PHARMACEUTICAL INFORMATICS

The Comprehensive Guide to Anatomical Therapeutic Chemical (ATC) Classification and DDD Methodology

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In the complex global ecosystem of modern medicine, the need for a standardized language to describe and categorize pharmaceuticals is paramount. The **Anatomical Therapeutic Chemical (ATC)** classification system, maintained by the **World Health Organization (WHO)**, serves as this universal lexicon. Since its inception, the ATC system, often paired with the **Defined Daily Dose (DDD)**methodology, has provided a structured framework for drug utilization research, facilitating the comparison of drug consumption across different regions, time periods, and healthcare settings. This article provides a deep dive into the technical architecture, operational principles, and clinical applications of the ATC/DDD system, serving as a definitive resource for healthcare administrators, researchers, and pharmaceutical professionals.

The Genesis and Evolution of ATC/DDD

The origins of the ATC system date back to the late 1960s and early 1970s. Before its widespread adoption, drug utilization studies were hampered by the lack of a common classification. Different countries used disparate systems, making it nearly impossible to aggregate data or perform international benchmarking. Recognizing this gap, the **European Drug Utilization Research Group (DURG)**initially developed the ATC system by expanding upon the Anatomical Classification (AC) system established by the European Pharmaceutical Market Research Association (EPhMRA).

In 1982, the WHO Collaborating Centre for Drug Statistics Methodology was established in Oslo, Norway. This center was tasked with the maintenance and development of the system, ensuring that it remains clinically relevant as new therapeutic classes and active ingredients emerge. Today, the ATC/DDD system is the global standard for **pharmacoepidemiology**and is essential for developing national essential medicines lists and monitoring antimicrobial resistance.

The Technical Architecture: The Five-Level Hierarchy

The ATC system is built on a hierarchical structure where drugs are divided into groups at five different levels. Each level represents a higher degree of specificity, moving from broad anatomical systems to specific chemical substances. This logic allows researchers to analyze data at various granularities, from total cardiovascular drug consumption down to the use of a specific molecule like **Lisinopril**.

Level 1: Anatomical Main Group

The first level consists of 14 main groups based on the organ or system on which the drug acts. These are represented by a single letter:

- 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, excluding sex hormones and insulins

- J: Anti-infectives 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

Level 2: Therapeutic Main Group

The second level provides a more focused therapeutic classification, identified by two digits. For example, within Group C (Cardiovascular), C03 refers to **Diuretics**.

Level 3: Therapeutic/Pharmacological Subgroup

The third level introduces the pharmacological mechanism or a more specific therapeutic category, identified by a single letter. Continuing our example, C03C refers to **High-ceiling diuretics**.

Level 4: Chemical/Therapeutic/Pharmacological Subgroup

The fourth level narrows the classification further based on chemical structure or pharmacological subgroup, identified by another letter. For instance, C03CA identifies **Sulfonamides**.

Level 5: Chemical Substance

The fifth and final level identifies the specific chemical substance (the active ingredient). It is represented by two digits. Thus, **C03CA01** is the unique ATC code for **Furosemide**.

Technical Summary Table: Hierarchy Breakdown

Level	Description	Code Example (Metformin)	Meaning
1st	Anatomical Main Group	A	Alimentary tract and metabolism
2nd	Therapeutic Main Group	A10	Drugs used in diabetes
3rd	Therapeutic/ Pharmacological Subgroup	A10B	Blood glucose lowering drugs, excl. insulins
4th	Chemical/Therapeutic/ Pharmacological Subgroup	A10BA	Biguanides
5th	Chemical Substance	A10BA02	Metformin

The Defined Daily Dose (DDD) Methodology

While the ATC system classifies what a drug is, the **Defined Daily Dose (DDD)**quantifies how much of it is being used. The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a technical unit of measurement, not a recommended clinical dose for individual patients.

Core Principles of DDD Assignment

The DDD is established based on a review of available information from manufacturers, clinical trials, and medical literature. Several critical rules govern the assignment of a DDD:

1. Single Main Indication: Only one DDD is assigned per route of administration for a specific ATC code. If a drug has multiple indications (e.g., Aspirin for pain vs. Aspirin for cardiovascular prophylaxis), the DDD is usually based on the main indication.
2. Adult Focus: DDDs are generally established for adults. There are currently no universal DDDs specifically for pediatric populations, which remains a challenge in pediatric drug utilization research.
3. Route of Administration: Drugs may have different DDDs if the bioavailability varies significantly between routes (e.g., oral vs. parenteral).

The Mathematical Framework for Utilization Metrics

In drug utilization research, volume data (grams or units) is converted into DDDs to allow for comparison. The most common metric used is **DDDs per 1,000 inhabitants per day (DID)**. The formula for this calculation is:

DID = (Total grams of drug used / DDD value) × 1,000 / (Population × 365 days)

This formula allows researchers to estimate the proportion of the population that could be treated daily with the drug. For example, if a community has a DID of 20 for a specific antihypertensive, it suggests that on any given day, 2% of the population (20 per 1,000) is receiving the standard maintenance dose of that medication.

Practical Implementation: Assigning ATC Codes to New Products

The process of obtaining an ATC code for a new pharmaceutical product involves a rigorous application process to the WHO Collaborating Centre. Manufacturers or national regulatory authorities must provide extensive documentation including:

- Chemical structure and pharmacological properties.

- Proposed indications and dosage regimens.
- Marketing status and regulatory approvals.
- Comparative clinical data.

The WHO Centre reviews these applications and proposes a code, which is then reviewed by the WHO International Working Group for Drug Statistics Methodology. This group meets twice a year to finalize new codes and updates to existing ones. This semi-annual review ensures the system evolves in tandem with medical breakthroughs like **monoclonal antibodies** and **gene therapies**.

Comparative Analysis: ATC vs. Other Classification Systems

It is important to distinguish the ATC system from other medical terminologies such as **ICD-10/11** (International Classification of Diseases) or **SNOMED CT**. While ICD focuses on the diagnosis and SNOMED CT provides a comprehensive clinical vocabulary, the ATC is uniquely drug-centric.

Comparison Matrix: Medical Coding Systems

System	Primary Purpose	Managed By	Granularity
ATC	Drug utilization research and consumption tracking	WHO (Oslo Centre)	Active Ingredient Level
ICD-11	Statistical tracking of diseases and mortality	WHO	Diagnosis/Symptom Level
SNOMED CT	Clinical documentation and EHR interoperability	SNOMED International	Concept/Relationship Level
EPhMRA	Market research and commercial sales analysis	EPhMRA	Market Category Level

The DU90% Method: A Practical Analytical Tool

A specific technical application of ATC/DDD is the **Drug Utilization 90% (DU90%)**method. This quality indicator identifies the number of drugs that account for 90% of the total volume of drug use in a specific setting (e.g., a hospital or a country). By analyzing the drugs within this 90% segment against clinical guidelines, researchers can assess the quality of prescribing. If the majority of the volume consists of drugs not recommended as first-line therapy, it signals a need for educational interventions or policy changes.

Challenges, Limitations, and Technical Nuances

Despite its utility, the ATC/DDD system is not without technical challenges that practitioners must understand to avoid misinterpretation of data.

1. Fixed-Dose Combinations (FDCs)

Classifying products that contain more than one active ingredient (e.g., an ACE inhibitor combined with a diuretic) is complex. Generally, FDCs are assigned a specific ATC code that differs from the codes of the individual components. The DDD for FDCs is typically based on the main active ingredient or the number of dosage units (e.g., 1 tablet per day).

2. The Gap Between DDD and PDD

The **Prescribed Daily Dose (PDD)**is what a physician actually writes on a prescription. Discrepancies between the DDD and PDD are common. For example, if clinical guidelines shift toward higher doses for aggressive treatment, the DDD (which is updated slowly) may remain lower than the current PDD. This can lead to an overestimation of the number of patients being treated when using DDD-based metrics.

3. Pediatric and Geriatric Dosing

Because the DDD is an "adult dose," it cannot be directly applied to pediatrics without significant adjustment. In pediatric drug utilization studies, researchers often use **weight-adjusted DDDs**or create localized reference doses, though these are not standardized by the WHO.

4. Biologicals and Biosimilars

With the rise of large-molecule biological drugs, the ATC system has had to adapt. While biosimilars of the same substance usually share the same ATC code (Level 5), their unique manufacturing processes and regulatory pathways sometimes necessitate specialized tracking at the brand name level, which the ATC system alone does

not provide.

Field Guide: Step-by-Step for Researchers

For a technical writer or researcher looking to integrate ATC/DDD into a study, the following workflow is recommended:

1. Data Extraction: Obtain drug procurement or prescription data including the active ingredient name and total quantity (e.g., 10,000 tablets of 500mg Paracetamol).
2. Code Mapping: Map each product to its current WHO ATC code. Always use the latest version of the ATC index, as codes are subject to change.
3. DDD Assignment: Look up the official DDD for that ATC code and route of administration (e.g., Paracetamol oral DDD is 3g).
4. Conversion to DDDs: Calculate the total grams (10,000 * 0.5g = 5,000g) and divide by the DDD (5,000g / 3g = 1,666.6 DDDs).
5. Normalization: Normalize by population and time (DID) to allow for comparative analysis.
6. Sensitivity Analysis: If PDD data is available, compare it with DDD results to identify any systematic bias in consumption estimates.

Broader Implications for Healthcare Policy

The ATC/DDD methodology transcends simple bookkeeping; it is a vital tool for **global health security**. By providing a clear picture of antibiotic consumption, for example, the system enables the monitoring of over-prescription, which is a primary driver of antimicrobial resistance. National health ministries use this data to negotiate drug prices, manage inventories, and design public health interventions.

Furthermore, in the era of **Big Data** and **Artificial Intelligence**, the ATC system provides the structured labels necessary for machine learning models to analyze prescribing patterns across millions of electronic health records. Without this standardized backbone, the signal within pharmaceutical data would be lost to the noise of differing nomenclature.

As we look toward the future, the integration of the ATC system with real-world evidence (RWE) platforms will likely enhance our ability to monitor drug safety and efficacy in post-market surveillance. While the system will continue to evolve, its core principle—the hierarchical organization of chemical substances by their anatomical and therapeutic targets—remains the bedrock of pharmaceutical informatics. For professionals in the field, a mastery of the ATC/DDD system is not merely a technical skill but a prerequisite for contributing to the advancement of evidence-based medicine and global health policy.

Tags: #ATC Codes #WHO DDD #Drug Utilization Research #Pharmacology #Healthcare Standardization