safety**: Medication errors and adverse reactions cause significant harm, mitigated by integrating INN, EML, and ATC in pharmacovigilance frameworks.
4. **EML Impact**: EML adoption improves medicine availability and reduces costs, particularly for life-saving treatments.
5. **Innovation**: Rapidly evolving therapies (e.g., biologicals, cell/gene therapies) require adaptive INN, EML, and ATC frameworks to remain relevant.
6. **WHO's Role**: WHO's leadership in standardizing these systems supports universal health coverage and Sustainable Development Goal 3.

Industry Input

Ms Janis Bernat, representing the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), provided insights on the ATC/DDD methodology. She stressed the need to clarify the long-term vision and goals for its future development. The ongoing survey's findings were noted as critical for advancing the ATC/DDD system. Furthermore, she emphasized the industry's readiness to actively participate in these discussions.

"Virtual toast" on the excellence in achievement awarded to Dr Nilima Kshirsagar by the ACCP

Dr Nilima Kshirsagar was congratulated with the award by the American College of Clinical Pharmacology (ACCP).

ATC Classification: addressing complexities

Professors Ilse Truter and Albert Figueras outlined several challenges with the ATC/DDD methodology, including its intended use in pharmacoepidemiological studies versus other applications, such as pricing and reimbursement, handling combination products, and varying implementations in national registries. They noted inconsistencies where substances with similar mechanisms of action or INN stems are placed in different ATC 4th levels, while some ATC groups contain substances with diverse mechanisms and INN stems. The Centre clarified that the ATC system is primarily a therapeutic and pharmacological classification focused on the clinical use of medicines in drug utilization research. In contrast, INN stems reflect pharmacological or chemical relationships. Due to these differing objectives, substances with the same INN stem may be assigned to different ATC 4th levels, or different stems may be grouped together. The ATC system also allows a single substance to have multiple ATC codes. When classifying, the substance's INN stem, its place in the INN system, and the indications of related substances are considered. To maintain efficiency and avoid creating numerous single-substance ATC 4th levels, new specific levels are typically established only when at least two marketed substances fit the group and enhance drug utilization research. As a result, multiple INN stems may be grouped into a single "other" category.

Short update from the WHO Collaborating Centre

Dr Mohammad Nouri Sharikabad shared a concise update from the Centre, noting that a comprehensive report is scheduled for October as per standard procedure. He expressed appreciation for the invitation to Chile and the Public Health Institute. He briefly highlighted the Centre's contributions and confirmed that written feedback on the agenda and List of Participants had been sent to AG members (cc WHO) via email prior to the meeting. He underscored the importance of maintaining high-quality work despite any differences between WHO and WHOCC and looked forward to productive discussions in Chile.

Review of Proposed ATC Codes

The ATC/DDD Centre proposed 40 new ATC codes, with the Working Group making the following decisions:

- Drospirenone, used for treating pelvic pain associated with endometriosis, will be classified under the existing code G03AC10 (drospirenone) in G03AC Progestogens.
- Paltusotine will be assigned to H01CB (Somatostatin and analogues), with a note included in the Guidelines.
- Libevitug will be categorized under J06BD (Antiviral monoclonal antibodies).
- Mifanertinib will be placed in L01EH (Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors).
- Tolebrutinib will be classified in L04AA (Selective immunosuppressants).
- The combination of tramadol and magnesium will be included under the existing code N02AX02 (tramadol) in N02AX Other opioids, with a comment in the Guidelines.
- Risperidone (powder and solvent for prolonged-release suspension for injection) will be assigned to the existing code N05AX08 (risperidone) in N05AX Other antipsychotics.
- 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.*

ATC classification items

The Advisory Group (AG) discussed two objections, two proposed alterations and two challenges for ATC codes and made the following decisions:

- To alter the name for the ATC 4th level L04AL Neonatal fragment crystallizable receptor (FcRn) inhibitors: blockers vs inhibitors. The WHO Expert Advisory Group decided to maintain the decision from the previous meeting, to keep the L04AL ATC 4th level name Neonatal fragment crystallizable receptor (FcRn) inhibitors and advised the Centre to continue to examine the terminology issue, which will be revisited at a future meeting.
- To alter the classification of chikungunya vaccines (J07BX07). The Advisory Group recommended to alter the classification and establish a new ATC 4th level J07BP Chikungunya vaccines, with separate 5th level codes for Ixchiq (J07BP01 chikungunya, live attenuated) and Vimkunya (J07BP02 chikungunya, virus-like particles).
- In October 2022 (M52), topical roflumilast was assigned to D05AX06 (Other antipsoriatics for topical use) for plaque psoriasis. Now approved for atopic dermatitis, seborrheic dermatitis, and plaque psoriasis, roflumilast, a PDE-4 inhibitor, sees 65% of U.S. prescriptions for atopic dermatitis (17%) and seborrheic dermatitis (48%), with higher prevalence (4.3% and 2.9%) than psoriasis (2.6%). The Advisory Group considered a request reclassification of roflumilast to D11AH, where crisaborole (D11AH06) and other multi-indication drugs are classified. The Advisory Group recommended to keep the current classification of topical roflumilast in D05AX Other antipsoriatics for topical use and add a comment in the Guidelines that topical roflumilast is classified here.
- To establish a new ATC 4th level for amyloid targeting therapies for the treatment of Alzheimer's disease: Several members of the Advisory Group suggested that creating a distinct ATC 4th level for amyloid-targeting antibodies could enhance drug utilization studies, as the requirement of at least two substances with marketing authorisation was fulfilled. However, due to aducanumab's withdrawal, safety and efficacy concerns for donanemab and lecanemab, and unclear usage patterns from their recent market entry, the group deemed it premature to establish a new therapeutic class. Noting that innovative drugs are typically classified in an "X" group pending further data, and with over 15 INN requests for amyloid beta-targeting monoclonal antibodies in development, the group decided to postpone the creation of a new 4th level and revisit the issue once more antibodies are marketed and their uptake is clearer.
- A request was received for an ATC code for baxdrostat, a selective aldosterone synthase inhibitor used orally to treat uncontrolled hypertension in adults by reducing aldosterone levels and increasing renin activity without affecting cortisol. A new 4th level under C02K (Other antihypertensives) for aldosterone synthase inhibitors was proposed, with alternatives including C02KN (Other antihypertensives), C03 (Diuretics), and C09XX (Renin-angiotensin system agents). The Advisory Group, aligning with the drug's primary indication, classified baxdrostat in C02KN, noting its novel mechanism and potential for a future 4th level as more similar drugs emerge, and assigned it a new 5th level in

C02KN.

- A new ATC 5th level code was requested for diazoxide choline, a prolonged-release tablet for treating hyperphagia in Prader-Willi syndrome (PWS) in patients aged four and older, under N07XX (Other Nervous System Drugs). It was considered that diazoxide choline should be classified under V03AH01 (diazoxide), as it hydrolyzes to diazoxide before absorption, shares tablet strengths and posology with existing V03AH01 products, and adheres to ATC guidelines assigning one code per administration route. The Advisory Group recommended to classify diazoxide choline in V03AH01 and recommending revisions to the Guidelines under V03AH/C02DA to specify its use for PWS treatment.

INN and ATC Classification

Professor Sarel Malan presented on the similarities and differences between the INN and ATC classification systems, highlighting INNs without ATC codes and ATC codes without INNs. A question arose about whether all marketed INNs should have ATC codes and all ATC-coded substances should have INNs. The Centre noted that some ATC codes cover multiple substances and that both INNs and ATC codes are assigned upon request. Achieving universal INN and ATC assignment for marketed substances would require further discussion on feasibility and appropriateness. The Centre also observed that users often create unofficial 4th or 5th level classifications when no ATC code exists, which is acceptable if clearly marked as non-official. The Advisory Group decided to defer any decision, agreeing to reflect on the purposes of both systems and explore how their insights could drive improvements.

Demo of the ATC IDMIS for virtual consultation

Dr Antonio Romeo presented a tool to strengthen communication between the AG and WHO and the Centre and earlier access to the ATC/DDD applications.

ATC/DDD around the world (Sweden, Italy, Australia, Spain)
Representatives from Italy, Australia, and Spain shared insights on the use of the ATC/DDD system and related challenges. The presentations highlighted national approaches, experiences, and context-specific issues in the use and implementation of the system. Dr Emilie Ahnfelt from Sweden shared on how ATC/DDD system is used in the setting of the Uppsala Monitoring Centre.

Defined Daily Dose Items

Dose protocol was presented by the Centre. The Advisory Group agreed with the rationale and approach to the derivations for the proposed DDDs. The Advisory Group had no additional comments to the DDDs suggested.

Review of the DDDs assigned three years ago

The Centre reviewed DDDs assigned in the 2023 ATC Index, using updated dose recommendations, with no prior change requests received.

Two substances were discussed:

Burosumab (M05BX05): The DDD of 2.5 mg (parenteral) for X-linked hypophosphatemia (XLH) in adults was reviewed. Burosumab is approved in Europe and the USA for XLH and FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) across pediatric and adult populations. The Advisory Group agreed to retain the DDD, as both indications are rare, and TIO is not the primary indication.

Fenfluramine (N03AX26): The DDD of 8 mg (oral) was based on Dravet Syndrome treatment in children (20 kg body weight) with stiripentol. Fenfluramine's indication now includes Lennox-Gastaut Syndrome (LGS) in patients aged 2+ in Europe and the USA. Dosage regimens vary, with maximum daily doses of 26 mg (without stiripentol) and 17 mg (with stiripentol). The Group decided to base the DDD on LGS (0.7 mg daily, without stiripentol) using a 20 kg body weight, as a 70 kg adult calculation would exceed the maximum dose. The DDD was increased to 14 mg (oral), with Guidelines revised to reflect this.

All DDDs remained unchanged except for fenfluramine's, increased to 14 mg (oral) for LGS. Guidelines will be updated for fenfluramine and include a note that burosumab's DDD is for XLH.

Cyclophosphamide DDD Discussion: At the prior meeting (M56), the Advisory Group reviewed DDD proposals for antineoplastic agents (L01), including cyclophosphamide, but deferred a decision pending more usage data. At this meeting, data from Denmark, Australia, South Africa, and Norway showed varied cyclophosphamide use (oral and parenteral) for cancers (e.g., breast cancer, lymphomas) and immunosuppression, with highly individualized dosing. Denmark noted stable sales but reduced community dispensing; Australia reported a mean daily dose of 83 mg (2020-2024) based on its Pharmaceutical Benefits Scheme data; South Africa lacked comprehensive data; and Norway highlighted breast cancer as the top indication with doses from 1000–9200 mg annually. The Group noted challenges in selecting a globally representative indication and dosage due to significant variations, rendering a DDD for cyclophosphamide impractical and of limited value. Assigning DDDs randomly within an ATC 4th level was deemed ineffective for aggregate statistics, unlike the systematic approach for protein kinase inhibitors (L01E). The Group decided against establishing a DDD for cyclophosphamide due to its variable use and dosing.

Classification of allogeneic faecal microbiota

WHO shared a recorded excerpt from a recent INN meeting where experts discussed challenges in assigning an INN to faecal microbiota products, citing their heterogeneity, lack of batch-to-batch standardization, and unclear mechanism of action. The ATC classification discussion focused on a request for an ATC code for MaaT013, an allogeneic faecal microbiota rectal suspension for treating corticosteroid- and ruxolitinib-resistant gastrointestinal acute graft-versus-host disease in adults. MaaT013, prepared from pooled donor material, aims to restore gut microbiota and modulate immune homeostasis. The Advisory Group noted it was proposed to classify these products in a new 2nd, 3rd, and 4th level within the L group, which conflicts with ATC guidelines requiring multiple 5th level codes for marketed substances. Alternatives considered included A07FA (Antidiarrheal Microorganisms), aligning with FDA-approved products Rebyota™ and Vowst™, or V03AX (Other Therapeutic Products). The Working Group debated assigning an ATC code given MaaT013's complex composition, unknown mechanism of action, and evolving regulatory

status, with some members favouring a delay until more data, including the EMA's upcoming marketing authorization assessment, is available. Others supported early classification to aid drug utilization and safety monitoring, noting FDA approvals for similar products and that an unknown mechanism or side effect profile does not justify denying an ATC code. The Centre emphasised that the request meets ATC code requirements, however the decision was postponed to gather further information and consultation before finalising the ATC code assignment.

INN, ATC, DDD Course for the WHO Academy

Professor Albert Figueras proposed a WHO Academy course combining lessons on INN and the ATC/DDD system. He outlined the course design and concepts, using examples from the finalized but unpublished ATC/DDD lessons in the WHO Academy course on Antimicrobial Consumption (AMC). The Centre expressed interest in contributing to the development and quality assurance of the ATC/DDD content, consistent with its role in the AMC course. The proposal was approved.

ATC DDD List in WHO Drug Information discussion on format, content and publication style; publication of DDD for cancer drugs

Dr Sophie Lasseur reported on the publication of the ATC/DDD List in WHO Drug Information, addressing inconsistencies in headings for new ATC 5th level codes ("ATC level name," "ATC level name/INN," and "Substance name") since the last meeting. The Centre proposed using "ATC Level Name" to avoid confusion, as some descriptors do not specify a substance or INN. WHO HQ agreed on the need for consistency, suggesting "ATC level name/INN" with the slash indicating the name may or may not include the INN. Dr Lasseur also inquired about publishing DDDs for cancer drugs. The Working Group decided that the Centre should draft an information letter detailing the background for these DDDs and circulate it to the Group for feedback before the next meeting.

Report on the ATC DDD teaching module for the School of INN (SoINN)

Dr Houda Sefiani reported that the online ATC/DDD teaching module for the School of INN (SoINN) has been completed. The working team, comprising Dr Houda Sefiani, Professor Ilse Truter, and Dr Ignatios Ioakeim Skoufa, finalized the course design and preparation. The module has been submitted to SoINN, which will manage its publication.

EMMA project

Professor Ilse Truter introduced the Exposure to Medications Measured using ATC/DDD classification system (EMMA) project, launched on 21 December 2023, following discussions at the EURODURG conference in Bologna. The project aims to enhance the harmonization of ATC/DDD system use globally through three objectives: an ongoing online survey collecting data on national procedures for linking the ATC/DDD index with National Medicinal Product Dictionaries and calculating DDDs per package, a systematic review of how pharmacoepidemiologists report ATC/DDD methodology in published studies, and the development of an online application prototype for certified DDD per package calculations. The Advisory Group recognized the value of such international initiatives and requested that survey results be presented at the next Advisory Group meeting.

Report on the results of the ATC DDD Questionnaire and on the upcoming in-person training in Oslo

Dr Ignatios Ioakeim Skoufa presented a summary of the results from the survey on the ATC/DDD methodology. The working team, which also includes Professor Ilse Truter and Dr Houda Sefiani, is currently preparing the corresponding publication. Dr Ioakeim Skoufa also informed that this year's annual ATC/DDD course in Oslo will take place on 12–13 June.

Protein Database

Dr Antonio Romeo informed about the WHO INN Open Database for Proteins available upon log in at the School of INN. The Protein Database allows for search for amino acid sequences including other information such post translational modifications as glycosylation.

Updates to Existing Working Points

During its 57th meeting, the WHO Working Group made several updates to the ATC/DDD Working Agenda. For Working Point 121, the Group discussed the future of the ATC/DDD Toolkit website, noting the challenge of limited responsible personnel. They agreed to keep it on the agenda until the WHO Academy's INN, ATC, DDD Course is completed and to clarify maintenance responsibilities. Working Point 152, which involves considering a reclassification of A16 (Other alimentary tract and metabolism products), and Working Point 154, which focuses on reclassifying substances in N06AX (Other antidepressants), had their initial discussions deferred to Meeting 58 or 59. Two new points were added: Working Point 155 will explore the use of the terms "inhibitor" or "blocker" for FcRn inhibitors, and Working Point 156 will consider reclassifying amyloid-targeting antibodies under N06DX (Other anti-dementia drugs), both scheduled for initial discussion in Meeting 59 or 60.

Closed Meeting of Advisory Group was held on 05 May 2025. Below is a concise summary of the key points discussed and agreed upon:

1. Standardized and Structured ATC/DDD Submission Process
   To enhance transparency, consistency, and efficiency, all ATC/DDD requests should be submitted in a standardized format and shared with the Working Group as a structured summary. The expert group, rather than the WHO Collaborating Centre, holds the responsibility for deciding on the assignment of new ATC codes or Defined Daily Doses (DDDs).
2. Timely Distribution of Documentation for Expert Review
   WHO Collaborating Centres should prepare and distribute draft materials at least two months prior to Working Group meetings. This timeline allows experts sufficient time to review proposals thoroughly and provide well-informed feedback.
3. Systematic Use of IDMIS for Virtual Collaboration
   The IDMIS platform should serve as the central hub for document sharing, expert consultation, and transparent communication of proposals and decisions, ensuring streamlined and accessible collaboration.
4. Mandatory ATC/DDD Assignment for Marketed INNs
   All International Nonproprietary Names (INNs) confirmed to be marketed should be assigned an ATC classification and, where applicable, a DDD. This practice supports global consistency and promotes rational medicine use.

5. Engagement of Countries with Alternative ATC/DDD Systems
   Countries using national or alternative classification systems should be actively included in the review process. Their involvement provides valuable insights, improves global applicability, and supports long-term harmonization.
6. Continuation and Expansion of DDD Assignment for Cancer Medicines
   The ongoing project to assign DDDs to oncology products should be sustained and broadened, given its critical role in global monitoring, rational use, and health policy development.
7. Strengthening the Working Group's Advisory Role.
   The Working Group's central role in the scientific and policy-driven evaluation of ATC and DDD decisions should be recognized and reinforced. Enhancing its authority, visibility, and engagement ensures it remains integral to WHO's medicines classification process.

Next meeting

The 58th Meeting of the WHO Advisory Group for Drug Statistics Methodology will be held virtually on 28 and 29 October 2025.