WHO ATC Classification System (Anatomical Therapeutic Chemical Classification)

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Main facts

- The ATC/DDD system was developed as a tool for drug utilization research with the aim of improving the quality of drug use.
- In the ATC Classification, drugs are divided into different groups in accordance with the organ or system on which they act and their chemical, pharmacological, and therapeutic properties.
- It contains five levels and drug consumption statistics can refer to each of these levels: from a more general to the most specific, the fifth level.
- The complete ATC Index with DDDs (Defined Daily Doses) is published as a paper copy or in electronic versions (English and Spanish) either in Excel or XML format. Also a searchable version of the ATC Index with DDDs is available free of charge from the WHO Collaborating Centre in Oslo.
- It is updated annually. The list of updates, which include new ATC/DDDs and alterations, are available in the WHO Collaborating Centre web page.

History and purpose

The Anatomical Therapeutic Chemical (ATC) Classification system and the accompanying Defined Daily Doses (DDD) - as measuring units - have their inception as a tool for drug utilization studies in the 1960s. After the study of Engel and Siderius on the consumption of drugs - showing great differences of drug consumption in six European countries during the period 1966-1967 - and the symposium held in Oslo in 1969 'The Consumption if Drugs' (organised by the WHO Regional Office for Europe) it was agreed that an internationally agreed classification system for drug utilization studies was needed. Norwegian researchers developed then the ATC classification system by modifying and extending the classification system of the European Pharmaceutical Market Research Association. It was realised at that time that both a classification system and a unit of measure were needed to measure drug use and, subsequently, the DDD as technical unit of measure was developed.

In 1981, the WHO Regional Office for Europe recommended the ATC/DDD system for international drug utilization studies. The WHO Collaborating Centre for Drug Statistics methodology was established in Oslo as the central body responsible for coordinating the use of the methodology for these studies. Subsequently, in 1996, WHO recognised the need to foster the use of the ATC system by modifying and extending the classification system of the European Pharmaceutical Market Research Association. It was realised at that time that both a classification system and a unit of measure were needed to measure drug use and, subsequently, the DDD as technical unit of measure was developed.

Today, the main activities of the Collaborating Centre consist on the development and maintenance of the ATC/DDD system, specifically: classifying drugs according to the ATC system; establishing the DDD for those drugs which have been assigned an ATC code; reviewing and revising as necessary the ATC classification system and DDDs; stimulating and influencing the practical use of the ATC system by

Relevant links and documents
- ATC/DDD Index (WHO Collaborating Centre for Drug Statistics Methodology, Oslo)
- Guidelines for ATC classification and DDD assignment | 2017. WHO Collaborating Centre for Drug Statistics Methodology, Oslo
- Introduction to Drug Utilization Research 2003. WHO
- More details on the update process of the ATC Classification here
cooperating with researchers in the drug utilization field; organising training courses in the ATC/DDD methodology and lecturing in courses and seminars organized by others; and providing technical support to countries in setting up their national medicines classification systems and build capacity in the use of medicines consumption information.

"The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels".

(Guidelines for ATC classification and DDD assignment | 2017)

The ATC/DDD system facilitates the comparison of drug statistics at any level (institution, local, regional, national, or international). By maintaining stable ATC codes and DDDs over time - as aimed by the Centre in Oslo and the Working Group -, research of trends in drug consumption can easily be performed. In fact, there is a strong reluctance to make changes to the classification or the DDDs, where such changes are requested for reasons not directly related to drug consumption studies.

It is emphasized that the classification of a substance in the ATC/DDD system is not a recommendation for use, nor does it imply any judgement about efficacy or relative efficacy of drugs and groups of drugs. Neither is it suitable for guiding decisions about reimbursement, pricing, or therapeutic substitution.

Structure

An active substance is classified in the ATC system according to the organ or system on which it acts and on its therapeutic, pharmacological, and chemical properties.

The structure has 5 levels; the first one allows active substances to be classified into 14 main groups, which in turn are divided into pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic and the 5th is the chemical substance.

The ATC System main groups or 1st level of the classification represent the organ or system in the body on which the therapeutic effect is exerted:

- A Alimentary tract and metabolism
- B Blood and blood forming organs
- C Cardiovascular system
- D Dermatologicals
- G Genito urinary system and sex hormones
- H Systemic hormonal preparations, excl. sex hormones and insulins
- J Antinfectives for systemic use
- L Antineoplastic and immunomodulating agents
- M Musculo-skeletal system
- N Nervous system
- P Antiparasitic products, insecticides, and repellents
- R Respiratory system
- S Sensory organs
- V Various

Example: complete classification of the commonly used analgesic ibuprofen, showing the structure of the code

<table>
<thead>
<tr>
<th>Level</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>MUSCULO-SKELETAL SYSTEM</td>
</tr>
<tr>
<td>2nd</td>
<td>ANTIINFLAMMATORY AND ANTIHEMORRHAGIC PRODUCTS</td>
</tr>
<tr>
<td>3rd</td>
<td>ANTIINFLAMMATORY AND ANTIHEMORRHAGIC PRODUCTS, NON-STEROIDS</td>
</tr>
<tr>
<td>4th</td>
<td>Acids and derivatives</td>
</tr>
<tr>
<td>5th</td>
<td>Ibuprofen</td>
</tr>
</tbody>
</table>

Nomenclature

The ATC System uses International non-proprietary names (INN); if INN names have not being assigned, USAN (United States Adopted Name) or BAN (British Approved Name) are usually chosen. The Biological Qualifier (BQ) is not part of the INN and the introduction of a new BQ will not have any implication on the ATC code for the specific INN (the BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance to aid in the prescription and dispensing of medicines - further reading on the Biological Qualifier is available here).

Inclusion of new entries and principles for classification
The WHO Collaborating Centre in Oslo establishes new entries in the ATC classification on requests from the users of the system. Not all substances have an ATC code assigned and the reason might be that no requests has been received for them.

The criteria that active ingredients need to fulfil to be included in the ATC system are:

- Be a new chemical entity or biological proposed for licensing in at least one country (normally a new entity is not included before an application for marketing authorisation is submitted)
- Existing well defined chemical entities used in a number of countries. Preferably, an INN should be established for the active ingredient, however other official names should be available (e.g. USAN or BAN)
- Herbal medicinal products assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (such as the procedure in place in the EU)
- Other medicinal products are considered on a case-by-case basis. Complementary, homeopathic, and herbal traditional medicinal products are in general not included in the ATC system.

**Medicinal products are classified according to the main therapeutic use of the main active ingredient, on the basic principle of only one ATC code for each route of administration.** i.e. pharmaceutical forms with similar ingredients and strengths will have the same ATC code. Likewise, immediate and slow release tablets will normally have the same ATC code. Although, a medicinal product may be given more than one ATC code if it is available in two or more strengths or routes of administration with clearly different therapeutic uses.

- **e.g.** Finasteride (a specific inhibitor of steroid Type II 5-alfa-reductase (intracellular enzyme that converts testosterone into 5-alfa-dihydrotestosterone) is available in two different strengths:

| Low strength tablet indicated to treat male pattern baldness | D11AX - Other dermatologicales |
| Higher strength tablet used to treat benign prostatic hypertrophy (BPH) | G04C - Drugs used in BPH |

In the same way, different pharmaceutical forms developed for various routes of administration (topical or systemic use, for example) are given distinct ATC codes:

- **e.g.** The corticosteroid drug prednisolone present in single ingredient products is given different ATC codes depending on the therapeutic use and the corresponding formulation:

| Enemas and foams | Intestinal anti-inflammatory agents | A07EA01 |
| Suppositories | Anti-hemorrhoidal for topical use | C05AA04 |
| Creams, ointments and lotions | Dermatological preparations | D07AA03 |
| Tablets, injections | Corticosteroids for systemic use | H02AB06 |
| Nasal sprays, drops | Nasal decongestants | R01AD02 |
| Eye drops | Ophthalmologicals | S01BA04 |
| Ear drops | Otologicals | S02BA04 |

Finally, it may happen that a drug may be used for two or more equally important indications and they are usually given only one ATC code. In such cases, the main indication is decided based on the available literature and discussed in the WHO International Working Group for Drug Statistics Methodology, where the final classification is decided.

**Classification of combination products**

It is interesting to know how medicinal products containing two or more active ingredients are classified in the ATC system.

- Firstly, combination products are given different ATC codes versus the product with a single component.
- Even though it may be difficult to decide where a certain combination product should be placed, it is the main therapeutic use what influences how it is classified:
  - **e.g.** a medicinal product containing an analgesic and a tranquilizer, which is used primarily to ease pain, should be classified as an analgesic.
- In some ATC groups a ranking is introduced to help in the classification of combination products (e.g. combinations of different antihypertensives or combinations of different analgesics). This ranking shows which drug takes precedence over others when the classification is decided and is detailed in the guidelines for the relevant groups.
- Specifically, combinations containing two or more active ingredients not belonging to the same 4th level are classified using the 50-series:
  - **e.g.** Paracetamol N02BE01 vs paracetamol, combinations N02BE51
- Different combination products sharing the same main ingredient are usually given the same ATC code:
  - **e.g.** Combinations of paracetamol + acetylsalicylic acid and paracetamol + caffeine are classified under the same code N02BE51 paracetamol, combinations
- All the active ingredients of a combination are given in some ATC 5th levels this principle is more commonly used in recent years to give a better identification of the various combinations:
  - **e.g.**
Brief insight into the DDDs

Even though DDDs are not used in the eHDSI Project, it is worth knowing what they are and their connection with the ATC codes.

The DDDs or Defined Daily Doses are the units of measure used in combination with the ATC codes to perform consumption analysis. The DDD is the assumed average maintenance does per day for a drug used for its main indication in adults.

As a unit of measure, a DDD should not be confused with the recommended or prescribed daily dose; doses for individual patients, patients' groups, other indications different to the main one may differ from the DDD. Only one DDD is assigned to an ATC code and route of administration for analytical purposes.

DDDs provide a fixed unit of measure independent of price, currencies, package size and strength, enabling researchers to assess trends in drug consumption and to perform comparisons between population groups.

The basic principles for DDD assignment are:

- DDDs are only assigned to drugs with an ATC code and will normally not be assigned before a product for the specific substance is approved and marketed in at least one country
- One DDD is assigned per route of administration within an ATC code:
  - e.g. The DDD for the antibiotic ciprofloxacin given systemically (J01MA02) is 1g when administered orally and 0.5g if administered via parenteral

Drug utilization studies and the ATC/DDD system

As explained above, the ATC/DDD system allows standardizing drug grouping and a stable drug utilization metric for comparing drug use between countries, regions, and individual healthcare institutions or settings, and for examining trends in drug use over time.

Drug consumption figures are usually presented as number of DDDs/1000 inhabitants/day or, for hospital use, as DDDs per 100 bed days. Sales or prescription data presented as number of DDDs/1000 inhabitants/day may provide a rough estimate of the proportion within a defined area treated daily with certain drugs: a figure of 10 DDDs/1000 inhabitants/day indicates that 1% of the population on average receives that treatment daily.

Use and limitations of the ATC Classification system

The development and decisions taken around the ATC system are based on its main purpose, i.e. to serve as a tool for presenting drug utilization statistics with the final aim of improving drug use. Consequently, using the system for other purposes may not be appropriate.

For its intended use, comparing drug utilization at international level for instance, it is important that the data retrieved are comparable. For that, the ATC code and DDD should be linked to each medicinal product at package level; sometimes it has been acknowledged by WHO that the necessary skilled staff has not been allocated to this task. An additional issue has been that some users were not aware of the dynamic nature of the classification and that the annual updates may require the subsequent update of the national lists. Finally, there will always exist medicinal products - either single or combination formulations - for which ATC codes or DDDs are not available.

Finally, as already mentioned, the ATC classification does not reflect recommended therapeutic use, neither does it imply any judgement about the efficacy of drugs or groups of drugs.

In the eHDSI Project, the ATC classification is included as one of the code systems in which the Master Value Sets Catalogue (MVC) is based, specifically as the way to represent:
It was evident that this choice was not the perfect solution to represent the active substance of medication (see the document “The experience of selecting the code systems for the development of the epSOS Master Value Catalogue (MVC)”), but it was also clear that it was the only feasible one. In fact, the EU is currently working, as part of the global implementation of the ISO IDMP Standards (Identification of Medicinal Products set of standards), on a Substance Management System for the EU, which should be also compatible internationally, according to the ISO IDMP Standard for substances. Therefore, we lack at EU as well as at international level, a univocal way of identifying the substances of medicinal products. And, as a consequence, the ATC classification continues as the most feasible means to convey information about the active ingredients of medicinal products.

Already in EXPAND, a number of proposals were presented and agreed (Semantic Maintenance Shop), later approved as CP-009 for the eHDSI Project, to overcome the limitations of using the ATC classification: coded data for some active ingredients and especially for combination medications are not available.

- e.g. there are many examples of widely used combined medications whose ATC code does not include the exact active ingredients; also active ingredients lack ATC code at the 5th level:

<table>
<thead>
<tr>
<th>Example</th>
<th>ATC description</th>
<th>ATC code (5th level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin + clavulanic acid (systemic use)</td>
<td>amoxicillin and enzyme inhibitor</td>
<td>J01CR02</td>
</tr>
<tr>
<td>Enalapril + hydrochlorothiazide</td>
<td>enalapril and diuretics</td>
<td>C09BA02</td>
</tr>
<tr>
<td>Levonorgestrel + estradiol</td>
<td>levonorgestrel and estrogen</td>
<td>G03FA11</td>
</tr>
<tr>
<td>Ferrimannitol ovoalbumin</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

It should be noted that, in recent years, the ATC classification is incorporating all active ingredients in combination medications at the 5th level (see the examples earlier for naproksen combinations or the extensively used combination of salbutamol and ipratropium bromide used in inhalers, with ATC code R03AL02).

To overcome those issues, **CP-009 (Formal approval of changes agreed in the EXPAND project for the description of medication)**, gives solutions that allow the listing of the multiple active ingredients that are present in combined medications as well as the communication of active ingredients as text when structured and coded information for active ingredients is not available.

### Other ATC Classification systems

- **ATCvet classification**: Anatomical Therapeutic Chemical classification for veterinary medicinal products. It is based on the same main principles as the ATC system for human use; in fact, the ATCvet classification is kept as close to the human system as possible, only introducing the necessary adaptations to make it suitable for the veterinary medicines.

- **ATC herbal classification**: provides a classification of herbal medicines by internationally approved Latin binomial classification and common therapeutic use. Just as the ATC classification, it allows capturing, grouping, and aggregating herbal remedies data at different levels of granularity.