Final implementation report

OSIAP

Ordonnances Suspectes Indicateur d'Abus et de Dépendance

The OSIAP Europe Study

(September 2004- June 2008)

Centre d'Evaluation et d'Information sur la Pharmacodépendance de Toulouse,

Centre Hospitalier Universitaire de Toulouse

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First part

DETAILED DESCRIPTION OF ALL ACTIVITIES CONDUCTED

Summary

Introduction

Data concerning drug abuse liability are habitually pointed out by experimental and clinical studies, but remain often insufficient when the drug is widely used in the real life. Following the report of *Bergman et al* in 1989, the French network of Centres d'Evaluation et d'Information sur la Pharmacodependance (CEIP) has begun a prescription forgeries survey with 11 community pharmacies networks in France. This system called OSIAP (Ordonnances Suspectes Indicateur d'Abus Possible) provides information about potential abuse liability of marketed drugs in France. In 2003, the Public Health Program of the European Commission approved a collaborative project which aims to extend the OSIAP system in Europe.

Aim of the project

The aim of this project was to systematise the identification, the collection and the analysis of suspect prescription forms, in order to validate a reproducible and reliable method for the assessment of the abuse potential of marketed drugs. The calculation of a diversion ratio for each drug would allow to better understand trends in medication abuse patterns, at an European level, and also at a regional or national level. This indicator could allow to assess prospectively and permanently the impact of preventive measures (warning to prescribers or pharmacists, rules of prescription or dispensation, scheduling of drugs…). Thus, it will also participate to the improvement of the rational use of medications, especially psychoactive medications with abuse potential. Six European countries took part to the project: France (coordinator), Belgium, Italy, Netherlands, Spain and Sweden.

Methods

The first step of the project was an inventory in each participating country, of the number and the characteristics of prescribers, the number and the repartition of community pharmacies, the availability of drug sales data. Despite all participating countries are very close, the list of medications and their rules of prescription or delivery widely differ across countries. It was then decided to prepare a registry of all prescription only medicines and their status in each country (for example, narcotic, psychotropic or any drug with a special rule of prescription and/or delivery). The second step was the constitution in each participating country of a network of community pharmacies for the collection of data concerning falsifications of prescription forms. These networks covered all the country (France, Sweden) or a part of the country (Belgium, Italy, Netherlands, Spain).The third step was data collection of falsified

prescriptions. Initially, 3 surveys were planed (May 2006 – November 2006 – May 2007). However, since the constitution of the networks needed some adaptation (new request and/or widening of the network in Netherlands, Italy, and Spain, post-pone in Sweden due to standardization of the data collection), it was decided to analyse the results by year (2006 – 2007).

Results

A total of 862 suspect prescription forms were collected, including 1220 different medications. The main concerned classes of drugs were anxiolytics (18.3%), sedative-hypnotics (13.4%), opioid analgesics (10.2%), antidepressants (4.7%) and drugs for addictive disorders (4.5%), but there were great differences between countries. Collection of data on drug use in each country will complete these comparisons. For the standardization of the comparison, data about drug utilization (sales data or health insurance reimbursement data) will be transformed in amount of defined daily doses (DDD) according to the WHO guidelines.

Conclusion

The project has confirmed the feasibility of the constitution of community pharmacies network to perform this kind of study in the public health domain. The constitution of the registry could be a basis fro the comparison of the availability of different medications according to their abuse potential. It could be extent to the other 21 European countries and annually actualized to compare the patterns of medications abuse between European countries. The results concerning medications in the falsified prescription show that benzodiazepines are the class of drugs which is most frequently subject of forged prescriptions, but there are differences between countries. In France, the most commonly diverted drug is one which is used by heroine addicts whereas in Spain it is a drug used by hyperactive children.

Introduction

During the recent years, the regular assessment produced by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) allowed to better understanding patterns of drug abuse and misuse and to identify emerging trends. Thus, since EMCDDA observed an increasing trend of pharmaceutical products diversion across European countries, it appears to be necessary to implement a specific monitoring system concerning this particular drug abuse problem. The jointed meeting of the Pompidou Group and the International Narcotics Control Board (INCBUN) in October 2002 in Strasbourg has shown that methods used in different European countries to investigate diverted drugs or falsified prescriptions are not homogeneous. One of the conclusions of this meeting concerned the need to develop efficient means to obtain accurate data on drug diversion: the OSIAP project could be one of these means. The aim of the project is to propose a standardized systematic and reproducible tool to measure drug misuse in complement with other information sources a drug abuse and dependence, potentially available in some countries, and according to geographical particularities and regulatory measures existing in each country.

The methods for the evaluation of drug abuse potential are based on experimental pre clinical studies (studies of self-administration, discrimination) and on clinical studies in human during the development of new drugs (phase1, 2 and 3 studies). These studies give information about the potential of abuse or dependence of several medications before their approval, however, these studies must be completed after their approval. For some narcotic or psychotropic drugs newly approved, the risk management plan must include these pharmacoepidemiologis evaluation during the approval process.

The data on drug abuse liability provided by experimental and clinical studies using selected drugs are insufficient when the drug is widely used in real life. Following the report of Bergmann et al. from Sweden, the French Centres for Evaluation and Information on Pharmacodependence (CEIP), created by the French health authorities in 1990, have begun a prescription forgeries survey within several community pharmacy networks. This system called OSIAP provides information about potential abuse liability of marketed drugs in France. Epidemiological evaluations of substance abuse in France have been based on the collection of multiple data from different sources such as the police or the health care system: specific tools such as Nots (spontaneous reporting of drug abuse and dependence compulsory since 1999), OPPIDUM (monitoring of illicit and licit drugs used by patients visiting heath care structures), and DRAMES (case reports of deaths in relation with abuse of psychoactive substances). These sources provided information about drug abuse events,

which resulted in a crisis in the addict's life. In contrast, data obtained by the survey of falsified or forged prescriptions are complementary since they concern drug requests in the everyday life of the addict. Since community pharmacies have direct access to the dependent population, this system may also serve as a signalling mechanism to detect new patterns of abuse.

1. Aims of the project

The aim of this project was to systematise the identification, the collection and the analysis of suspect prescription forms, in order to validate a reproducible and reliable method for the assessment of the abuse potential of marketed drugs. The implementation of this kind of survey could give information to assess prospectively and permanently the impact of preventive measures (warning to prescribers or pharmacists, modification of rules of prescription or dispensation, scheduling of drugs…). Thus, it would participate to the improvement of the rational use of medications, especially medications with abuse potential.

2. First part:

a. Inventory

The project began in January 2005 and includes finally 6 participating countries: France (project coordinator), Belgium, Italy, Netherlands, Spain and Sweden.

The table 1 presents the principal demographic and health characteristics of the participating countries.

The EMCDDA published a report about narcotic and psychotropic legislations across Europe. We used data collected in this report to compare similarities and differences between the 6 countries involved in the project. EU Member States classify drugs and precursors according to the three UN Conventions of 1961, 1971 and 1988 (abbreviated to UN61, UN71 and UN88), controlling and supervising their legitimate scientific or medical use while taking into account the particular risks to public or individual health. The list of these substances and their specific legislation in the 6 countries involved in the OSIAP study is presented in annex 1.

Table 1: Population and health care resources in each participating countries (source WHOSIS 2008, OECD 2004)

Country	*Population* (thousand inhabitants)*	*Pharmaceutical personals*	*Number of community pharmacies£*	*Number of Physicians*	*Medical density*
Belgium	10430		5256	44124*	
France	61330	69431*	20 384	207277*	
Italy	58779	44000*		215000*	
Netherlands	16379	2842$	1732	60519$	
Spain	43887	39900*	20 348	135300§	
Sweden	9078			29190£	

*** 2006 data, $ 2005 data, £ 2004 data, § 2003 data.**

Some 250 substances are listed in the Schedules annexed to the United Nations Single Convention on Narcotic Drugs (New York, 1961, amended 1972), the Convention on Psychotropic Substances (Vienna, 1971) and the Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (introducing control on precursors) (Vienna, 1988). The purpose of this listing is to control and limit the use of these drugs according to a classification of their therapeutic value, risk of abuse and health dangers, and to minimize the diversion of precursor chemicals to illegal drug manufacturers.

Narcotic drugs

Narcotic drugs are classified and placed under international control by the 1961 UN Single Convention on Narcotic Drugs, as amended in 1972 (table 2). The Single Convention limits “exclusively to medical and scientific purposes the production, manufacture, export, import, distribution of, trade in, use and possession of drugs”.

Table 2 : Classification of narcotic drugs in four schedules according to the 1961 Convention

Schedules	*Harmfulness*	*Degree of control*	*Examples of listed drugs*
I	Substances with addictive properties, presenting a serious risk of abuse	Very strict; 'the drugs in Schedule I are subject to all measures of control applicable to drugs under this Convention' (art. 2.1)	Cannabis and its derivatives, cocaine, heroin, methadone, morphine, opium
II	Substances normally used for medical purposes and given the lowest risk of abuse	Less strict	Codeine, dihydrocodeine, propiram
III	Preparations of substances listed in Schedule II, as well as preparations of cocaine	Lenient; according to the World Health Organisation, these preparations present no risk of abuse	Preparations of codeine, dihydrocodeine, propiram
IV	The most dangerous substances, already listed in Schedule I, which are particularly harmful and of extremely limited medical or therapeutic value	Very strict, leading to a complete ban on 'the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research' (art. 2.5.b)	Cannabis and cannabis resin, heroin

All countries have similar rules regarding narcotics, as harmonized by the Convention of New York in 1961, and in most countries a number of narcotics are registered medicinal products (or available as magistral preparations in the pharmacy). In all countries, these narcotic medicinal products are placed under prescription, with special prescription rules (sometimes special prescription pads) and delivery rules.

Psychotropic substances

Psychotropic substances are placed under international control by the 1971 United Nations Convention on Psychotropic Substances. The objectives of this Convention are again to limit the use of these substances to medical and scientific purposes (arts. 5 and 7). While some psychotropic substances may have therapeutic value, they also present a dangerous risk of abuse (table 3).

Table 3 : Classification of substances in four schedules according to the 1971 UN Convention on Psychotropic Substances

Schedules	*Harmfulness*	*Degree of control*	*Examples of listed drugs*
I	Substances presenting a high risk of abuse, posing a particularly, serious threat to public health which are of very little or no therapeutic value	Very strict; use is prohibited except for scientific or limited medical purposes	LSD, MDMA (ecstasy), mescaline, psilocybine, tetrahydrocannabinol
II	Substances presenting a risk of abuse, posing a serious threat to public health which are of low or moderate therapeutic value	Less strict	Amphetamines and amphetamine-type stimulants
III	Substances presenting a risk of abuse, posing a serious threat to public health which are of moderate or high therapeutic value	These substances are available for medical purposes	Barbiturates, including amobarbital, buprenorphine
IV	Substances presenting a risk of abuse, posing a minor threat to public health with a high therapeutic value	These substances are available for medical purposes	Tranquillisers, analgesics, narcotics, including allobarbital, diazepam, lorazepam, phenobarbital, temazepam

Within their domestic legislations, some countries distinguish between narcotic and psychotropic substances. Others combine the two in a list that is based on the level of medicinal use or potential harm. Some also classify narcotic and psychotropic substances in order to determine the prosecution procedure or the punishment for illegal activities involving those substances.

Table 4: Main law and list of substances for 4 of the 6 participating countries

Country	*Main laws and lists of substances*
Belgium	There are two lists, in the Royal Decree of 1930 on narcotic substances (including cannabis, heroin, cocaine, codeine, methadone), and the Royal Decree of 1998 on psychotropic substances (including some amphetamines, buprenorphine, hallucinogens, MDMA).
Spain	The Order of 8th July 1967 and the Royal Decree 2829/1977 classify narcotic drugs and psychotropic substances, respectively, in accordance with the UN Conventions.
Netherlands	The Opium Act contains two lists: I: unacceptable risk (a, b, c-d): - Ia: opiates, coca derivatives, cannabis oil; - Ib: codeine; - Ic-d: psychotropic substances; II: others (a, b): - IIa: tranquillisers; - IIb: cannabis.
Sweden	The Ordinance on Prohibition of Certain Goods Dangerous to Health (1999:58) lists substances under control but which are not classified as narcotics. It is common that those substances become classified as narcotic drugs after further investigation. For substances already classified as narcotic drugs, the Medical Products Agency Regulation 2000:7 has five lists. I: drugs without medicinal use (cannabis, heroin, MDMA, LSD); II: drugs with a limited medicinal use and a high risk of addiction (amphetamines, cocaine, methadone); III: drugs with medicinal use and a risk of addiction (codeine); IV: drugs with medicinal use and a low risk of addiction (barbiturates, benzodiazepines, buprenorphine). V: drugs prohibited in Sweden but not internationally.

All the countries have rules and regulations for the prescription of some psychotropics (e.g. not anti-depressants), as harmonised by the Convention of Wien in 1971, but with more variation in the number and nature of medicinal products under surveillance.

In all countries, supervised psychotropics are under prescription, with varying methods of limitations. Most countries also have limitations for the dispensing of these medications by the pharmacist (e.g. special signs on the package, separate registration by the pharmacist). In some countries these supervised psychotropics are reimbursed, in others not (e.g. benzodiazepines in Belgium).

Some countries have regulations limiting the dispensing of medicinal products, which are potentially poisonous (e.g. paracetamol, dextropropoxyphene). Sometimes these products are Over The Counter, sometimes on prescription. Regulation varies from restriction of the registered pack size, special rules for delivery, prescription limitations.

Finally, some countries have used the regulations for narcotics, psychotropics, and potentially poisonous medicinal products as a legal basis for prescribed medications under special supervision for safety (e.g. the Thalidomide, cisapride, isotretinoine). It is unlikely that these medicinal products will be subject of falsification of prescriptions. However, falsification of the regulation is possible by foregoing reimbursement.

In most countries, a number of prescribed, reimbursed new medicinal products are controlled for indication by a prior approval system through health insurance physicians. This system is clearly not the topic of this project, although this system may be falsified by foregoing reimbursement.

b. Registry of medications subject to specific rules of prescription or delivery

Because there were some discrepancies between the 6 countries despite a common regulation according to the 1961 and 1971 UN conventions, it was decided to create a register of all medicinal products which are “Prescription Only Medecine” and subjected to special rules of prescription and/or dispensation. For the purpose of the study, a prescription rule could concern:

- The prescriber (initial prescription only by hospital or only by specialist)
- The form of prescription (« ordonnance sécurisée » in France, « receta de estupefacientes » in Spain….)
- The medicine (limited duration of the prescription or fractional delivery by the pharmacist).

This inventory excludes illicit drugs, which are prohibited in each participating country and medicinal products for which the only limitation is prior approval by health insurance system. The list will include the following items for each medication:

- Name of medicinal product, (International non-proprietary names - INN)

- Classification code according to the 1961 and 1971 UN Conventions,

- Classification code according to the Anatomic Chemical Therapeutic Classification (ATC, 5 level),

- Defined Daily Dose (DDD).

The final list retained in the registry was checked by the Belgian team of experts of the national Drug Information Centre in accordance with the European Standard for the Identification of Medicinal Products (ENV 12610). The framework was filled in by each participant with national information (medicinal product packages, descriptive label, strength, unity of strength, unity of volume, pack size, galenic form, route of administration, national unique identification number, the number of DDDs per medicinal product package). The registry is presented in annex 2 by country.

The support for prescription is also different. Some examples are given in the following figures. In Sweden, the initial prescription is always electronic (in more than 90% of cases). However, when the patient asks for his prescription at the pharmacy, the pharmacist gives him a “prescription support”, indicating the name of the drug, the daily dose prescribed and the number of days of supply. In the other countries, the support of the prescription is always a paper form.

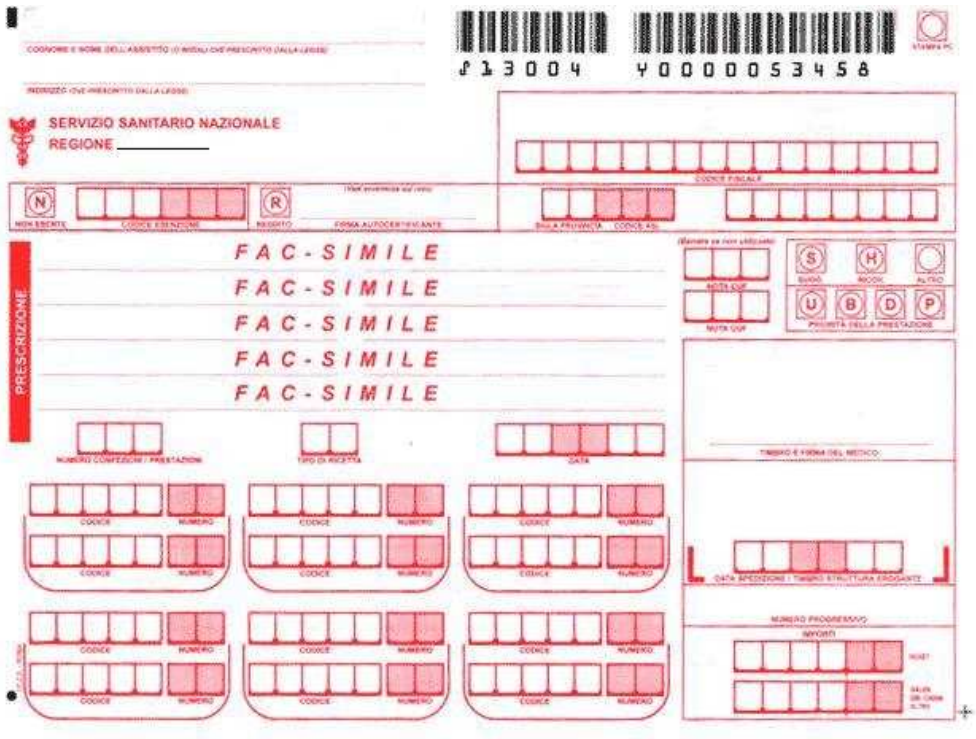
The different forms are presented in the following figures:

Figure 1 : France

Prescription form for narcotics “Ordonnance sécurisée” could be used for any other drug. This is a duplicate form (the copy is given to the patient when the pharmacist provides the prescription, on a tamper-proof paper (not visible on this figure).

Figure 2 : Italy

Prescription form for drugs reimbursed by the health Insurance System



Prescription form for narcotics

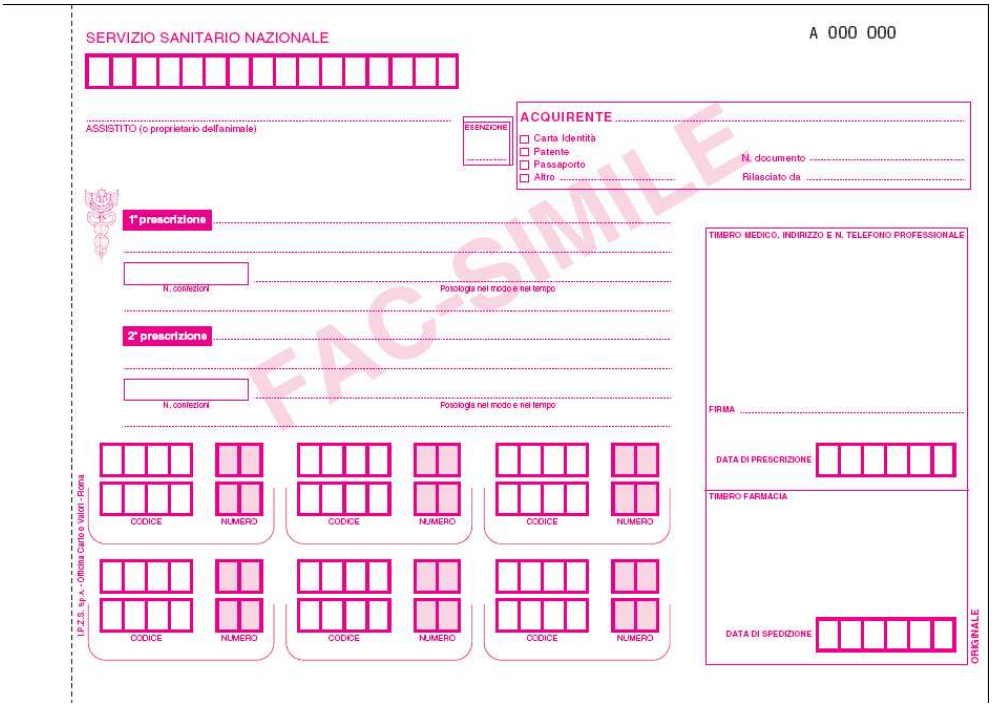
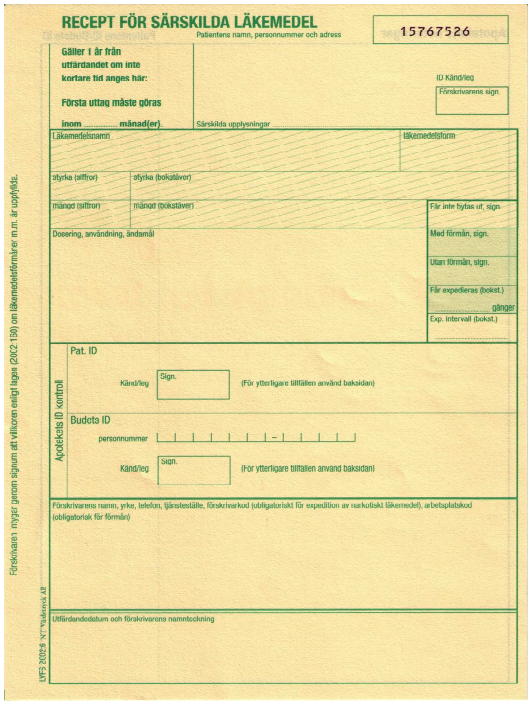


Figure 3 : Spain

Figure 4 : Sweden



The pharmacy part of the label contains information of the filled prescription. The pharmacist signs the label but some falsifier may manipulate the prescription by removing the label. Thus the support of the prescription could be presented again in another pharmacy to obtain more quantities of the prescribed drug.

c. Availability of medication consumption data in each country

In each country the figures of sales are available near the national medicines agencies or the Ministry of heath. In some case, data on drug utilization could also be obtained from Health Insurance systems (for reimbursed medications) or from independent organizations:

i. Belgium:

Drug Information Center

Agence Fédérale des Médicaments et des Produits de Santé (AFMPS) ; Federaal Agentschap voor Geneesmiddelen en Gezondheidspoducten (FAGG) (https://portal.health.fgov.be/portal/)

ii. France :

The French Medicine Agency (Agence Française de Sécurité Sanitaire des Produits de Santé Afssaps) publishes annually a report about the use of drugs in community and in hospitals. Data concern all medications sold in France with or without medical prescriptions and are expressed as DDD per thousand of inhabitants (http://afssaps.sante.fr/pdf/5/rapport_vente_medicament_1996-2006.pdf). Data concerning reimbursed and prescribed drugs are also annually available on the Health Insurance System website in the MEDIC'AM database (http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/).

iii. Italy: Agenzie per i Farmaci

Sales data for prescription drugs are available at the regional and national levels.

iv. Netherlands:

In the Netherlands, pharmacies preserve their data but two institutions are entitled to recover them: Pharmo Institute (independent institution of scientific research) and SFK (Stiching Farmaceutische Kengetallen).

Z-Index / Ministerie van Volksgezondheid, Welzijn en Sport Den Haag (Z-Index / Ministry of Health, Welfare and Sport)

College voor Zorgverzekeringen, Geneesmiddelen Informatie Project/ Stichting Farmaceutische Kengetallen (Health Care Insurance Board, Pharmaceutical Products Information Project / Foundation for Pharmaceutical Statistics)

v. Spain:

There is a register ECOM (ESPECIALIDADES CONSUMO DE MEDICAMENTOS) at the Ministry of Health which contains utilisation data about reimbursed and prescription only medicines used outside hospitals (Ministerio de Sanidad y Consumo http://www.msc.es).
Agencia Espanola del Medicamento in Spain (http://www.agemed.es/)

vi. Sweden Läkemedelsverket Medical Product Agency

Data are based on Apoteket AB's (publicly owned pharmacy corporation) statistics on drug deliveries to pharmacies reported according to ATC classification
Sweden Apoteket AB (http://www2.apoteket.se)

3. Second part: implementation of community pharmacies networks

The situation in the 6 participating countries at the beginning of the project was quite different concerning the size of the population as well as the medical and community pharmacies' density or the organisation of pharmacies open to the public (private or public community pharmacies).

Because the size of the population in the 6 countries varies from 9 millions to 66 millions of inhabitants, and because the density of community pharmacies opened to the public varies from 1 to 5 per 10 thousands of inhabitants, the implementation of pharmacies networks in the 6 countries was different (table 5).

The Osiap data collection was already ongoing in France at the beginning of the project, and there was no modification in the design of the survey. In Sweden, the identification and the reporting of suspect prescriptions to the National Pharmacy Corporation (Apoteket) was also already ongoing from several years, it was only modified concerning some details about data collection (specifically the date of the presentation of the suspect prescription form).
In the other countries, it was necessary to explore the feasibility of the implementation of this kind of network and to investigate the willingness of the pharmacists to take part to this kind of approach.

Table 5 : Medical density and number of pharmacies.

	Belgium	*France*	*Italy*	*Netherlands*	*Spain*	*Sweden*
Number of doctors *	39	34	37	25	43	30
Number of Community pharmacies*	5	3.7	3	1.1	4.8	1

*** Per 10 000 inhabitants.**

The first step was the constitution in each country of an ad-hoc network of the national Pharmaceutical Inspectorate, professional organisations of pharmacists, deontological pharmaceutical and medical bodies (Orders), and at least one relevant institute in clinical pharmacology of clinical pharmacy. When getting duly authorizations, a first mailing survey was done in autumn 2005. The aim of this survey was to investigate if community pharmacies were aware about falsified prescriptions, the estimated frequency of this kind of phenomenon, and the willingness to participate for data collection about this topic.

For Belgium, Italy, Netherlands and Spain, it was decided to set up a network of sentinel pharmacies in at least one significant region of the country (annex 3).

d. Implementation of pharmacies network in Belgium

The approach in the Belgian Osiap program was based on the cooperation with:

- Heymans Institute of Pharmacology, Faculty of Medicine, University of Ghent

(Vander Stichele R, National OSIAP Representative)

- Pharmaceutical Care Unit, Faculty of Pharmacy, University of Ghent

(Mehuys, project leader)

- National Pharmaceutical Inspectorate

(De Schutter J, Van Den Bossche B, Pauwels, Bouffioux ML, Steering committee)

The principles of recruitment of community pharmacies were base don the following items:

- Volunteers (non-teaching pharmacy's)
- Minimal size
- Dedication to exhaustiveness and to respect for methodology
- Availability of automated registration
- Readiness to participate on a longitudinal basis in OSIAP
- Readiness to participate in short registration projects on specific topics

A retrospective mailing, asking for the prevalence and nature of falsified prescriptions over the past three months and for willingness to participate in a future prospective observational survey, was performed in Flanders (Belgium) in November 2005.

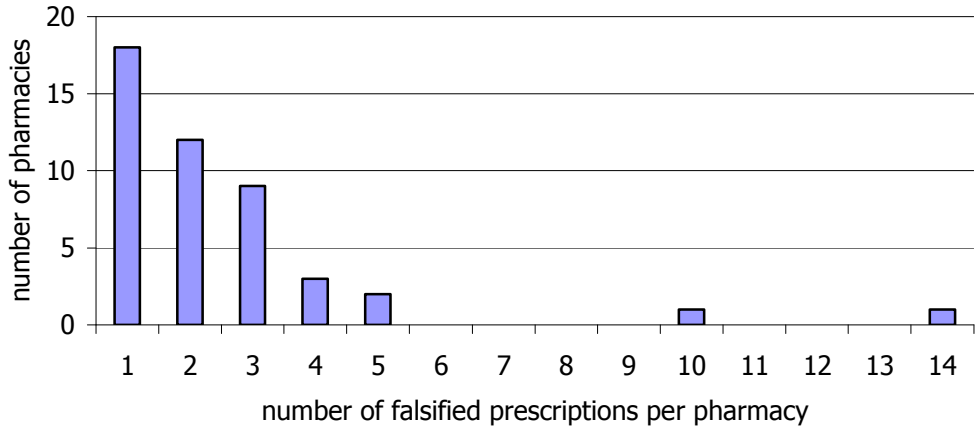


Figure 5 : Distribution of the number of pharmacies per number of falsified prescriptions per pharmacy.

From the 155 pharmacies responding to the mailing, 46 pharmacies (29.7 %) reported falsified prescriptions (n=115) in the past three months. Most of these pharmacies reported 1, 2 or 3 falsifications, however 1 pharmacy reported 10 falsifications and 1 pharmacy 14 falsified prescriptions (Figure 5).

Table 6: Prevalence per type of falsification.

Type of falsification	*Prevalence*
Modification of the prescription (writing over or different writing)	n = 35
Abnormal recommended dose or abnormal quantity or abnormal duration	n = 6
Prescription not in agreement with prescriptions rules	n = 13
Spelling mistakes	n = 10
Copy of prescription form	n = 20
Stolen prescription form	n = 6
Young patient	n = 9
Unknown prescriber	n = 4
Non-EU prescriber	n = 0

The three most frequently reported natures of falsification were modification of the prescription, copy of a prescription form and prescription not in agreement with prescription rules (Table 6).

Sixty nine percent (n=107) of the responders declared to be willing to participate in a future observational survey.

e. Implementation of pharmacies network in France

France has since several years a sentinel pharmacies network. The collection of suspected prescriptions is performed since 2001 by the French network of CEIP. The sentinel network of community pharmacies involves around 2200 voluntary pharmacies, i.e. about 10% of the 22000 pharmacies in France. The main results of the OSIAP survey in France have been already published in the scientific literature (*Boeuf et al Drug Safety 2007, Llau et al Eur J Clin Pharmacol 2002, Lapeyre-Mestre et al, Eur J Clin Pharmacol 1997*) as well as in periodic reports to the French Medicine Agency or to the Mission Inter-Ministerielle contre la Drogue et la Toxicomanie (MILDT).

(http://agmed.sante.gouv.fr/htm/10/pharma/pharma7.htm).

f. Implementation of pharmacies network in Italy

The Italian team was included in the project in 2006. Between October 2005 and March 2006, several contacts were made between the Department of Medicine and Public Health , Section of Pharmacology of the University of Verona and professional orders (Ferderfarma) in the area of Verona. After a translation of the protocol and formularies, an information campaign was done to the pharmacies of the province of Verona (about 200). Two surveys with data collection were launched during June 2006 and December 2006, with the participation of only 30 pharmacies, collecting none suspect prescription. The network of pharmacies was secondarily extended to other areas in 2007, with contacts with professional orders of Milano (Lombardy, 2720 pharmacies), Genoa (Liguria 592 pharmacies), Vicenza, Belluno, and Treviso (Veneto, 4592 pharmacies). Out the 5 professional orders, one confirmed its participation, leading to the constitution of a network of 218 volunteer pharmacies.

g. Implementation of pharmacies network in Netherlands

The Utrecht Department of Pharmacoepidemiology performed a retrospective mailing in November 2005 on a sample of 185 pharmacies in the Utrecht area (about 12% of the 1500 pharmacies). The response rate was 31% and the 59 responders reported that falsification of prescriptions is uncommon and probably less than 1 per year. According to this survey, the

most problematic drugs would be benzodiazepines and pethidine, however, because the system of electronic prescription and the direct contact with the identified prescriber, falsifications to obtain these drugs would be exceptional and concern only unlicensed prescribers (dentists or retired doctors).

Dutch community pharmacies are typically 3-4 times larger than their counterparts in other Western European countries, having 8-14 thousand patients per pharmacy.

All Dutch pharmacies are automated. Each time a patient presents a prescription order in the pharmacy, patient, prescriber and medication information is updated and stored for monitoring and billing purposes in patient-based drug dispensing histories. Before dispensing and filing of the information, new prescriptions are routinely checked with reference to the patients' drug history. If potential errors are detected, the pharmacist might communicate these with the prescriber eventually resulting in substitution or cancel of the prescription or dose adaptations.

In 2006, 260 pharmacies were solicited and forty declared to be willing to participate.

h. Implementation of pharmacies network in Spain

The Valladolid Institute of Pharmacology contacted the pharmacist professional association of the area of Valladolid about the project, and asked for permission to contact pharmacists and for a list of pharmacies willing to participate. A total of 260 pharmacies in the area of Valladolid were identified. A first selection was done with 20 volunteers, and completed by an intensive recruitment by phone. Finally, thirty one declared to be willing to participate in the survey (22 located in Valladolid).

i. Implementation of pharmacies network in Sweden

In Sweden, the collection and transmission of suspected prescription forms is continued and exhaustive in all country's pharmacies in the context of the National Pharmacy Corporation (Apoteket). During the eighties, data were transmitted to the Health Ministry and to Drug Medicine Agency (U. Bergmann. O. Dahl-Puustinen. Use of prescription forgeries in drug abuse surveillance network. *Eur J Clin Pharmacol*, 1989, 36: 621-623). During the last years, these data were not systematically transmitted but were used inside the Apoteket network as a tool of communication and warning about the risk of drug diversion. Because the number of falsified prescriptions remained high, it was decided to implement a system of electronic prescription to limit the falsification of prescription order, and this system was progressively widened to the all country between 2000 and 2005.

4. Data collection

j. Definition of common criteria for identifying suspect prescription forms.

In order to make easier the identification of an abnormal prescription, a common definition of suspect prescription is given. A suspect prescription could be:

- *A false prescription*: prescription written on a stolen form, counterfeit prescription (copies)
- *A forged prescription:* any falsification of an initial true prescription by addition or modification
- *An abnormal prescription*: which varies from national prescription guidelines

The following criteria were chosen to be included in the formulary of data collection sent to the pharmacies, in order to facilitate the identification and the characterization of a suspect prescription form. The list would be not exhaustive since the pharmacist could identify one or more of these criteria, or any other observation which he would consider as relevant:

- Unknown patient, unknown prescriber, unknown requester (specific criterion of suspicion in Netherlands)
- Modification of the prescription (writing over or different writing)
- Abnormal recommended dose or abnormal quantity or abnormal duration
- Prescription not in agreement with prescriptions rules (mentioned in the Summary Product Characteristics of drugs or specific rules for narcotic or psychotropic drugs)
- Abnormal refilled request
- Spelling mistakes
- Copy of prescription form
- Stolen prescription form

k. Periods of data collection

In a first step, it was decided to perform data collection on the basis of the periodic survey done in France, i.e. in May and November of each year: three data collection were initially planed, in May 2006, November 2006, and May 2007. The first data collection was done in May 2006 in Belgium, France, Netherlands and Spain. However, since the constitution of the pharmacies networks in each country needed some adaptations (new request and/or

widening of the network in Netherlands, Spain) and because the modifications of participants during the year 2006 (withdrawal of the participating team in Sweden and in Switzerland and replacement by two new participants in 2006), it was decided to perform at least 3 data collection (in Spring and in Fall-Winter) and to analyse results by year (2006 and 2007).

5. Results

a. Number of requested pharmacies and participation rate

The table 7 presents the number of pharmacies and their participation rate in each country.

Table 7: Periods of data collection with the corresponding number of requested pharmacies, of participating pharmacies and of pharmacies with at least one suspected prescription form.

Rank	*Country*	*Month*	*Number of requested pharmacies*	*Number of pharmacies which took part*	*Population coverage (crude estimate)*	*Number of pharmacies with at least one suspected prescription*
1	**Spain**	May-06	260	31	65 000	13
1	**Belgium**	May-06	109	34	68 000	6
1	**Netherlands**	May-06	260	40	364 000	0
1	**Sweden**	Nov-06	880	880	8 800 000	32
1	**Italy**	May-06	200	30	100 000	1
1	**France**	May-06	2262	902	2 440 000	121
2	**Spain**	March-07	50	50	104 000	12
2	**Belgium**	Nov-06	109	21	42 000	5
2	**Netherlands**	Feb-07	110	60	550 000	0
2	**Sweden**	Mai-07	880	880	8 800 000	25
2	**Italy**	Jan-07	40	40	135 000	1
2	**France**	Nov-06	2275	896	2 420 000	95
3	**Spain**	May-07	50	49	102 000	13
3	**Belgium**	Jun-07	270	44	88 000	8
3	**Netherlands**	May-07	0	0	0	0
3	**Sweden**	Nov-07	880	880	8 800 000	25
3	**Italy**	Oct-07	218	22	73 300	6
3	**France**	May-07	2229	895	2 420 000	120
4	**Spain**	*Nov-07*	*50*			
4	**Belgium**					
4	**Netherlands**					
4	**Sweden**					
4	**Italy**					
4	**France**	*Nov-07*	*1931*	*734*	*1 984 000*	*125*

A total of 862 suspect prescriptions (OSIAP) concerning1220 different drugs were reported, 418 prescriptions in 2006 (599 drugs) and 444 in 2007 (621 drugs).

b. Number of collected suspect prescriptions (OSIAP)

The repartition of the number of prescriptions and of corresponding drugs in each country is reported in table 8 and figure 6. The highest number of reports concerns France, but it must be weighted by the population coverage of each pharmacies' network. According to the crude estimate of population coverage at each collection period (table 7), the frequency of suspect prescriptions per 10 000 inhabitants would be the lowest in Sweden (0.04/10000 in

2006, 0.08/10000 in 2007), followed by Italy (0.1/10 000 and 0.66/10000), France (1.36/10000 and 1.22/10000), Belgium (2.8/10000 and 0.9/10000) and Spain (3.3/10000 in 2006 and 6.2/10000 in 2007). None suspect form was reported in Netherlands.

Table 8 : Number of suspect prescriptions (OSIAP) in 2006 and 2007 in each country

	Total				***2006***				***2007***			
	Prescription (n = 862)		**Drugs (n = 1220)**		**Prescription (n = 418)**		**Drugs (n = 599)**		**Prescription (n = 444)**		**Drugs (n = 621)**	
	N	%	N	%	N	%	N	%	N	%	N	%
France	618	71,69%	963	78,93%	326	77,99%	502	83,81%	292	65,77%	461	74,24%
Sweden	111	12,88%	113	9,27%	39	9,33%	39	6,51%	72	16,22%	74	11,92%
Spain	96	11,14%	103	8,44%	33	7,89%	38	6,34%	63	14,19%	65	10,47%
Belgium	27	3,13%	30	2,46%	19	4,55%	19	3,17%	8	1,80%	11	1,77%
Italy	10	1,16%	11	0,90%	1	0,24%	1	0,17%	9	2,03%	10	1,61%
Netherlands	0	0	0	0	0	0	0	0	0	0	0	0

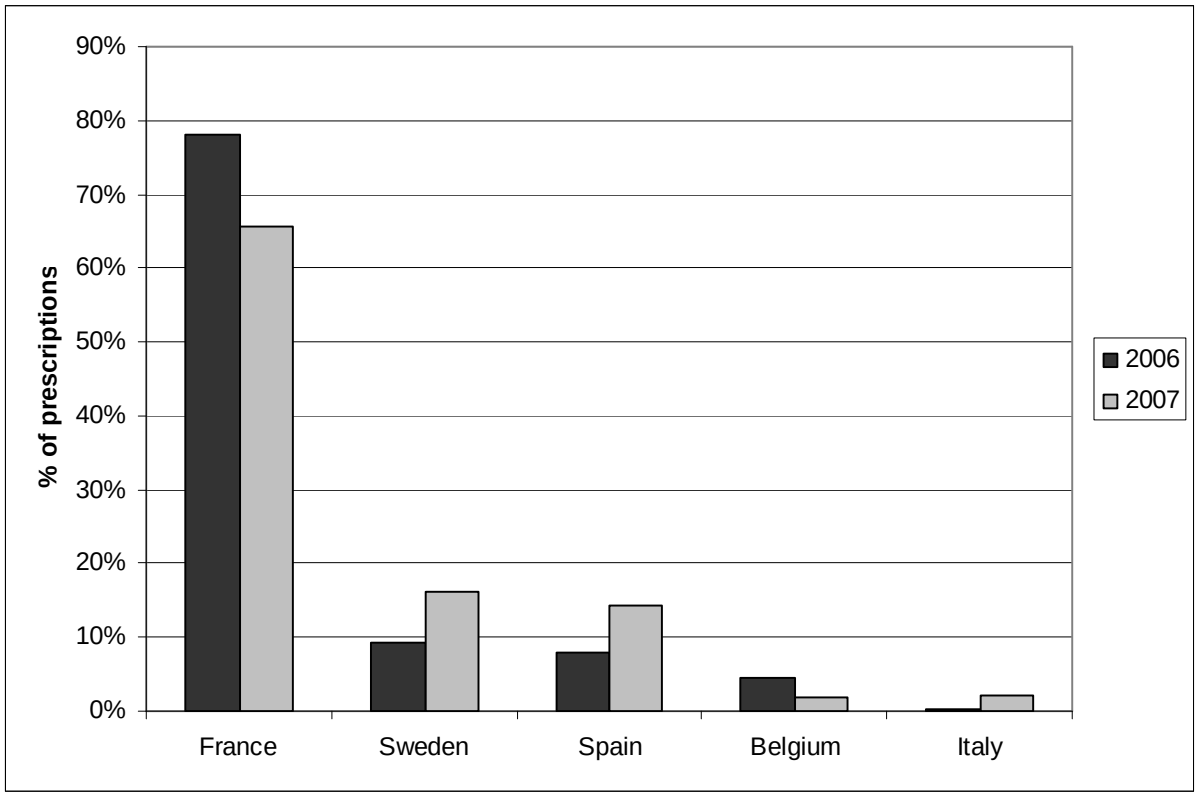


Figure 6: repartition of the 862 suspect prescriptions OSIAP by country

c. Characteristics of patients presenting the suspect prescriptions OSIAP

The characteristics of patients presenting suspect prescriptions identified in the pharmacies networks during the survey are presented in table 8. Age and gender of the patient were not available in respectively 12% and 3% of cases. The category of “unknown patient was not available in 21% of prescriptions.

Table 9 : characteristics of patients presenting suspect prescriptions OSIAP

		2006-2007		***2006***		***2007***	
		(n = 862)		**(n = 418)**		**(n = 444)**	
Age	Mean (SD)	45,32 (16,75)		45,49 (17,36)		45,17 (16,17)	
	Min-Max	1 - 98		6 - 98		1 - 88	
	Missing value	104		53		51	
		N	%	N	%	N	%
Gender	Men	384	44,55%	183	43,78%	201	45,27%
	Women	452	52,44%	218	52,15%	234	52,70%
	Missing value	26	3,01%	17	4,07%	9	2,03%
Patient	Unknown Patient	180	20,88%	82	19,62%	98	22,07%
	Known Patient	482	55,92%	250	59,81%	232	52,25%
	Missing value	200	23,20%	86	20,57%	114	25,68%

d. Different criteria of suspicion

The distribution of criteria of suspicion in 2006 and 2007 is similar, the most frequently reported criterion being the modification of a true prescription. The details of criteria per period of survey (2006 and 2007) are given in table 9 and in figure 7.

The most frequently reported criterion was “modification of a true prescription”, followed by “not obeying to prescription rules”, “suspect writing”, “copy/scan” and “addiction of a drug”.

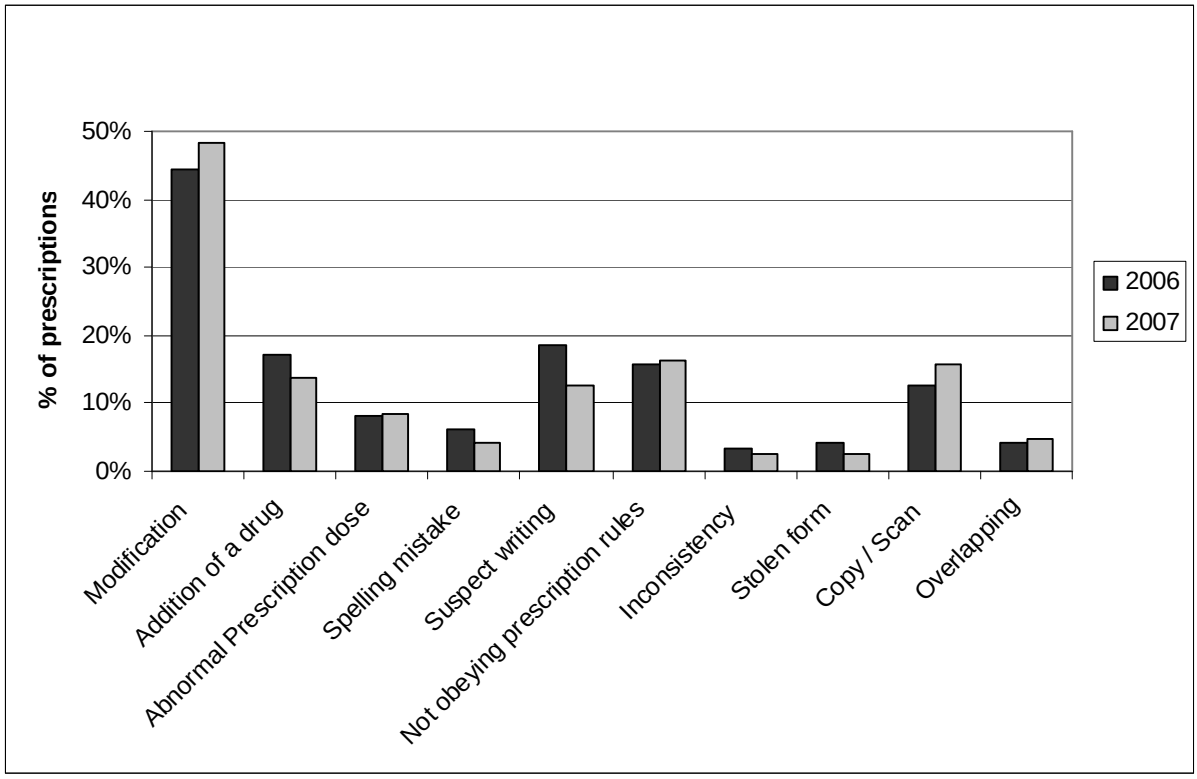


Figure 7: distribution of suspect prescriptions (OSIAP) by suspicion criteria

Table 10 : suspicion criteria identified in the OSIAP survey

	2006-2007 ***(n = 862)***		***2006*** ***(n = 418)***		***2007*** ***(n = 444)***	
	N	%	N	%	N	%
Modification						
Non	461	53,48%	232	55,50%	229	51,58%
Yes	399	46,29%	185	44,26%	214	48,20%
Missing value	2	0,23%	1	0,24%	1	0,23%
Addition of a drug						
Non	727	84,34%	345	82,54%	382	86,04%
Yes	133	15,43%	72	17,22%	61	13,74%
Missing value	2	0,23%	1	0,24%	1	0,23%
Abnormal dose						
Non	789	91,53%	383	91,63%	406	91,44%
Yes	71	8,24%	34	8,13%	37	8,33%
Missing value	2	0,23%	1	0,24%	1	0,23%
Spelling mistake						
Non	815	94,55%	391	93,54%	424	95,50%
Yes	45	5,22%	26	6,22%	19	4,28%
Missing value	2	0,23%	1	0,24%	1	0,23%
Suspect writing						
Non	726	84,22%	339	81,10%	387	87,16%
Yes	134	15,55%	78	18,66%	56	12,61%
Missing value	2	0,23%	1	0,24%	1	0,23%
Prescription rules						
Non	722	83,76%	351	83,97%	371	83,56%
Yes	138	16,01%	66	15,79%	72	16,22%
Missing value	2	0,23%	1	0,24%	1	0,23%
Inconsistency						
Non	835	96,87%	403	96,41%	432	97,30%
Yes	25	2,90%	14	3,35%	11	2,48%
Missing value	2	0,23%	1	0,24%	1	0,23%
Stolen						
Non	831	96,40%	399	95,45%	432	97,30%
Yes	29	3,36%	18	4,31%	11	2,48%
Missing value	2	0,23%	1	0,24%	1	0,23%
Copy/Scan						
Non	737	85,50%	364	87,08%	373	84,01%
Yes	123	14,27%	53	12,68%	70	15,77%
Missing value	2	0,23%	1	0,24%	1	0,23%
Overlapping						
Non	821	95,24%	399	95,45%	422	95,05%
Yes	39	4,52%	18	4,31%	21	4,73%
Missing value	2	0,23%	1	0,24%	1	0,23%

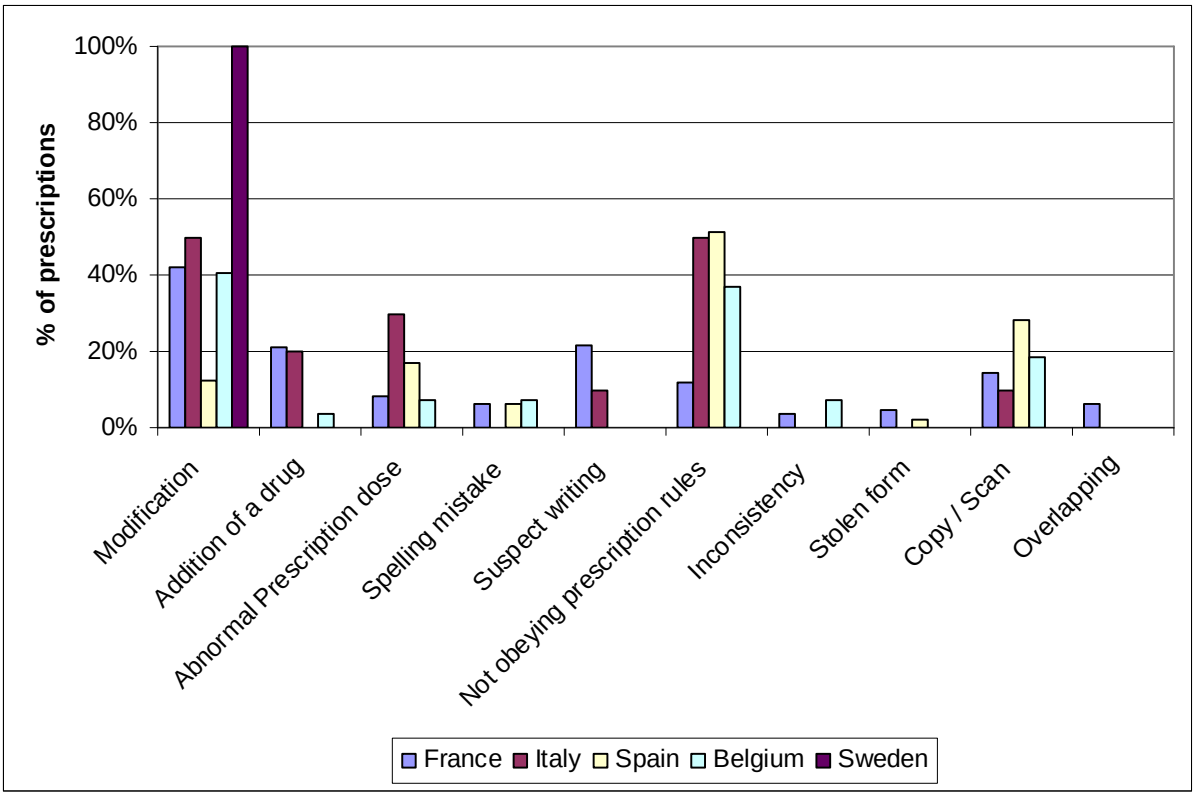


Figure 8: Repartition of suspicion criteria by country in the 2006-2007 collection periods.

The analysis of suspicion criteria by country underlines specificity of prescription and delivery rules in relation with national guidelines (figure 8). For example, in Sweden, only the criterion "modification of a true medical prescription" could be reported (100% of suspicion criteria), because more than 90% of prescription are directly electronic, without any paper support. By contrast, "overlapping" is only reported in France, and concerns the violation of the rule for duration of prescription for narcotic drugs.

e. Main ATC classes identified during the data collection

Among the 1220 different drugs identified in the suspect prescriptions, more than 60% belonged to the ATC Class "N Nervous system" (figure 9). The following classes were "A "Alimentary Tract And Metabolism", C "Cardiovascular System", M "Musculo-Skeletal System" and R "Respiratory System".

The comparison by country indicates that cardiovascular drugs are identified only in France, whereas respiratory drugs are mainly identified in Belgium. Genito-urinary drugs and anti-infective drugs are mainly identified in Italy and in Spain.

The details of the repartition of drugs according to level 2, level 3 and the complete classification are given in annex 4.

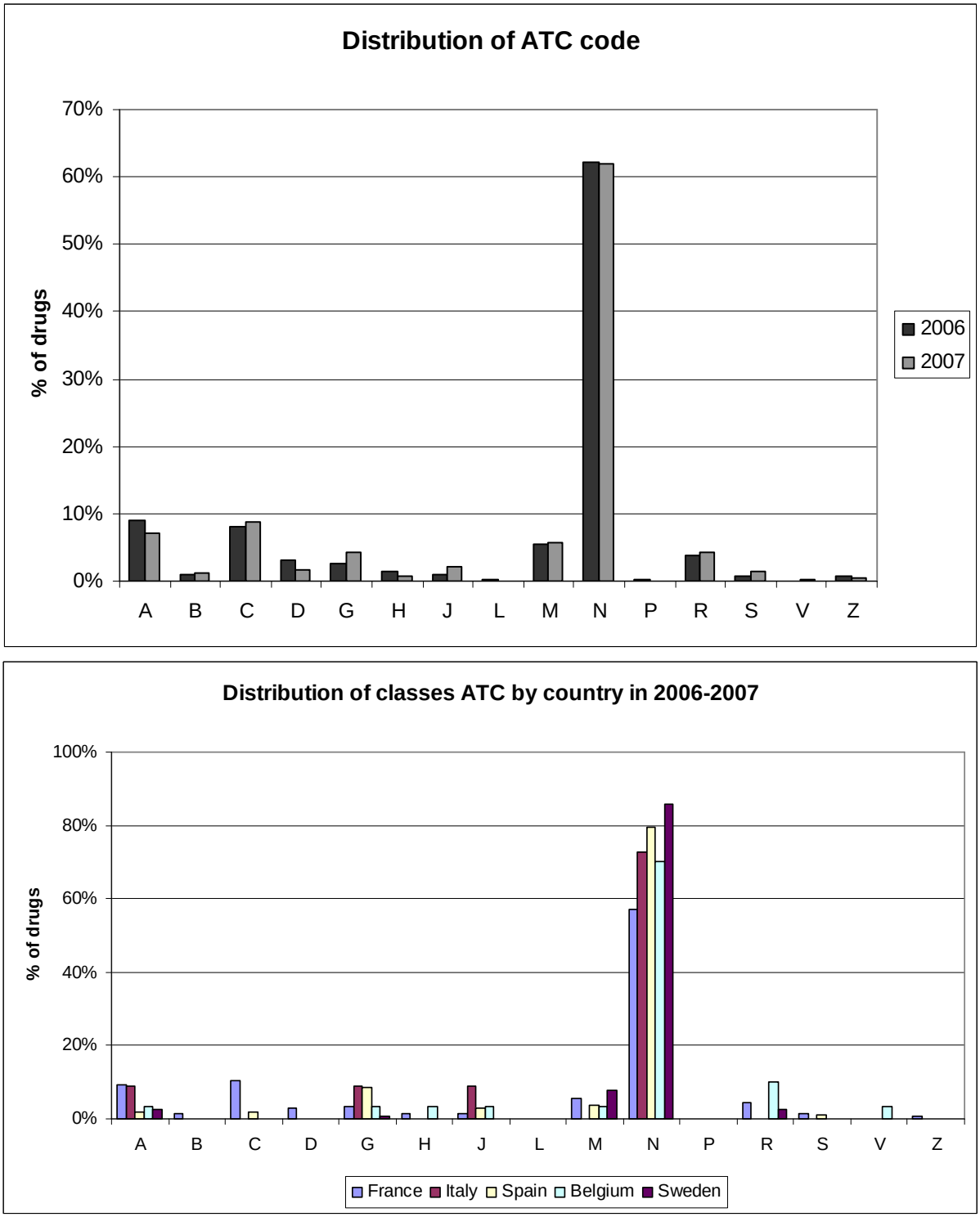


Figure 9: Repartition of drugs according to the ATC classification level 1 in the 2006-2007 collection periods and by country.

The figure 10 presents the repartition of drugs of the “Nervous system” class by country. Opioîd analgesics are mainly found in Sweden, whereas hypnotics are more frequent in Italy and psycho stimulants in Spain and Belgium.

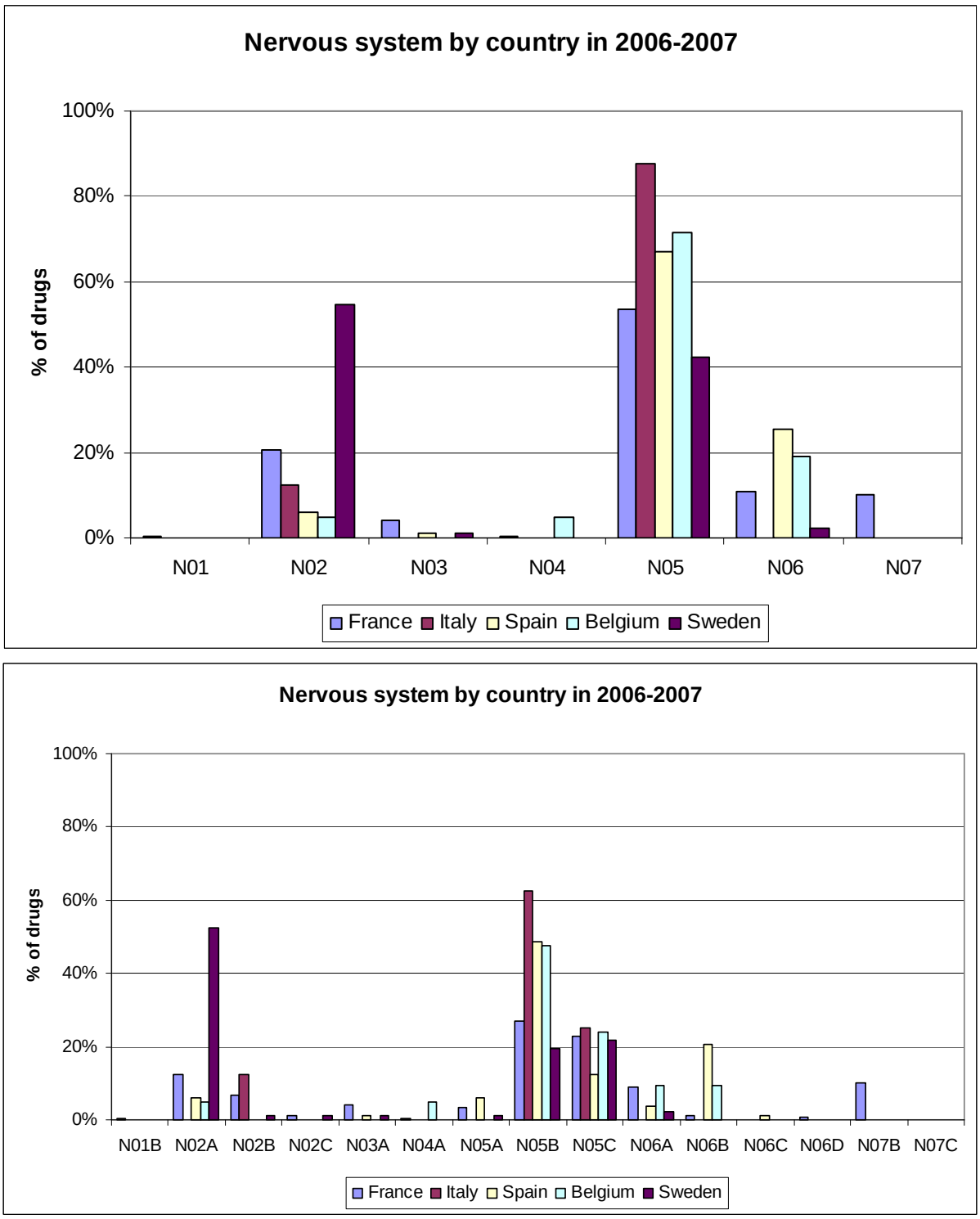


Figure 10: Repartition of the percentage of drugs belonging to the ATC class “Nervous system”, level 2, in 2006-2007 and by country.

f. Medications most frequently identified

The table 11 presents the Top 20 of the main frequently reported medications during the OSIAP survey in 2006-2007.

The main cited drugs are benzodiazepines or analogues: zolpidem, bromazepam, and alprazolam are the 3 main cited drugs (bromazepam decreases at the 3rd rank in 2007 and alprazolam increases at the 2nd rank). Benzodiazepines represent half of the 20 most cited drugs. Flunitrazepam, largely abused in the late nineties in France has decreased in the French data. Since 2001, flunitrazepam has been limited to 14 days of prescription, without overlapping, and must be prescribed on specific prescription from for scheduled substances. These rules explain the decreasing number of cases reported from this period. In the data collected in 2006-2007 in France, flunitrazepam is at the 8th rank (it was at the 1st rank in 2003), but it remains the most frequently cited drug in Belgium, followed by bromazepam and lorazepam.

The 4th most cited drug is buprenorphine (approved in the treatment of opiate dependence) and is only identified in France.

In Italy, the most frequently cited drugs were lorazepam and lormetazepam. In Spain, there were as many reports with alprazolam as with methylphenidate. In Sweden, the most frequently involved drugs are opiate analgesics not scheduled as narcotics: the fist one was tramadol, representing more than 25% of all cited drugs, followed by combination including codeine.

Several drugs were found in diverted prescriptions even if they are not known for their addictive potential, but probably for misuse: these drugs belong to the ATC class G04BE, corresponding to “Drugs used in erectile dysfunction”. These drugs were identified in Spain, Italy and at a less extent in Sweden and in France.

Several drugs were found in diverted prescriptions even if they are not known for their addictive potential. Some drugs could be diverted for other purposes: thyroid hormones or diuretics (specifically furosemide) could be used against overweight. We also suspect an “unrecognized pharmacodependence”, for example paracetamol combined with dextropropoxyphene, largely found in cases of drug induced headache. Drugs such as antiinfectious or cardiovascular drugs could also be modified on prescription forms for economic and reimbursement purposes. A misuse for doping could not be excluded.

Table 12 presents the repartition of patients’ characteristics according to the therapeutic classes. The profile of patients is associated with the category of drugs: users of maintenance treatment or psychostimulants are younger (30 years old) and more likely male (70%), there were older and more likely women for antidepressants and anxiolytics/hypnotics.

Table 11: Top 20 of the main cited medications

	ATC code	*DCI*	*2006-2007*		*2006*		*2007*	
			(n = 1050)		**(n = 522)**		**(n = 528)**	
			N	%	N	%	N	%
1	N05CF02	Zolpidem	68	6,48%	36	6,90%	32	6,06%
2	N05BA08	Bromazepam	60	5,71%	39	7,47%	21	3,98%
3	N05BA12	Alprazolam	60	5,71%	27	5,17%	33	6,25%
4	N07BC01	Buprenorphine	49	4,67%	25	4,79%	24	4,55%
5	N02AA59	Codeine, combinations excl. psycholeptics	45	4,29%	11	2,11%	34	6,44%
6	N05CF01	Zopiclone	42	4,00%	16	3,07%	26	4,92%
7	N02BE01	Paracetamol	33	3,14%	14	2,68%	19	3,60%
8	N02AX02	Tramadol	31	2,95%	12	2,30%	19	3,60%
9	N05BA06	Lorazepam	31	2,95%	13	2,49%	18	3,41%
10	N06BA04	Methylphenidate	25	2,38%	6	1,15%	19	3,60%
11	N05CD03	Flunitrazepam	24	2,29%	15	2,87%	9	1,70%
12	N05BA04	Oxazepam	21	2,00%	13	2,49%	8	1,52%
13	N05BA05	Potassium clorazepate	20	1,90%	8	1,53%	12	2,27%
14	N05CD06	Lormetazepam	16	1,52%	5	0,96%	11	2,08%
15	N03AE01	Clonazepam	15	1,43%	11	2,11%	4	0,76%
16	N02AC54	Dextropropoxyphene, comb. excl. psycholeptics	14	1,33%	7	1,34%	7	1,33%
17	C03CA01	Furosemide	12	1,14%	6	1,15%	6	1,14%
18	N02AA01	Morphine	12	1,14%	9	1,72%	3	0,57%
19	N05BA01	Diazepam	12	1,14%	6	1,15%	6	1,14%
20	M03BX07	Tetrazepam	11	1,05%	4	0,77%	7	1,33%

Table 12 : Main characteristics of patients presenting suspect prescription forms for selected classes of medications.

	N05B		***N05C***		***N02A***		***N06A***		***N07B***		***N02B***		***N06B***	
	Anxiolytics (n = 223)		**Hypnotics and sedatives (n = 164)**		**Opioids (n = 125)**		**Anti depressants (n = 57)**		**Drugs used in addictive disorders (n = 55)**		**Other analgesics and antipyretics (n = 40)**		**Psychostimulants, agents used for ADHD and nootropics (n = 25)**	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gender														
Men	96	43,05%	77	46,95%	58	46,40%	17	29,82%	47	85,45%	9	22,50%	16	64,00%
Women	120	53,81%	78	47,56%	66	52,80%	39	68,42%	6	10,91%	29	72,50%	8	32,00%
Missing value	7	3,14%	9	5,49%	1	0,80%	1	1,75%	2	3,64%	2	5,00%	1	4,00%
Patient known														
Patient unknown	67	30,04%	36	21,95%	18	14,40%	12	21,05%	15	27,27%	9	22,50%	13	52,00%
Patient known	107	47,98%	73	44,51%	46	36,80%	39	68,42%	30	54,55%	25	62,50%	11	44,00%
Missing value	49	21,97%	55	33,54%	61	48,80%	6	10,53%	10	18,18%	6	15,00%	1	4,00%
Country														
Belgium	10	4,48%	5	3,05%	1	0,80%	2	3,51%	0	0,00%	0	0,00%	2	8,00%
France	149	66,82%	126	76,83%	68	54,40%	50	87,72%	55	100,00%	38	95,00%	6	24,00%
Italy	5	2,24%	2	1,22%	0	0,00%	0	0,00%	0	0,00%	1	2,50%	0	0,00%
Sweden	19	8,52%	21	12,80%	51	40,80%	2	3,51%	0	0,00%	1	2,50%	0	0,00%
Spain	40	17,94%	10	6,10%	5	4,00%	3	5,26%	0	0,00%	0	0,00%	17	68,00%
Age														
Mean (SD)	43,23 (15,37)		43,62 (16,24)		45,03 (14,42)		45,27 (15,53)		32,91 (9,63)		50,94 (20,58)		30,90 (11,22)	
Min-Max	15 - 90		20 - 87		19 - 86		17 - 80		22 - 80		16 - 84		9 - 50	
Missing value	24		31		10		9		11		6		2	

g. Comparison with drug consumption data

At the time of this report, data concerning sales or reimbursement data are not completely available in all countries. This analysis is ongoing and needs some adaptation because the sources of drug exposure could differ. In order to compare results obtained by country for suspect prescriptions, we used data about the level of consumption of narcotic and psychotropic drugs provided by the International Narcotics Control Board in the Report 2007: Estimated World Requirements for 2008 - Statistics for 2006 for narcotics (http://www.incb.org/incb/en/narcotic_drugs_reports.html) and the Report 2007: Statistics for 2006 : Assessments of Annual Medical and Scientific Requirements for Substances in Schedules II, III and IV of the Convention on Psychotropic Substances of 1971 (http://www.incb.org/incb/en/psychotropics_reports.html).

Data concerning consumption of narcotics are extracted from Table XIV.1 of the 2007 INCB report. This table presents information on the average consumption by countries of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, excluding preparations in Schedule III of the 1961 Convention, in the three-year period 2004-2006. Average consumption levels of additional narcotic drugs, for which defined daily doses for statistical purposes were adopted by the Board, are reflected in the column entitled “Others”. Preparations listed in Schedule III are excluded from table XIV.1, since Governments have no obligation to report to the Board on the consumption of and international trade in those preparations. Governments only have to report the quantities of narcotic drugs utilized for the manufacture of those preparations.

However, preparations in Schedule III are frequently exported from the country of their manufacture and are consumed in other countries. The term “defined daily doses for statistical purposes” (S-DDD) replaced the term “defined daily doses” (DDD), which had previously been used by the Board in its publications. The defined daily doses for statistical purposes are technical units of measurement for the purpose of statistical analysis and are not recommended prescription doses. Their definitions are not free of a certain degree of arbitrariness. Certain narcotic drugs may be used in certain countries for different treatments or in accordance with different medical practices and, therefore, a different daily dose could be more appropriate. The defined daily doses for statistical purposes indicated should be considered approximate and subject to modification if more precise information becomes available. The defined daily doses for statistical purposes for hydromorphone, morphine, oxycodone and tilidine were modified in 2003, following the recommendations made by an expert group that reviewed the defined daily doses for statistical purposes used by the Board

for the analysis of the consumption of narcotic drugs, taking into account the developments in the most common dosages, indications and methods of administration.

Levels of consumption of groups of psychotropic substances in defined daily doses for statistical purposes (DDD) per thousand inhabitants per day are calculated on the basis of statistics on manufacture and trade provided by Governments. To exclude the impact of yearly fluctuations on the calculated annual consumption, the average for the three-year period 2004-2006 was calculated. In countries that do not manufacture and export psychotropic substances, quantities declared as imported are considered to be destined for consumption. For countries with manufacture and exports of psychotropic substances, the average annual manufacture is added to the average annual import; the average annual export and amounts of psychotropic substances used for conversion into other psychotropic or non-psychotropic substances are deducted.

The table XIV.1 of the 2007 report for narcotics indicates that Belgium is at the second rank for the average consumption in defined daily doses per million inhabitants per day (1st rank USA), with 18 765 DDD per million (period 2004-2006), Spain is at the 8th rank with 8 842 DDD per million, Netherlands at the 13th rank with 7 089 DDD, Sweden at the 16th rank with 6431 DDD, France at the 18th rank with 5697, and Italy at the 25th rank with 3241 DDD per million of inhabitants.

The level of use of narcotics higher for Belgium is mainly due to tilidine, a medication with a specific approval for euthanasia (table 13).

The report 2007 for psychotropic drugs gives figures of average consumption for the period 2004-2006, expressed in DDD per million of inhabitants and aggregated for stimulants, sedatives-hypnotics, anxiolytics, anti-epileptics and some specific drugs, buprenorphine and methylphenidate specifically (table 14).

Some data were not available for classes of psychotropics in the 2007 INCB report, but they were extracted from the previous report published in 2007, for the period 2003-2005. The main lacking data concerned hypnotics and anxiolytics in France. They could be also available in the different way in the most recent annual report of the French Health Products Agency: "Analyse des ventes de médicaments aux officines et aux hôpitaux en France: données 1996-2006" (http://afssaps.sante.fr/pdf/5/rapport_vente_medicament_1996-2006.pdf).

Actually, the use of buprenorphine is the highest in France, in relation with the availability of the drugs in community pharmacies (and a prescription possible for any prescriber). In the Osiap survey, suspect prescription forms concerning buprenorphine are only found in France. Stimulants such as methylphenidate (scheduled as narcotic drug in France) are less

available in this country in comparison with other countries. By contrast, methylphenidate and drugs belonging to the N06B class is principally identified in Spain and at a less extent in Belgium. Moreover, these crude results do not reflect the difference in the population coverage between countries (50 pharmacies involved in Spain, 170 in Belgium, about 2000 in France).

Table 13 : levels of consumption of narcotic drugs: average consumption in defined daily doses for statistical purposes per million inhabitants per day, excluding preparations in schedule III, 2004-2006 (extracted from the INCB 2007 Report on narcotic drugs)

Rank	*Country*	*Codeine*	*Fentanyl*	*Hydrocodone*	*Hydromorphone*	*Methadone*	*Morphine*	*Oxycodone*	*Pethidine*	*Tilidine*	*Others*	*Total*
2	**Belgium**	32	11999	157	104	2778	334	1	21	2338	1001	18765
8	**Spain**	-	4737	-	-	3788	238	31	21	-	27	8842
13	**Netherlands**	89	3989	-	16	1847	387	235	12	-	514	7089
16	**Sweden**	-	3843	2	190	747	710	665	4	-	270	6431
18	**France**	30	3333	2	58	814	1179	89	2	-	190	5697
25	**Italy**	-	1269	-	-	1784	104	30	4	-	50	3241

Table 14 : levels of consumption of psychotropic drugs: average consumption in defined daily doses for statistical purposes per million inhabitants per day, excluding preparations in schedule III, 2004-2006 (extracted from the INCB 2007 Report on psychotropic drugs)

Country	*Stimulants*	*Sedative-Hypnotics*	*Anxiolytics*	*Anti-epileptics*	*Buprenorphine*	*Methylphenidate*
Belgium	4.57	101.65	51.00*	2.86		1.22
Spain	1.26	20.81	17.30*	3.30	2.95	0.95
Netherlands	2.89	22.91	22.47	2.52	3.05	2.12
Sweden	1.09*	19.43	15.74		3.20	1.01
France		75.90*	58.26*	3.72	11.02	
Italy	4.60	28.07	40.65	5.98	2.53	

**Values of the 2003-2005 period*

Conclusion

The diversion of prescription controlled drugs or medication in general into illicit channels are a public heath and safety issue. These medications could be diverted in numerous ways, including theft, forgery and counterfeiting of prescriptions. People commit prescription fraud in various ways, including forging prescriptions, doctor shopping, or altering prescriptions to increase quantity. The true magnitude of prescription fraud remains largely unknown. Misuse of these drugs could lead to serious health consequences, including dependence, overdose or death. Despite the fact that preclinical and clinical behavioral studies in animals and humans (self-administration, discrimination, appetence studies...) could suggest which medications could be abused, these methods have limited validity when the drug is available in the “real life” context. Actually, epidemiological assessment, which underlines the extent of abuse, is the ultimate gold standard index that other approaches, experimental or clinical, are trying to predict.

The project has confirmed the feasibility of the constitution of community pharmacies network to perform this kind of study in the public health domain. The constitution of the registry could be a basis fro the comparison of the availability of different medications according to their abuse potential. It could be extent to the other 21 European countries and annually actualized to compare the patterns of medications abuse between European countries. The results concerning medications in the falsified prescription show that benzodiazepines are the class of drugs which is most frequently subject of forged prescriptions, but there are differences between countries. In France, the most commonly diverted drug is one which is used by heroine addicts whereas in Spain it is a drug used by hyperactive children.

Second part

Manpower for the execution of the activities

Dr. M Lapeyre-Mestre, National official study coordinator, CEIP de Toulouse, Unité de Pharmacoépidémiologie, Université de Toulouse, France

Pr A Roussin, pharmacist, Centre d'Evaluation et d'Information sur la Pharmacodépendance

MA Courné, pharmacist, French Health Products Agency, department of narcotics and psychotropics : sales data

M Gony research assistant, coordination, data collection and analysis in France

S Grolleau research assistant

L Pourcel research assistant

E Gorsse: secretary of the project and monitoring of the OSIAP survey in France

P Morandi: secretary of the project and monitoring of the OSIAP survey in France

Participants

Dr. R Vander Stichele, national official, Heymans Institute of Pharmacology, Ghent University, Belgium

D Mehuys, pharmacist Pharmaceutical Care Unit, Faculty of Pharmacy, University of Ghent (project leader)

J De Schutter, National Pharmaceutical Inspectorate

B Van Den Bossche, National Pharmaceutical Inspectorate

Pauwels, National Pharmaceutical Inspectorate

ML Bouffioux, National Pharmaceutical Inspectorate

Secretary (mails to pharmacies network)

Dr. A Conforti, national official, Department of Medicine and Public Health, Section of Pharmacology. University of Verona, Italy

P D'incau, pharmacist, Department of Medicine and Public Health, Section of Pharmacology.

Representative of FEDERFARMA (pharmaceutical corporation)

Secretary (mails to pharmacies network)

Pr. H Leufkens, national official, Departement of Pharmacoepidemiology, Utrech University, Netherlands
Pr R Heerdink, national official (project leader), Departement of Pharmacoepidemiology,
Secretary (mails to pharmacies network)

Pr. A Carvajal, national official, Unit of Pharmacoepidemiology, Valladolid University, Spain
D Macias Pharmacist, project leader, Unit of Pharmacoepidemiology,,
Secretary (mails to pharmacies network)

Pr. U Bergman, national official, Karolinska Institutet, Division of Clinical Pharmacology, Huddinge University Hospital, Stockholm, Sweden, coordination Sweden
B Forsberg, pharmacist, (project leader) Apoteket AB
B Sundström-Nilsson, pharmacist Apoteket AB
Secretary (mails to pharmacies network)

First meeting

OSIAP EUROPE meeting Toulouse 1st -2nd April 2005

Faculté de Médecine

37 Allées Jules Guesde,

31073 Toulouse

Participant countries: Belgium, France, Netherlands, Spain, Sweden, Switzerland

Friday 1st April 2005

11:00-12:00	Welcome and visit of the Department of Clinical Pharmacology
13:00:	Lunch
14:00:	Presentation of the French system of Drug abuse and dependence assessment, including the OSIAP survey – Maryse Lapeyre-Mestre
15:00	Presentation of the Project submitted to the European Commission and expected timetable – Maryse Lapeyre-Mestre
15:30:	Data collected for the inventory in the different participating countries- Mireille Gony
16:30	Coffee/Tea
17:00	Discussion and proposal for implementation of data collection in each country. All
18:30	Close meeting
20:30	Dinner

Saturday 2nd April 2005

09:00	Definition of common criteria for identifying suspect prescription forms.
10:30	Coffee break
11:00	Preparation of the 1st intermediary report for EC (sept 2005). Other sources of funding.
12:30	Lunch
14:30	End of the meeting

Second meeting

OSIAP EUROPE Toulouse 25-26th September 2006

Faculté de Médecine

37 Allées Jules Guesde,

31073 Toulouse

Participant countries: Belgium, France, Italy, Netherlands, Spain, Sweden

Monday 25th September 2006

10:00 Reception in the Department of Clinical Pharmacology.

10:30 (Mireille Gony) Bollinelli room

OSIAP Europe since april 05:

18 months assessment, medicines register

12:00 (all) Discussion

13:00 Lunch

15:00 (all) Bollinelli room

Oral presentation by each country representant on the following items:

(To envisage 20 / 30 minutes each one)

Set up of pharmacies network, Set up of the survey in the pharmacies,

Observed problems and difficulties,

Results may 2006, Suggestions and perspectives.

18:00 - 19:00 Discussion

20:30 Dinner

Tuesday 26th September 2006

09:00 - 09:30 (Maryse Lapeyre) Bollinelli room

Administrative and financial parts of the study

09:30 (Mireille Gony)

2nd intermediate report preparation:

Medicines register

Prescription forms, Collection data forms,

Data analysis (may / november 2006)

Figures of sale of medicines

Perspectives.

11:30 (all) Discussion

13:00 Lunch

15:00 Expected end of the meeting

Third meeting

OSIAP EUROPE Toulouse 15-16th November 2007

Faculté de Médecine

37 Allées Jules Guesde,

31073 Toulouse

Participant countries: Belgium, France, Italy, Netherlands, Spain, Sweden

Thursday 15th November 2007

09:00 .Reception in the Department of Clinical Pharmacology.

09:30 Bollinelli room

OSIAP Europe since September 06:

- Set up of pharmacies network
- Results of collections data for each country
- Drug utilisation data for medicines found on suspected prescriptions

13:00 Lunch

Bollinelli room

- Administrative and financial parts of the study
- Medicines register
- Perspectives.

19 :00 End of day meeting

20:30 Dinner

Friday 16 th november 2007

08:30 .Reception in the Department of Clinical Pharmacology.

09:00 Bollinelli room

- Final report preparation

10:30 Expected end of the meeting

Third part
COUNTRIES INVOLVED

The detail of the activities conducted in each of the countries is described in the first part (detailed description of activities), as well as that involving appropriate partners when relevant.

Coordination

Dr. Maryse Lapeyre-Mestre, CEIP de Toulouse, Unité de Pharmacoépidémiologie, Université de Toulouse, France, study coordinator

Participants

Dr. Robert Vander Stichele, Heymans Institute of Pharmacology, Ghent University, Belgium

Dr. Anita Conforti, Department of Medicine and Public Health, Section of Pharmacology. University of Verona, Italy

Pr. Hubert Leufkens, Departement of Pharmacoepidemiology, Utrech University, Netherlands

Pr. Alfonso Carvajal, Unit of Pharmacoepidemiology, Valladolid University, Spain

Pr. Ulf Bergman, Karolinska Institutet, Division of Clinical Pharmacology, Huddinge University Hospital, Stockholm, Sweden

Fourth part

ACHIEVEMENT OF THE OBJECTIVES

The diversion of prescription controlled drugs or medication in general into illicit channels are a public heath and safety issue. These medications could be diverted in numerous ways, including theft, forgery and counterfeiting of prescriptions. People commit prescription fraud in various ways, including forging prescriptions, doctor shopping, or altering prescriptions to increase quantity. The true magnitude of prescription fraud remains largely unknown. Despite the fact that preclinical and clinical behavioral studies in animals and humans (self-administration, discrimination, appetence studies...) could suggest which medications could be abused, these methods have limited validity when the drug is available in the “real life” context. Actually, epidemiological assessment, which underlines the extent of abuse, is the ultimate gold standard index that other approaches, experimental or clinical, are trying to predict.

The project has confirmed the feasibility of the constitution of community pharmacies network to perform this kind of study in the public health domain. It also confirms that electronic prescription is a good way to avoid drug diversion from prescriptions. The constitution of the registry could be a basis for the comparison of the availability of different medications according to their abuse potential. It could be extent to the other 21 European countries and annually actualized to compare the patterns of medications abuse between European countries. The results concerning medications identified through the collection of suspect prescriptions show that benzodiazepines are the class of drugs which is most frequently subject of forged prescriptions, but there are differences between countries. In France, the most commonly diverted drug is one which is used by heroine addicts whereas in Spain it is a drug used by hyperactive children. A more detailed analysis taking into account consumption of medications in the same area and for the accurate periods should be useful to compare the extent of drug diversion via prescription forms, but these data are not completely available at this time.

This report was produced by a contractor for Health & Consumer Protection Directorate General and represents the views of the contractor or author. These views have not been adopted or in any way approved by the Commission and do not necessarily represent the view of the Commission or the Directorate General for Health and Consumer Protection. The European Commission does not guarantee the accuracy of the data included in this study, nor does it accept responsibility for any use made thereof.