



# DRUG CONSUMPTION DATABASES IN EUROPE

## Executive Summary

Different initiatives have arisen in Europe to gather information on drug utilization (DU) for the last 15 years. Knowledge of the quantitative and qualitative patterns of drug use is a key element for the rational assessment of the risk-benefit ratio and for decision-making on risk minimising actions for medicines.

In DU studies information on prevalence, incidence, indication and duration of a treatment can be derived from different sources. First, data stemming from the different stages in the distribution chain of medicines: (i) dispensation with or without prescription, (ii) acquisition of medicines by hospital and community pharmacies or other outlets, straight from pharmaceutical manufacturers or through wholesalers, and (iii) reimbursement data. This data may be collected by governmental agencies or stored in pharmacies' databases or insurance companies databases. These sources of data are known as non-commercial data providers. In addition, data mining companies can conduct market surveys and thereafter sell the data stored in their databases. These sources of data are known as commercial data providers. In this report only IMS Health is mentioned as a commercial data provider. Second, sources of data on drug exposure obtained from the prescriptions registered in clinical databases. Third, interviews to patients collecting the current ingestion of medicines and finally, pharmacoepidemiological studies from which the utilization rate for a class of drugs can be obtained.

Furthermore, the growth of new technologies with the establishment of automated databases, results in an increasing number of patient- healthcare encounters electronically registered. These databases cover large sizes of

population, and the data is readily available and easy to access. However, these databases were initially created with an administrative purpose hampering their use in research: not all variables regarded as potential confounders of the association drug-adverse event may be collected. Another problem is the inexistence of a standard method to evaluate the validity and accuracy of the data collected by these databases. Finally, the information is only registered for those individuals that reach the healthcare system, leaving out a segment of the population.

The objective of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) is to address the limitations of methods currently used in pharmacovigilance and pharmacoepidemiology, and to strengthen the monitoring of the benefit-risk assessment of medicines in Europe. The project is organized into seven working packages (WP). The overall objective of WP2 "Framework for Pharmacoepidemiological Studies" is to develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies. WP2 is organized in three working groups (WG). WG3 is in charge of reviewing and compiling knowledge about European sources of data on DU in the out- and inpatient healthcare sector. The project follows the World Health Organisation (WHO) recommendations on the adoption of the Anatomical Chemical Therapeutic classification (ATC) of drugs and the measurement of drug exposure in defined daily doses (DDD). The PROTECT project includes the following drug-adverse events: Calcium channel blockers (C08) - malignancies; antiepileptics (N03A)- suicide; benzodiazepine derivatives (N05BA, N05CD) – hip fracture; antidepressants (N06A, N06CA) – hip fracture; beta-2-adrenergics (R03AC,

R03AK) – acute myocardial infarction (AMI); macrolides (J01FA) and amoxicillin-clavulanic acid (J01CR02) – drug induced liver injury.

To find out information on national drug consumption databases we elaborated a search strategy that allowed for getting different sources of data on drug consumption considered of interest for drug utilization studies. Data providers, pricing and reimbursement agencies, information on marketed active substances, healthcare systems and reimbursement decisions adopted in each European country, and international drug utilization working groups. The European countries included in this inventory were limited according to their population, tradition in DU research and participation in the PROTECT project. We conducted, first, a specific website search from global European institutions to country-specific governmental websites; second, a bibliographic database search to find articles published by international working groups; third, google search, and finally interviews with experts. For each of the national drug consumption databases, the following information is provided: data provider, website, source of drug consumption, setting, population coverage, accessibility, drug codification, unit of measurement, drug-based, prescriber and pharmacy information, potential confounders of a drug exposure, language of the database, record period and record linkage.

For the inpatient sector, the search strategy was slightly different. First, we reviewed the main available information on hospital drug utilization for the PROTECT selected drugs by means of a website and a bibliographic database search. Then, because of the importance of antibacterial consumption in the inpatient sector which is linked to the emergence and selection of antibiotic-resistant bacteria, a specific literature review was conducted to establish the

availability of inpatient macrolides and amoxicillin-clavulanic acid consumption data in the selected PROTECT countries.

One of the aspects of interest was to determine the validity of the national drug consumption databases. In the context of the PROTECT project, validity is understood as to which degree the results obtained from these national databases are comparable across different countries and over time.

Considering the vast bibliography available on the validity and application of automated databases in research we elaborated a questionnaire including most of the items considered of relevance when measuring drug exposure and interpreting the results obtained in drug consumption studies. The key items referred to the definition of in- and outpatient drug consumption, population coverage, drug- and patient-based information, database internal validity and accessibility.

This complex methodology yielded to a list of comprehensive and more specific institutional European websites, and international networks on DU studies (table 3). From them, we derived what we term background data: data providers of authorised medicinal products (table 4), healthcare systems (Appendix 3), pricing and reimbursement agencies (table 5), pharmaceutical data sources by country (table 6) and international networks and working groups in pharmacoepidemiology. For each of the international working groups, the following information was collected: website, definition, objectives, work period, country-participants, information, funding and publications. At the same time, these international networks have been divided in those offering general information: general research groups, and those groups studying either

specific diseases or groups of drugs of interest for the PROTECT project, the specific research groups (points 3.1.5.1 and 3.1.5.2).

Information on national drug consumption databases in Europe is provided for Denmark, Finland, France, Germany, Italy, Norway, Poland, Spain, Sweden, the Netherlands and the United Kingdom (point 3.2.1.1). Appendix 7 and 8 show the data available at the Foundation Catalan Institute of Pharmacology (FICF), both from non-commercial and commercial data providers. Only Denmark, France, Italy and Norway can provide data on the inpatient sector. The consumption at ATC level 1 for the cardiovascular system (C), nervous system (N) and respiratory system (R) for the inpatient sector, year 2009, represented in Denmark < 4% (table 9, for ATC level 3 or 4, table 11), in Sweden < 3%, and in France (ATC level 3 or 4) <7%. From the bibliographic database search in the inpatient sector, regardless of the country concerned and the type of drug utilization research study, the majority of articles were set in the outpatient setting and expressed drug consumption as a percentage of the active substance (table 13, appendix 6). For inpatient antibacterial consumption, the PubMed search conducted yielded up to 20 papers with relevant data (table 14 and 15). The results of the website search for antibacterial consumption are summarized in table 16.

The questionnaires were received from Denmark, France (AFSSAPS), Italy, Norway, the Netherlands and Sweden. Table 17 summarizes the comparability of national drug consumption databases.

The PROTECT inventory provides information on 18 European working groups, 12 national drug consumption databases and 3 national sources of sales of medicines from wholesalers (France, Norway, Sweden). In addition,

sources of inpatient antibacterial consumption were identified from 7 countries and 1 region of Spain. For Denmark, France, Italy, Norway and Sweden inpatient drug consumption is available for other drugs than antibacterials. As expected, the Nordic countries and the Netherlands with their long tradition in drug utilization research, are the ones to provide drug consumption data free online. For the rest of the countries, information should be applied for. Finland recommends to give 1-1.5 years ahead of the planning study to receive such information.

The interest in compiling such information has evolved in the last 15 years. From the EuroMedicines project that elaborated a drug directory for 14 European countries, through the EUROMEDSTAT project and CNC (Cross National Comparison) project, to the EuroDURG-ISPE (European drug utilization group and International Society of Pharmacoepidemiology) collaboration and the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance). Also, several specific international working groups have been established around a disease that indirectly implies drug utilization research. Other specific groups targeted a specific drug group.

Generally speaking, there is a scarcity of national hospital drug consumption information, mainly attributed to the high heterogeneity in the management of medicines at a hospital level. In addition, when studying drug consumption in inpatient settings, the WHO recommendations of adjusting drug consumption to clinical activity are barely followed. In contrast with this lack of information on inpatient drug utilization from non-commercial data providers, IMS Health started in 2008 the Hospital Audit Prescription which collects

information on drugs dispensed from hospital pharmacies to the patient, containing more clinical information (diagnostic) of utter interest in research.

The evaluation of validity of national drug consumption databases within the scope of the PROTECT project, provides enough information regarding the comparability of the results in drug consumption across different countries. 3 European databases collect dispensed medicines which best assess drug exposure, as they include over-the-counter (OTC) drugs. 5 databases collect reimbursed data, and 3 prescription data. The population coverage of most of these databases reaches 100%, except for 3. Only one of them provided the weighting methodology. ATC/DDD methodology has been adopted by all the databases, even the British database which collects information according to the British National Formulary/Average Daily Quantity (BNF/ADQ) provides ATC codes and DDD upon request. Most of the databases update retrospectively the ATC codes and DDD according to the WHO guidelines released every year. The problem of the ATC/DDD methodology is still the same that have been pointed out by other authors: the lack of an ATC code or the not assignment of a DDD to some of the marketed drugs. In this case, the strategy adopted for each of the databases varies considerably. The questionnaire allowed to evaluate the different degrees of ascertainment of those variables considered potential confounders of the drug exposure. Very few databases provide age and sex of the patient, some provide information on the prescriber and the community pharmacy where the patient purchased the drug.

The PROTECT inventory is a comprehensive and structured source of information on drug consumption that should promote the correct interpretation of the results of a study comparing different European countries.

In addition a brief summary of the data provided by IMS Health is available. For academic researchers the PROTECT offers the basis for future collaborations, and for regulatory agencies and pharmaceutical companies, the possibility of supporting post-marketing and safety studies. This inventory would not have been possible without the previous initiatives in compiling such information and knowledge.