New drug substances with abuse potential:

Points to consider for the development and marketing

- Regulatory environment in the European Union and the United States -

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To my husband

- for his patience and support -

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Abbreviations

2CB	4-Bromo-2,5-dimethoxyphenetylamin
4-MTA	4-methylthioamphetamine
ADHD	Attention-Deficit Hyperactivity Disorder
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (ES)
Afssaps	Agence Francaise de Sécurité Sanitaire des Produits de Santé (FR)
AIFA	Agenzia Italiana del Farmaco (IT)
AMA	American Medical Association (U.S.)
ARCI	Addiction Research Center Inventory
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (DE)
BtMG	Betäubungsmittelgesetz (DE)
CD	Controlled Drug (UK)
CDER	Center for Drug Evaluation and Research (FDA, U.S.)
CEIP	Centres d'évaluation et d'information sur la pharmacodépendance (FR)
CMD	Coordination Group for Mutual Recognition and Decentralised Procedures (EU)
CMS	Concerned Member State (EU)
CND	Commission on Narcotic Drugs (U.N.)
CNS	Central Nervous System
CP	Centralised Procedure (EU)
CSA	Controlled Substances Act (U.S.)
CSS	Controlled Substances Staff (FDA, U.S.)
DAWN	Drug Abuse Warning Network (U.S.)
DDMAC	Division of Drug Marketing, Advertising, and Communications (FDA, U.S.)
DE	Germany
DEA	Drug Enforcement Administration (U.S.)
DHHS	Department of Health and Human Services (U.S.)
Diab	Diabetic
DPR	Decreto del Presidente della Repubblica (IT)
DSRCS	Division of Surveillance, Research and Communication Support (FDA, U.S.)
ECDD	Expert Committee on Drug Dependence (WHO)
ED	Emergency Department
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction (EU)
EMEA	European Medicines Agency (EU)
ES	Spain
EU	European Union
Europol	European Police Office (EU)
FDA	Food and Dug Administration (U.S.)
FD&C Act	Food, Drug, and Cosmetic Act
FM	Fibromyalgia (FM)
FR	France
GABA	gammaaminobutyric acid
GHB	gammahydroxybutyric acid
HHS	Health and Human Services (U.S.)
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IEWG	International Epidemiology Work Group
INCB	International Narcotics Control Board (U.N.)

IT	Italy
LBP	Low Back Pain
LSD	D-Lysergic acid diethylamide
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MDA	Misuse of Drugs Act (UK)
MDMA	3,4-Methylenedioxymethylamphetamine (Ecstasy)
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MRP	Mutual Recognition Procedure (EU)
NDA	New Drug Application (FDA, U.S.)
NIDA	National Institute on Drug Abuse (U.S.)
NIH	National Institutes of Health (U.S.)
NP	Neuropathic Pain
OA	Osteoarthritis
OCI	Office of Criminal Investigations (FDA, U.S.)
ODS	Office of Drug Safety (FDA, U.S.)
ONDCP	Office of National Drug Control Policy (U.S.)
PMMA	N-methyl-1-(4-methoxyphenyl)-2-aminopropane
Post-op	Post-Operative
RA	Rheumatoid Arthritis
Reitox	European Information Network on Drugs and Drug Addiction (EU)
RiskMAP	Risk Minimization Action Plan (U.S.)
RMP	Risk Minimisation Plan (EU)
RMS	Reference Member State (EU)
SAMHSA	Substance Abuse and Mental Health Services Administration (U.S.)
TEDS	Treatment Episode Data Set
SWP	Safety Working Party (EMEA, EU)
UK	United Kingdom
UMC	Uppsala Monitoring Centre (WHO)
UN	United Nations
U.S.	United States
U.S.C.	United States Code (U.S.)
WHO	World Health Organisation

1. Introduction

Large parts of the population suffer from neurological and psychiatric disorders, such as pain, anxiety, depression, cognitive disorders, attention-deficit hyperactivity disorder (ADHD), obesity, or drug dependence. In the U.S. alone, approximately 100 million people suffer from acute and chronic pain (also see Table 0). Because of this potentially large market, pharmaceutical industry is in continuous search for new substances to treat neurological and psychiatric disorders.

Table 0: Prevalence of the selected acute and chronic pain conditions in 2003/2004 the U.S. and the 5 largest European markets (France, Germany, Italy, Spain, United Kingdom) (in millions)

Countries	Post-op pain	OA pain	LBP	FM pain	Cancer pain	Diab NP	RA pain
U.S.	54.2	26.0	11.6	5.0	4.1	3.8	2.3
Europe Big 5	56.3	31.2	12.8	6.7	3.0	3.4	1.7
France	11.3	5.8	2.5	1.3	0.7	0.5	0.2
Germany	15.6	8.6	3.6	1.9	0.9	0.8	0.6
Italy	10.8	6.2	3.5	1.3	0.6	1.0	0.2
Spain	7.5	4.8	1.8	0.9	0.3	0.6	0.2
UK	11.2	5.8	2.4	1.3	0.6	0.5	0.4

Diab NP: diabetic neuropathic pain, FM: Fibromyalgia, LBP: Low back pain, OA: Osteoarthritis , Post-op: post-operative, RA: rheumatoid arthritis

Source: modified from Internal Grünenthal report: Global Pain Report (2005): Key facts and market overview

Many of the substances that are suitable to treat such disorders have stimulant, depressant or hallucinogenic effects on the higher functions of the central nervous system (CNS) and thus may have an inherent tendency to promote abuse and addiction. All substances that can be associated with the development of addiction are somehow capable of producing pleasure and reward, especially when used in a manner resulting in rapid increases in brain levels of these substances (Koob, 2000).

While it is important to make efficacious medicines containing psychoactive substances available to patients who need them, it is at the same time imperative to judge their potential for abuse, i.e. their “abuse liability” and, if necessary, take special precautions to prevent abuse and diversion of these products. A sensible balance between access to useful drugs and protecting the public from the consequences and dangers of ready access to substances of abuse must be found.

1.1. Regulatory control of substances of abuse

The ambivalent nature of psychoactive substances, i.e. their potential to offer medical benefit but also to promote abuse, have been known for a long time. As a consequence an international control system was established already at the beginning of the last century to prevent the abuse of these substances and to limit their licit use to purely medical and scientific purposes (also see Bayer and Ghodse, 1999). The first control on an international level was established with the International Opium Convention signed at The Hague in 1912, which mainly focussed on

controlling the traffic of crude and processed opium and on limiting the manufacture and use of morphine to medical and other legal purposes. Opioids can thus be considered as prototypical examples of controlled substances. About one decade later, the League of Nations established the International Opium Convention (Geneva, 1925) by which international control was extended to a whole array of substances and the measures of control of abuse liable substances were more precisely defined. Today the control of abuse-liable substances is regulated by three international Conventions issued be the United Nations (UN):

- Single Convention on Narcotic Drugs, New York, 1961
- Convention on Psychotropic Substances, Vienna, 1971
- Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Vienna, 1988.

While the Conventions provide for a general framework of international control, a detailed country-by-country analysis is necessary to get a full picture of all principles that govern the control of abuse-liable substances worldwide. It should be noted that some psychoactive substances of high abuse potential have been completely banned because they offer no, or only limited medical benefit ($\Rightarrow$ illicit drugs). Others are tightly controlled but licitly available for medical purposes.

Despite tight international control, diversion and abuse of psychoactive substances still constitute major public health and social problems in the majority of countries worldwide. For details on the size of the problem of abuse of psychoactive substances, please refer to Appendix I of this thesis. Interestingly, in the U.S., which is the world's largest single market for illicit drugs (2004 INCB report: E/INCB/2004/1), abuse of prescription medicines, especially of those containing morphine, oxycodone, hydrocodone, codeine and other opioids, has become a major problem. By contrast prescription opioid abuse is not considered a major problem in the European Union (see Appendix I).

1.2. Medicinal products and substances of abuse

Three classes of substances are currently most often abused (NIDA InfoFacts, 2005). These are opioids, CNS depressants and stimulants.

1.2.1. Opioids

Opioids are used in the management of moderate to severe, acute and chronic pain. They are currently considered to be the only products that ensure adequate relief of severe pain. In addition to their pain-relieving properties, some of the drugs are also used for substitution therapy and to relieve coughs and diarrhoea.

Opioids block the transmission of pain messages and thus the perception of pain by attaching to specific proteins, the so-called opioid receptors, which are found in the cell membrane of nerve cells in the brain, spinal cord and gastrointestinal tract. Medicines that fall in this class are sometimes referred to as narcotics and include morphine, oxycodone, hydromorphone, codeine, and related drugs.

Apart form their effective analgesic properties, medicinal products containing opioids can also induce euphoria by affecting the brain regions that mediate what we perceive as pleasure. This property of opioids to induce euphoria is considered the basis for their potential to be abused.

Opioids are safe and effective drugs when used properly. However, when single large doses of an opioid are consumed, severe respiratory depression can occur that may even result in death.

According to the U.S. National Institute of Drug Abuse (NIDA, InfoFacts 2005), opioid abuse and dependence may contribute to other serious health problems including the spread of HIV or hepatitis (because of risky behaviour like needle sharing and unsafe sex), adverse cardiovascular effects, ranging from abnormal heart rate to heart attacks, liver damage. Opioid abuse may also be associated with psychiatric illness such as depression and generalized anxiety disorder (Hahesy *et al.,* 2002), and cognitive impairment (Ornstein *et al.,* 2000). In addition to these adverse medical consequences, opioid abuse and dependence is also known to contribute to severe social problems such as individual, family and community disintegration.

1.2.2. Barbiturates and benzodiazepines (CNS depressants)

Depressants of the central nervous system, sometimes referred to as sedatives and tranquilizers, are prescribed for anxiety and sleep problems, tension, panic attacks, acute stress reactions or anaesthesia (at high doses). Although the different classes of CNS depressants work in unique ways, it is through their ability to increase the activity of neurotransmitter gammaaminobutyric acid (GABA) that they produce a drowsy or calming effect that is beneficial to those suffering from anxiety or sleep disorders.
A severe risk associated with the use of CNS depressants is a rebound in brain activity after reducing or discontinuing use, potentially leading to seizures and other harmful consequences.

1.2.3. Stimulants

As the name suggests, stimulants elevate blood pressure and increase heart rate and respiration, as well as increase alertness, attention, and energy. Stimulants are derivatives of key brain neurotransmitters called monoamines, which include norepinephrine (noradrenaline) and dopamine. Historically, they were used to treat asthma and other respiratory problems, obesity, neurological and a variety of other disorders. But as their potential for abuse and addiction became apparent, their medical use began to wane. Today, stimulants are mainly prescribed for the treatment of ADHD, narcolepsy (a sleep disorder), depression that does not respond to other treatment or obesity.
After taking high doses of stimulants dangerously high body temperature or an irregular heartbeat can be observed. Cardiovascular failure or lethal seizures may be a consequence of stimulant misuse. When high doses are taken repeatedly over a short period of time, hostility or feeling of paranoia may occur. Withdrawal symptoms associated with discontinuing stimulant use include fatigue, depression, and disturbance of sleep patterns.

1.3. Market access for medicinal products containing new psychoactive substances

Before a medicinal product is approved for marketing in the U.S. or in Europe (the same holds true for many other countries/regions worldwide), the regulatory agencies (“Medicines Agencies”) in these regions will decide whether the data submitted by the applicant have adequately demonstrated that the drug has a positive risk-benefit profile under the conditions of use proposed in the product information. The job of regulatory agencies however is not only to assure that safe and effective products reach the market in a timely manner but also to monitor marketed products for continued safety after they are in use by adequate pharmacovigilance systems.

During the approval process of medicinal products containing psychoactive substances, the products' potential for abuse and misuse has to be assessed as this represents an individual and public health risk associated with these products. For medicinal products containing new psychoactive substances, regulatory control may be considered necessary to assure that the potential benefits for the individual patient and the general risks to public health are appropriately balanced: patients who require these products for treatment of their disease need appropriate access to them, while at the same time misuse, abuse and diversion of these products is limited to the extent possible. Post-marketing-surveillance for new psychoactive substances may include a re-assessment of the necessity for or efficiency of control measures such as prescription restrictions or others.

2. Issues under Examination

Many pharmaceutical companies have become global players, i.e. they develop products to be marketed worldwide. For companies developing medicinal products containing new psychoactive substances, it is important to understand what the potential implications might be.

Depending on the countries where marketing authorisation is to be sought for, there may be additional data requirements, e.g. additional animal or human studies that have to be performed to allow judgment to be made on the relative abuse potential of a new psychoactive substance as compared to known substances of abuse. There may also be additional requirements regarding post-marketing surveillance and the appropriate management of risks associated with these products.
One way to prevent or reduce the risk of abuse and diversion of medicines with new psychoactive substances is to subject these medicinal products to regulatory control. To put these medicines under control, scheduling activities need to be triggered. These activities may not be linked to the actual marketing authorisation procedures and thus may potentially delay the market entry of these products.
Once a medicinal products is subject to regulatory control, not only the provisions laid down in the general drug laws of a country apply but also those of the specific national legislation on controlled substances.
The scheduling of products is important from a general economic perspective because it may influence physician's prescribing practices and patient access to new medicinal products.

Comprehensive overviews of national and international classification systems, scheduling procedures and their potential impact on the time of market access of medicinal products are currently not available; at least they are not to be accessed publicly. The primary objective of this master thesis is therefore to compile relevant data in this area. The focus is on the two largest pharmaceutical markets, the United States and the European Union. The following topics are addressed:

- additional requirements to be covered during the development of new psychoactive substances
- national and international classification systems for scheduled substances and identification of key players in the field of abuse-liable substances, both on an international and national level
- legal provisions regarding control of psychoactive substances
- national and international scheduling activities and their potential link to marketing authorisation procedures

To avoid this study becoming too extensive, the analysis is mainly focused on the prototypical example of abuse-liable substances: opioids. Many of the statements are also valid for stimulants or CNS depressants, however, the main emphasis will be on opioids and examples will normally be taken from the field of opioids.
The complexity of the European Union (EU) is a further constraint on the present study. The EU currently is a conglomerate of 25 Member States and the legislation on controlled substances is, to a significant extent governed by purely national law. To cover the legal situation in all Member States would definitely go beyond the scope of this thesis. Therefore, the description and discussion of the legal situation regarding controlled substances will be limited to the big five European pharmaceutical markets: Germany (~ 80 million inhabitants), the United Kingdom

(~ 60 million inhabitants), France (~ 60 million inhabitants), Italy (~ 60 million inhabitants) and Spain (~ 40 million inhabitants). As is detailed in Chapter 3, this restriction will nonetheless allow a glimpse at the diversity of regulatory systems in the EU.

With all these restrictions, the current thesis can naturally only be a starting point for a broader analysis of the situation regarding the development of new drug substances with abuse potential.

3. Material, Methods and Glossary

3.1. Material and Methods used

The study of the literature on which this master thesis is based embraced:

- original legislative texts of the territories under investigation
- international and national drug surveys published by the United Nations, U.S. governmental bodies, Reitox, a network that has been established in each Member State of the European Union, the European Monitoring Centre for Drugs and Drug addiction (EMCDDA), being the central reference point for drug information in the European Union
- guidelines and other guidance documents published by the International Conference on Harmonisation (ICH), the World Health Organisation (WHO), the European Medicines Agency (EMEA), the Food and Drug Administration (FDA) and other national medicines agencies
- general publications on the European Union, on international and national drugs policy
- scientific publications on abuse liability assessment

Most of these texts were accessed via the worldwide web. Others were accessed via databases such as Medline (PUBMED) or IDRAC.
Apart from the above sources of information, material was also incorporated from interviews with people of different nationalities working for pharmaceutical companies or European regulatory agencies.

3.2. Glossary

Conceptional confusion over wording can affect proper communication. This glossary is intended to help avoid potential misunderstandings:

Abuse – misuse – non-medical use:
According to the definition of the WHO, abuse should be defined as intentional excessive drug use, be it persistent or sporadic, which is inconsistent with or unrelated to the acceptable medical practice. A similar definition is used in the European Directive 2001/83, as amended. According to the WHO, misuse and non-medical use can be considered as synonyms of abuse.

Abuse potential/liability:

The abuse potential is the ability of a CNS-active drug to produce a positive psychic effect which is viewed as correlated with or predictive of the risk of dependence. The abuse liability of a drug does not only capture its abuse potential but also other factors, e.g. ease of synthesis, drug abuse and diversion history and thus reflects the likelihood of abuse.

Drugs – substances - preparations -medicinal products
These different terms will be used throughout the entire thesis. The term “drug” is used to designate a substance in pure form or in a preparation. “Drug” does not necessarily imply its use for medical purposes nor should it be understood as only referring to psychoactive substances with addictive properties. Medicinal products are preparations of substances with an accepted medical use.

Drug Dependence:
The simplest explanation for the term dependence is a state in which the individual has a need for repeated dosing of a drug to feel good or to avoid feeling bad. It is characterised by one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
This is consistent both with the general public understanding and the more sophisticated definition used by the WHO Expert Committee on Drug Dependence (ECDD) and the International Diagnostic Classification of Diseases (ICD-10: *Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines.* Geneva. World Health Organisation, 1992). Determinants and problematic consequences of drug dependence may be biological, psychological or social, and usually interact.

Narcotic
Narcotic is both a legal as well as a medical term. The legal term may differ in meaning depending on the context it is used in. On international level, the term "narcotic" refers to all substances covered by the 1961 UN Convention including opiates, opioids, marijuana and cocaine. In German legal texts, the term "narcotic" applies to all substances covered by the Schedules (Anlagen I-III) annexed to the law on controlled substances and thus comprises all substances listed in the 1961 and the 1971 UN Conventions. Medically, the term narcotic describes a group of active substances that are suitable to produce general anaesthesia. General anaesthetics not only include opioids but also ethers, halogenated hydrocarbons, barbiturates (plain or in combinations) and other substances such as propofol, droperidol or ketamine (see ATC code N01A Anaesthetics, General)

New psychoactive substances
The term is used to describe new active substances with effects on higher functions of the central nervous system which may pose a threat to public health comparable to the substances controlled by the 1961 United Nations *Single Convention on Narcotic Drugs* or the 1971 United Nations *Convention on Psychotropic Substances*.

Opiate - Opioid
The term "opiate" refers to substances that are produced from the poppy plant, such as e.g. codeine and morphine. Opioid is a scientific term that refers to both natural and synthetic drugs whose effects are mediated by specific receptors in the central and peripheral nervous systems. Opioids include codeine and morphine, but also oxycodone and fentanyl.

Schedules
Many countries define a list of drugs that are subject to regulatory control. This list is often subdivided in sub-lists combining substances of similar abuse potential or of similar chemical structures. The listings of controlled substances are generally referred to as Schedules.

4. Results & Discussion

4.1. Additional data requirements for new psychoactive substances

4.1.1. General methods used to assess the abuse liability of drugs

The abuse potential of new psychoactive substances can be tested both in the preclinical and clinical setting. Abuse liability assessments are usually multidisciplinary approaches ranging from animal pharmacology through human laboratory tests to postmarketing surveillance (for review see Balster and Bigelow, 2003). Animal and human studies have generally been shown to yield similar findings and both seem to agree with the population profiles of abuse (Brady, 1991; Griffiths and Balster, 1979; Johanson and Balster, 1978).

4.1.1.1. Abuse liability assessment in animal studies

In pre-clinical work, the techniques used include testing the pharmacological profile, drug discrimination testing, self-administration and physical dependence testing (Ator and Griffiths, 2003; Balster and Bigelow, 2003; Brady *et al*., 1990; Johanson, 1990). Prediction of the abuse liability of a new psychoactive substance is carried out by evaluating the results across several measures.

4.1.1.1.1 Pharmacological profile

When developing a new drug for a specific therapeutic indication, its pharmacological characteristics are usually evaluated in comparison to prototypic drugs of that class, the assumption being that the degree of concordance is an indication of the level of similarity. A similar pharmacological profile to prototype drugs of a class is not only considered to be a measure for therapeutic utility but also for abuse liability.
The types of procedures used to evaluate the pharmacological profile of a drug are largely drug class-specific. Studies may include evaluations of receptor binding, activation or inhibition of neurochemical effects. For certain types of psychoactive drugs, also behavioural procedures exist which are considered animal models of a therapeutic action. For instance, increases in the latency of paw lick or of jumping of a mouse placed on a hot-plate are considered a measure of analgesia.

4.1.1.1.2 Drug discrimination testing

Drug discrimination testing in animals can be considered very useful in assessing the pharmacological equivalence between reference drugs and test drugs. In a typical drug discrimination experiment in laboratory animals, differential reinforcement procedures are used to strengthen one response (e.g. pressing the right lever) after a certain drug dose is administered and a different response (e.g. pressing the left lever) after the drug vehicle alone is administered. When animals learn this discrimination and a dose-response function has been generated, other drugs can then be tested to determine whether they share similar discriminative stimulus effects. This procedure thus permits to study not only the discriminability of individual drugs, but also of the range of drugs that will occasion the same response as the training drug. Drug discrimination procedures have proven valuable in the development of opioid analgesics, but their validity for other classes of compounds is not yet as well established.

It should be recognised that the finding that a drug has discriminative stimulus effects is not itself evidence for an abuse potential since many non-abused drugs can serve as discriminative stimuli. Rather the principal use of this methodology is to predict whether drugs will produce subjective effects similar to known drugs of abuse.

4.1.1.1.3 Self-administration testing

The extent to which animals self-administer a psychoactive drug is considered to be a measure of its reinforcing properties. The procedures most commonly used are direct access to the test compound (via automatic oral-drinking systems) or instrumental lever-pressing by animals with intravenous and/or intragastric catheters. Substitution procedures (training of self-administration using a drug of known reinforcing properties) are most commonly used for evaluating new compounds, but conditions of unlimited access in drug-naïve animals are also applied. Self-administration testing with nonhuman primates currently seems to be of more relevance in abuse liability assessments than testing in other species, although a wealth of data on self-administration testing has been done especially with rodents.
Self-administration has perhaps the greatest validity as an animal test of abuse potential and is widely used for this purpose.

4.1.1.1.4 Physical dependence testing

Physical dependence is a condition produced by repeated administration of a drug and revealed by the occurrence of a withdrawal symptom when drug administration is stopped. To demonstrate a true withdrawal syndrome, it must be demonstrated that withdrawal signs disappear by re-administration of the drug. Physical dependence testing differs for different types of psychoactive substances. Fairly standardised models have been developed for opioids, whereas methodologies for assessing the physical dependence of CNS depressants seem to be far less standardised.
To assess the physical dependence of opioid-type drugs, a so-called single-dose substitution test is usually conducted first, which is designed to determine to what extent (if at all) a test drug is able to suppress withdrawal signs in opioid-dependent animals that have been denied their usual dose of morphine. Positive results on this test do not however provide information in terms of the dose and duration of exposure required for physical dependence to the test drug to develop. Therefore, additionally, direct assessment of dependence will become necessary once the test compound has been shown to be able to produce morphine-like effects. This is done in animals that receive the test drug chronically and where administration is abruptly stopped or which suffer “precipitated withdrawal” by application of an antagonist. Direct assessments are more tedious as test drugs have to be administered over extended periods of times. Typical measures of opioid dependence include autonomic signs, somatomotor effects and behavioural changes.

4.1.1.1.5 Other methodologies

Other pre-clinical tests such as e.g. drug tolerance and cross-tolerance testing, preference conditioning, locomotor activation, or biodisposition research, are less frequently used in abuse liability assessments and most often standardised procedures have not been developed for these tests.

4.1.1.2. Abuse liability assessment in human studies

Regarding abuse liability assessment in humans, there is currently one "gold standard" approach: the classic acute dose-effect comparison study in volunteers with histories of drug abuse (Griffiths *et al.*, 2003). Evaluations are best performed in subjects with extensive histories of polydrug abuse, including abuse of drugs from the same pharmacological class as the test drug. One reason for this choice of patient population is that these patients based on their experiences can provide meaningful ratings in the laboratory such as estimates of drug high, estimated drug value on the street, categorisation of overall drug effects as being similar to specific classes of known drug of abuse. Furthermore, they represent the population at greatest risk for illicit use of the test drug and they have been shown to provide extremely low false positive rates (measured by response to placebo administration) as well as false negative results as compared to people without drug abuse history. Typically human abuse liability studies are conducted on an inpatient basis (ideally on a closed residential drug abuse pharmacology research unit), are double-blind and have a cross-over design in which each subject (n = 10-14) is tested with all test conditions, i.e. acute administration of

- placebo (negative control)
- usually 3 doses of the test drug
- usually 3 doses of the reference drug (positive control) which has a known abuse potential (preferably a drug from the same pharmacological class)

As the formulation can have a significant role in the abuse liability of prescription drugs (formulation may affect the pharmacokinetics and thus alter the subjective effects), it is important to use the final dosage form intended for marketing (Mansbach *et al.*, 2003). Three types of outcome measures are usually considered in human abuse liability studies. These are measures most directly related to predicting the likelihood of abuse (e.g. ratings of drug liking, disposition to take the drug again, street value and drug vs. money choice behaviour), measures that should be considered when interpreting likelihood of abuse (e.g. drug identification, subject-rated side effects and mood changes) and other concurrent measures of drug effect (e.g. subject-rated strength of drug effect, behavioural and cognitive performance, observer-rated measures, physiological effects). A battery of standardised questionnaires is used repeatedly over time to assess the profile and time course of subjective effects. For opioid drugs, these questionnaires usually include selected scales of the Addiction Research Center Inventory (ARCI) designed to detect euphoric effects (MBG scale), sedative effects (PCAG scale) and dysphonic and somatic effects (LSD scale), plus drug class-identification questions, a checklist of symptoms related to opioid use and a rating of liking.
A human abuse liability trial is most appropriate to predict the likelihood of abuse by recreational users and the extent of drug diversion and illicit street sales if the test drug became widely available to the drug abuse community. It is less clear whether it can also predict the likelihood of misuse in patient populations receiving the drug for therapy, though many believe this to be the case (Griffiths *et al.*, 2003). Failure to detect a signal in a drug abusing population may be good evidence of lack of abuse liability in normal (i.e. less vulnerable) populations; a positive signal however is not sufficient to conclude that there is a risk of abuse in a wider population.

Further information relevant to the abuse liability of medicinal products containing psychoactive substances can also be obtained from "normal" clinical trials. However, at present, subjective effects are generally not collected systematically in clinical trials, although adverse events are carefully tracked. While it is known that each additional assessment or procedure in a trial adds

in terms of time, cost and patient burden, some minimal modification in the trial scheme to systematically gather information about subjective effects is considered fairly easy for routine trials (Brady *et al.*, 2003). Medication adherence data, i.e. pill counts and patient self-report may be of considerable use for assessing both efficacy and potential for abuse liability (Brady *et al.*, 2003). In addition, the emergence of withdrawal or drug discontinuation-related symptoms could also be more systematically explored (Brady *et al.*, 2003).

Apart from human abuse-liability studies and general information obtained from clinical trials, post-marketing surveillance may provide excellent insight in the abuse liability of a substance in a "real-world" setting (Arfken and Cicero, 2003). Assessment must however be based on rates (relative to exposure) of adverse events not on absolute number of cases.

Taking all the above-said into account, it is important to note that epidemiologic experience, i.e. the extent of actual abuse, is the ultimate criterion that all other approaches just try to predict.

4.1.2. Additional data requirements in the U.S.

According to the *Code of Federal Regulations* (Title 21, Part 314.50), the risk for misuse, physical dependence and addiction of a drug must be specifically evaluated by FDA whenever a marketing authorisation application for a new psychoactive substance is submitted in the U.S. As a consequence, the applicant has to provide the "U.S. Medicines Agency" (*Food and Drug Administration*, FDA) with all data pertinent to the abuse of a CNS-active drug, including data on overdoses and with a proposal for scheduling under the *Controlled Substances Act* (CSA, Title 21, United States Code (U.S.C.) § 801 et seq.). The applicant must organise and identify the sections of an application dossier related to abuse liability in a manner that facilitates FDA review of this matter.

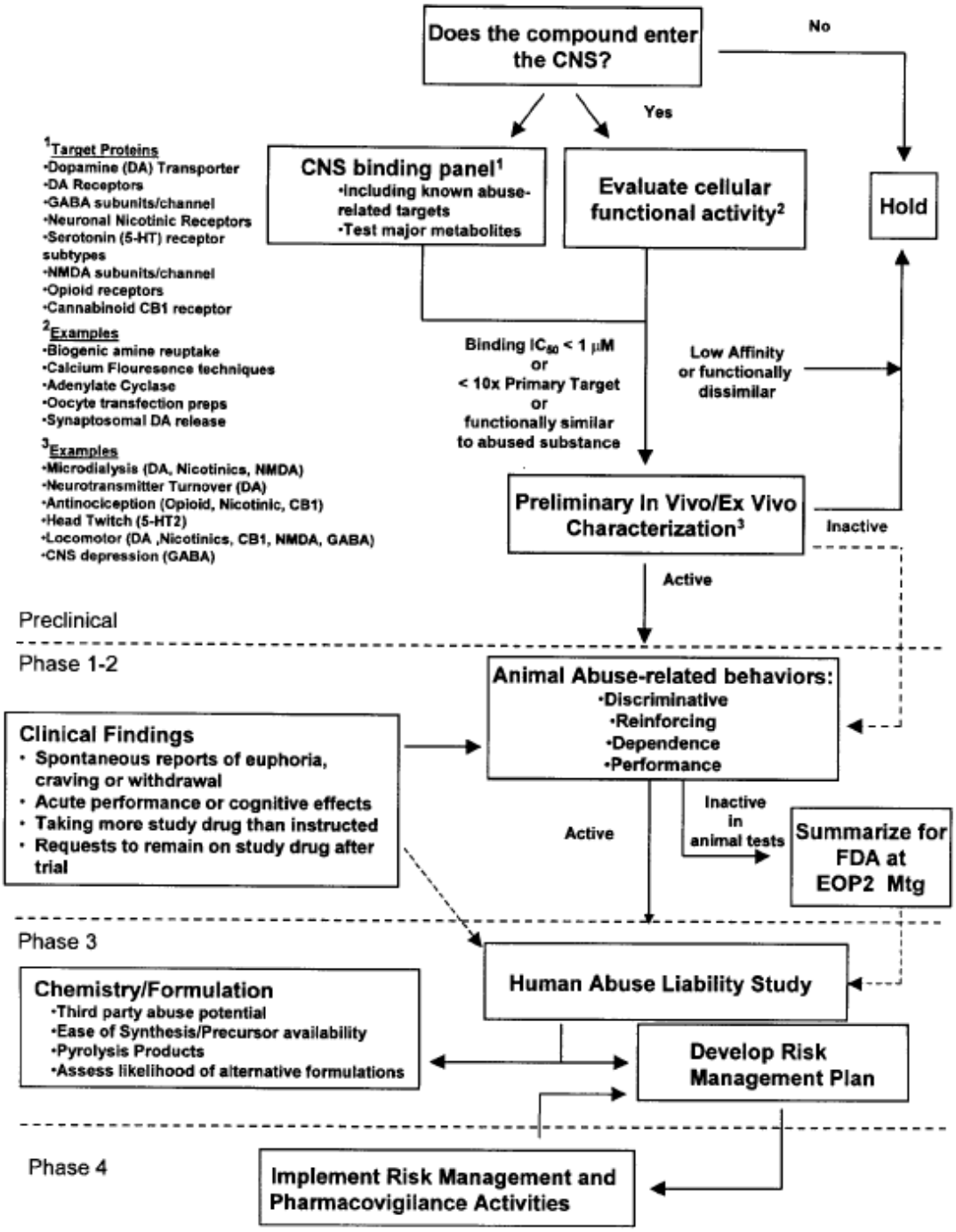
Specific guidance on abuse liability assessment was provided by FDA in 1990 in the form of the *Guidelines for Abuse Liability Assessment*. This document was periodically revised by the FDA until distribution was stopped in 2002. According to these outdated *Guidelines*, abuse potential has two aspects: the likelihood of nonmedical self-administration and the likelihood of adverse consequences. The *Guidelines* recognised that a wide array of both nonclinical as well as human assessment procedures was required to provide a full picture of the abuse-liability of a CNS-active drug. They indicated that human data carried more weight than animal data and that real-world epidemiological data had more weight than laboratory data. Although not longer in effect, many of the aspects covered by these *Guidelines* still seem to reflect the current view of FDA on abuse liability assessment as can be seen from various recent presentations by FDA representatives (e.g. Calderon, 2003; Leiderman, 2003; Klein, 2005). According to FDA, abuse liability assessments should include an overview on drug's chemical and pharmacological characteristics (chemical structure and class, its profile of biochemical and pharmacological activity), animal behavioural studies (self-administration, drug discrimination, physical dependence and tolerance), evidence for certain adverse event profiles form clinical trials as well as specific assessment of subjective effects in a human abuse liability study. The assessment should take the route of administration and the dosage form into account as these may affect the abuse liability of a product, by influencing the pharmacokinetics or pharmacodynamics or the potential for diversion from appropriate use. The available abuse liability assessment data influences product labelling and the scheduling recommendations/decisions.

FDA's general expectation on data requirements for abuse-liable substances may go beyond the actual development phase (i.e. pre-marketing phase) of a new drug. In their marketing

authorisation applications, pharmaceutical companies are required to include post-marketing surveillance and in certain cases also risk minimisation strategies. These requirements are detailed in a set of guidances published by FDA in March 2005. The guidances are on *Premarketing Risk Assessment*, *Good Pharmacovigilance Practices and Pharmacoepidemilogic Assessment*, and *Development and Use of Minimization Action Plans*. As part of risk management, FDA requires applicants to provide a pharmacovigilance plan that foresees collection of specific information after the product is launched to improve the speed and sensitivity of detecting suspected safety problems. Actions to minimise risks however may go beyond providing an informative package insert and may lead to what is called a risk minimisation action plan or RiskMAP. A RiskMAP is a strategic safety program designed to decrease known product risks by one or more interventions, such as specialised education or restrictions on typical prescribing, dispensing, or use. The RiskMAP is to be implemented at the time the drug is marketed.
To date RiskMAPs are largely customised programs, but with growing experience consistent approaches are being sought for the future. In response to concerns of prescription opioid abuse in the U.S. (see Appendix I), FDA explicitly states in its Guidance to Industry on *Development and Use of Risk Minimization Action Plans* (March 2005) that opioid drugs are associated with significant risk of overdose, abuse and addiction. It is thus FDA's expectation that pharmaceutical companies submit a RiskMAP together with new drug applications for potent opioids.

Taken together, abuse liability assessments made by the FDA are based on a composite profile of a drug's chemistry, pharmacology, clinical manifestations, similarity to other drugs in a class, and the potential for public health risks following introduction of the drug to the general population. FDA requires preclinical, clinical, and if available epidemiological data to determine whether the product under review requires further abuse liability data, scheduling under the CSA. Additionally, especially for opioids, a RiskMAP designed to reduce abuse, overdose, or diversion is considered an essential component of new drug applications. A potential algorithm for abuse liability assessments that are required to obtain market access in the U.S. was suggested by Mansbach *et al*. (2003, s. Fig. 1).

Fig. 1 **Potential algorithm for use in abuse liability assessment.** Dotted lines indicate alternative pathways for evaluation. EoP2 = End of Phase II (Source: Mansbach *et al*., 2003)



4.1.3. Additional data requirements in the European Union

Directive 2001/83/EC *on the Community Code Relating to Medicinal Products for Human Use*, as amended, does not mention any obligation of European regulatory agencies to specifically assess the risk for misuse, physical dependence and addiction of a new psychoactive drug for which marketing authorisation is sought. However, even if not required by law, abuse liability

assessments can be expected to influence the risk-benefit evaluations that govern the drug approval process.

Specific regulatory requirements in the area of abuse liability assessments were first formulated for the European Union in April 2005, when a draft guideline on this topic was released for consultation by the Safety Working Party (*Guideline on the Non-Clinical Investigation of the Dependence Potential of Medicinal Products*, EMEA/CHMP/SWP/94227/2004). This draft guidance emphasises the need for data from well-designed animal studies to provide information on the dependence potential of new psychoactive substances. According to this guidance, the primary goal of these animal studies should be to provide reliable information and sound instructions to the prescriber and the patient. It is also mentioned that animal data on the dependence potential of a psychoactive drug would be included in the risk-benefit assessment and aid regulatory decision-making regarding the conditions of the marketing authorisation. Although not explicitly mentioned, one condition might be the need to subject the new product to regulatory control.
According to the draft guidance, animal studies on the dependence potential should be conducted for psychoactive substances with a new mechanism of action and for those belonging to classes known to cause dependence, but not normally for compounds which act similar to compounds from a class with a documented absence of dependence potential. A two-tiered approach is recommended: The first tier comprises *in vitro* studies on receptor binding, functional assays at cellular level, characterisation of effects as agonistic or antagonistic or both as well as *in vivo* studies in neuropharmacological models to confirm the binding and functional properties observed *in vitro*. Further investigations might not be necessary when:

a) the type and extent of dependence potential would already be obvious from the first tier (e.g. for a full μ-opioid receptor agonist)
b) no interaction with relevant molecular targets occurs and *in vivo* investigations do not point towards a dependence potential and the compound does not have a novel mechanism of action.

In the second tier, specific behavioural models should be investigated to assess the withdrawal syndrome, drug discrimination and the reinforcing properties of the compound. For methodological aspects, the guideline specifically refers to two recent review articles (Ator and Griffiths, 2003; Balster and Bigelow, 2003).
All data obtained from these animal studies should be made available at the time of the marketing authorisation application. The non-clinical data obtained following this guideline should be integrated in a risk assessment of dependence potential that also takes into account important aspects of the dosage form and of pharmacological data.

It is important to note that European Union regulatory agencies do not currently require human abuse liability studies to be performed. The overall abuse liability assessment should however address the potential for abuse of a new drug either in the clinical or non-clinical setting.

While Directive 2001/83/EC, as amended, does not mention an obligation of regulatory agencies to specifically assess the risk for misuse, physical dependence and addiction of a new psycho-active drug for which marketing authorisation is sought, it does however request applicants to provide a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which is suggested to be introduced upon marketing (Art. 8(3)(ia)). This requirement is specified in more detail in the *Guideline on Risk Management Systems for Medicinal Products for Human Use* (EMEA/CHMP/96268/2005) which came into effect in November 2005. Risk management systems are considered important because information on the

safety of a product is generally only limited at the time of authorisation. The *Guideline on Risk Management Systems* describes the circumstances under which risk management plans (RMPs) should be provided and how they should be presented. EU-RMPs consist of two parts: Part I comprises a safety specification (summary of the safety profile according to ICH-E2E: *Note for Guidance on Planning Pharmacovigilance Activities* CPMP/ICH/5716/03) and a pharmacovigilance plan based on the safety specification. Part II contains an evaluation of the need for risk minimisation activities and in case there is a need for non-routine risk minimisation strategies as risk minimisation plan. EU-RMP are generally required for all marketing authorisations for products containing a new active substance, i.e. also for new psychoactive drugs. It is an explicit requirement of the EU-RMP to consider the potential for misuse for illegal purposes when evaluating the need for risk minimisation activities. Controlled distribution or limited pack sizes should be discussed as a potential mitigation of diversion and misuse. With the introduction of the EU-RMP, pharmaceutical companies are thus required to formulate recommendations whether or not new psychoactive substances should be subjected to regulatory control.

4.1.4. Role of abuse liability assessments

Abuse liability assessments can be considered an important component in the development of psychoactive substances. They are important for several reasons:

- *for the selection of candidate molecules*
  Preclinical testing always forms an important basis on which pharmaceutical companies select promising candidates or to deselect less promising ones[1]. Abuse liability assessment in animals can contribute already at an early stage of development to strategic decisions on how and whether to proceed with development of a new psychoactive candidate drug. Compounds or preparations tested for abuse liability are often drugs that are being developed to "replace" therapeutically important drugs of abuse. They will thus be compared with existing drugs regarding their therapeutic value, side effect profile, and abuse liability. If for example preclinical testing showed that a new drug did not offer a therapeutic advantage as compared to existing drugs but exhibited a considerably higher abuse potential, this might lead to halting further development.

- *to support marketing authorisation procedures*
  By law, abuse liability studies are an integral part of marketing authorisation applications in the U.S. Here not only animal but also human abuse liability studies are required. In the European Union, requirements for reliable data on the dependence potential of psychoactive substances have only recently been formulated. Focus is currently only on animal studies.
  Abuse liability assessment will also help to set up risk minimisation plans that are required in both the U.S. and the European Union for new substances of abuse potential.

- *to support scheduling decision*
  In the U.S., abuse liability data provided with the marketing authorisation application forms the basis for scheduling decisions (i.e. decisions on the necessity of a new psychoactive drug to be brought under regulatory control, also see Chapter 4.3.2.2). Likewise in Europe, scheduling actions may result from marketing authorisation

[1] Studies in laboratory animals can be done relatively early in development than in studies in volunteers or patients. In addition, greater dose ranges and more extended administration periods can be used.

application procedures. The new EU-RMP clearly requires sponsors to formulate their position towards the necessity of regulatory control of a new psychoactive drug.

- *to provide information to physicians and patients*
  Beyond the above mentioned regulatory requirements, a compelling reason to perform comprehensive abuse liability assessments in the process of the development of new psychoactive substances is to be able to provide information on appropriate use and on the dependence potential of drugs to the prescriber and the patient. When physicians are not aware of all risks associated with a psychoactive drug, inappropriate prescribing behaviour may result. This could have negative effects on public health and eventually impact i.e. on sales figures and image of pharmaceutical companies.

4.1.5. Conclusions

For globally acting pharmaceutical companies, the regulatory requirements in the key markets of interest, mostly the U.S. and the European markets, have to be taken into account. This means that in most cases, the broader U.S. requirements on abuse liability assessments have to be fulfilled.

As abuse liability assessments during development become increasingly important in regulatory decision-making worldwide, it is important to identify more than it has been done so far an accepted battery of core testing methods that are used in abuse liability studies with animals and humans. There is also a critical need to develop post-marketing research methodology, an area which is currently underdeveloped but seems to have come into focus both in the U.S. and the European Union. This would be helpful for pharmaceutical companies in designing their development programs, avoid delays in the market access of new psychoactive substances and make cost forecasts easier.

4.2. Classification and control of psychoactive substances

In the following, the classification of psychoactive substances and the applied levels of regulatory control are described both on international and national level. Key knowledge in this area is summarised and presented in form of a comparative tabulated analysis.

4.2.1. Supra-national regulations

4.2.1.1. International regulatory framework

4.2.1.1.1 Scope of international provisions

Three UN conventions currently form the basis for international drug policy. These are the *Single Convention on Narcotic Drugs* (1961), as amended, the *Convention on Psychotropic Substances* (1971), as amended, and the *Convention against Illicit Trafficking in Drugs and Psychotropic Substances* (1988), as amended. The 1988 UN Convention is intended to minimise the diversion of precursor chemicals used in illegal drug manufacture and is not be further reviewed here.

As of November 2004, the number of parties to the 1961 UN Convention stood at 180 (out of a total of 192 states), and the number of parties to the 1971 UN Convention stood at 175 (INCB Report 2004). This means that most countries worldwide, among them the United States and all EU Member States, have committed themselves to limit the production, manufacture, possession and use of the drugs specified in the UN Conventions to medical and scientific purposes and to actively pursue the fight against illicit drug trafficking

4.2.1.1.2 Classification and control according to UN Conventions

About 250 individual substances are listed in the schedules annexed to the 1961 and the 1971 UN Conventions. The purpose of the listings in the UN Conventions is to control and limit the use of these substances according to a classification of their therapeutic value, risk of abuse and the health dangers associated with their abuse. Different drugs are assigned to different listings, so-called “Schedules” which ultimately determine the level of control to be applied to a given drug. It is of utmost importance to note that the schedules contain listings of individual chemical substances (and/or preparations) and not chemical or pharmacological classes or families of substances. This means that a specific substance must be individually mentioned in at least one of the listings to fall under the control of the UN Conventions.

Narcotic substances are classified and placed under international control by the 1961 UN *Single Convention on Narcotic Drugs*, as amended. Its annex, the so-called "Yellow List" classifies narcotic drugs in four Schedules (see Table 1). Psychotropic substances are classified and placed under international control by the 1971 UN *Convention on Psychotropic Substances*. Like the 1961 UN Convention, the annex to the 1971 Convention, the "Green List", classifies psychotropic substances in four Schedules (see Table 2).

This is however where the similarity between the Conventions already ends. The ordering of the Schedules in the two UN Conventions is, for example, not comparable: In the 1961 UN Convention, Schedule IV is most restrictive whereas it is least restrictive in the 1971 UN Convention.

Table 1: Classification of narcotic drugs according to the annex of the 1961 *Single Convention on Narcotic Drugs* ("Yellow List")

Schedule	Harmfulness	Degree of Control	Examples of listed substances
NI	• high risk of abuse	**Very strict** subject to all measures of control applicable to drugs under the 1961 UN Convention (Art 2.1)	cannabis and its derivatives cocaine heroin opium methadone, morphine, hydromorphone
NII	• relatively low risk of abuse • normally used for medical purposes	**Less Strict**	codeine, dihydrocodeine, propiram, dextropropoxyphene
NIII	Certain preparations of substances listed in Schedule II, as well as certain preparations of cocaine: • no risk of abuse	**Lenient**	preparations of codeine, dihydrocodeine, propiram
NIV	• most dangerous substances of those already listed in Schedule I • particularly harmful • extremely limited medical and therapeutic value	**Very strict** (Art. 2.5b: complete ban on "the production, manufacture, export and import of, trade in, possession of, use of any such drug except for amounts which may be necessary for medical and scientific research "	Cannabis and cannabis resin heroin

Source: European Legal Database on Drugs (ELDD), Classification on controlled drugs

Table 2: Classification of psychotropic substances according to the annex of the 1971 *Convention on Psychotropic substances* ("Green List")

Schedule	Harmfulness	Degree of Control	Examples of listed substances
PI	• high risk of abuse • especially serious threat to public health • very little or no therapeutic value	**Very strict** use is prohibited except for scientific or limited medical purposes	lysergide (LSD), MDMA (ecstasy), mescaline, psilocybine, tetrahydrocannabiol
PII	• risk of abuse • substantial threat to public health • low or moderate therapeutic value	**Less strict**	Amphetamines and amphetamine-like stimulants
PIII	• risk of abuse • substantial threat to public health • moderate to high therapeutic value	**These substances are available for medical purposes.**	barbiturates (incl. amobarbital), buprenorphine
PIV	• risk of abuse • smaller but still significant threat to public health • high therapeutic value	**These substances are available for medical purposes.**	tranquilisers, analgesics, narcotics, (e.g. allobarbital, diazepam, lorazepam, phenobarbital, temazepam)

Source: European Legal Database on Drugs (ELDD):, Classification on controlled drugs

In many cases there are only historical reasons why a substance is classified under one and not the other Convention. Cocaine and cannabis e.g. are stimulants and do not really have narcotic effects but are nevertheless controlled under the 1961 UN Convention. Delta-9-tetrahydrocannabinol, the main active principle in cannabis, exhibits the same perception-altering effects possessed by cannabis but is covered by the 1971 UN Convention.

4.2.1.1.3 Traditional opioids in the international scheduling system

According to the UN international scheduling system, most opioids (e.g. morphine, methadone, pethidine etc.) are classified under Schedule I of the 1961 UN Convention. Codeine and dextropropoxyphene are classified under Schedule II of the same Convention. By contrast, buprenorphine and pentacozine are currently scheduled under Schedule III of the 1971 UN Convention. Tramadol, oripavine and the well-known opioid antagonists naloxone and naltrexone are currently not under international control, i.e. they are neither classified under the 1961 nor the 1971 UN Convention.

4.2.1.1.4 Levels of control

The UN Conventions provide for quite a number of different control measures. For the purpose of this master thesis, the main focus is not on penalties for illicit trafficking but rather on provisions for licit trafficking and supply to patients, i.e. on those control measures that are most likely to have an impact on the marketing and availability of medicinal products containing new psychoactive substances. It should be noted that the below presentation of control measures (Tables 3A, 3B, and 3C) is by no means exhaustive. It will however serve as a basis for a comparative analysis of international provisions and their national implementation in the countries that are within the scope of this thesis.

It should be noted that extensive record-keeping requirements are foreseen for all transactions involving controlled substances (Art. 11 of 1971 UN Convention). Records should be preserved for at least 2 years. The entry, exist and use of each amount of controlled drug have to meticulously recorded and annual statistical returns have to be provided to the International Narcotic Control Board (INCB) on special forms (Art. 13 of 1971 UN Convention, Art. 16(4) of 1971 UN Convention). The aim of these records is to balance the demand and supply in order to reduce diversion to the extent possible.

Furthermore, the Parties to the Conventions are required to furnish the Secretary General with information on important changes in their national laws and regulations, significant developments in the abuse and illicit trafficking of psychotropic substances, and on new trends observed.

Relevant bodies on international level are the Commission on Narcotic Drugs (CND) for decision-making in the field of the Conventions, including supervision of the implementation of its provisions (also see 3.1.1) and the INCB as an independent quasi-judicial control body, also responsible for the preparation of annual reports on the drug abuse situation worldwide. Furthermore the Secretary-General of the United Nations plays an important role in the information exchange.

Table 3A: Different measures of international control relating to manufacture, domestic and international trade for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
General prohibition	Art. 2(5)[1]	• Drugs in Schedule IV should be subject to most severe control and production, manufacture, export and import, or trade in, possession or use may even be prohibited by Parties if considered necessary to protect public health an welfare	NIV
	Art.7[2]	• all use of drugs in Schedule I should be prohibited except for scientific and very limited medical purposes and require special license	PI
Authorisation by license required (general)	Art. 29, 30[1] Art 8(1)[2]	• manufacture, trade (incl. import & export) and distribution require license • manufacture, trade (incl. import & export), distribution require license or similar control measures	NI-NIV PII, III, IV
Authorisation by license required (international trade)	Art. 31[1] Art. 12[2]	• - separate import/export authorisation required for each shipment - format: to be established by CND - issuance of an export authorisation always requires an import authorisation issued by competent authority of importing country	NI-NIV PI, PII
		• declarations in triplicate to be used for international trade	PIII
	Art. 13[2]	• Parties may prohibit import into their territory of one or more substances but have to notify all other countries and UN about prohibition	PII, III, IV
	Art. 31[1]	• limits of total estimates must not be exceeded	NI-NIV
Balancing demand & supply	Art. 12, 19[1]	• International estimate system established: Parties to inform INCB each year of quantities of drugs to be consumed, to be used for manufacture of other drugs, quantity of stocks, approximate quantity of opium produced and quantities of synthetic drugs manufactured • Any supplementary estimates during a year require explanation	NI-IV
	Art. 21, 21 bis, 22, 24[1]	• Limitation of manufacture and importation (incl. special limitations for opium)	

CND Commission of Narcotic Drugs
INCB International Narcotics Control Board
UN United Nations
[1]UN Single Convention on Narcotic Drugs, 1961, as amended
[2]UN Convention on Psychotropic Substances, 1971, as amended

The main objective of the 1961 and 1971 UN Conventions was to create an international control system to monitor the production of narcotic and psychotropic drugs, prohibiting the use of certain substances unless explicitly permitted by national authorities. Basically under the Conventions any use, possession, production etc. of scheduled substances is forbidden, except when exclusively intended for "medical and scientific purposes" (Art. 4c 1961 UN Convention, Art. 5.2 1971 UN Convention). From the preambles of the 1961 and 1971 UN Conventions, it is clear that their intention is to reduce abuse of certain substances but to ensure at the same time

the availability of these substances to relieve patients' suffering. This means while building a system based on a general prohibitive approach, the regulators were concerned with allowing the availability of some of those substances to be used in therapy.

Table 3B: International provisions for prescriptions / legal classification of supply of controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control	Art. 30[1] Art. 9 (1)[2]	• to be supplied or dispensed to medical prescription only	NI, II, III, IV PII, III, IV
Form of prescriptions	Art. 30[1]	• official forms may need to be used; to be issued as counterfoil books by national competent authorities	NI-IV
Provisions related to supply on prescription	Art. 9 (2)[2]	• number of refills, duration of validity should be nationally regulated to protect public health and welfare	PII, III, IV

[1]UN Single Convention on Narcotic Drugs, 1961, as amended
[2]UN Convention on Psychotropic Substances, 1971, as amended

Table 3C: Further provisions, including reference to the relevant legal basis

Packaging & labelling	Art. 10[2]	• interior package may be required to bear red band • directions of use, incl. cautions and warnings to be indicated where practicable	NI, II, III, IV PII, III, IV
Safe custody		• not regulated	
Samples		• not regulated	

[1]UN Single Convention on Narcotic Drugs, 1961, as amended
[2]UN Convention on Psychotropic Substances, 1971, as amended

4.2.1.2. Classification and control system in the European Union

4.2.1.2.1. Legal framework relating to controlled substances and preparations

As will be discussed in detail below, Member States of the European Union (EU) vary quite considerably in their legislation on the classification of controlled substances and the control measures to be applied. Despite the fact that the policy on controlled substances is primarily the responsibility of individual member states, the Council of the European Union and the European Commission have started taking actions in certain matters related to drugs of abuse. Cooperation between the Member States on drugs of abuse has increased as a result of the new powers conferred on the Community by the *Treaty on the European Union* (Maastricht Treaty, 1992). To date such cooperation is however mainly limited to enforcement actions in the fight against diversion and misuse drugs. Whatever the European Union does in this area, it has to follow the principles of subsidiarity, i.e. must be complementary to actions taken by national governments (Boeckhoat van Solinge, 2002).

The establishment of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 1993 (Regulation (EEC) No 302/93) can be considered an important milestone towards a more harmonised EU policy on controlled drugs. The Centre became operational in 1995. Its objective is to provide the Community and its Member States with objective, reliable

and comparable information concerning drugs and drug addiction and their consequences at a European level. The statistical, documentary and technical information processed or produced is intended to help the Community and the Member States when they take measures or decide on actions in their respective areas of competence. To be able to fulfil its purposes, the Centre has at its disposal the *European Information Network on Drugs and Drug Addiction* (Reitox), a computer network forming the infrastructure for collecting and exchanging information and documentation.
Apart from the establishment of a European Monitoring Centre, it is also worth mentioning that the European Union has appeared in the arena of international drugs control by becoming a Party to the UN Conventions and by formulating European positions on international control matters. The influence of the European Union on matters of controlled substances is likely to be growing in the future and may eventually leave the Member States less and less autonomy when devising domestic policies related to controlled drugs.

4.2.1.2.2. Classification of controlled substances

All European Member States are Parties to the UN Conventions. With the exception of precursor chemicals (the 1988 UN Conventions is currently implemented by Regulation (EC) 273/2004), there is no harmonised classification system for controlled substances at the level of the European Union but rather only national classification systems that are all based on the 1961 and 1971 UN Conventions.

4.2.1.2.3. Levels of control

There is likewise no harmonised system of control measures available in the European Union for controlled substances (except for precursor chemicals). As described in Table 4, there are only some harmonised provisions resulting from the legal aspects governing the marketing of medicinal products for human use. Despite the lack of a harmonised European classification and control system, the EU can exert some influence on decisions to control new psychoactive substances by making use of a provision called a "Joint Action". The relevant Joint Action (97/396/JHA) and its update by Council Decision 2005/387/JHA will be described in more detail in Chapter 4.3.3.1.

Table 4: European provisions for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control	Art. 70[1]	• Where Member States provide for the subcategory of medicinal products subject to special medical prescription, they shall take account of the medicinal products containing, in a non-exempt quantity, controlled substances	1961 and 1971 UN Conventions
Samples	Art. 96(g) [1]	• No supply of samples of medicinal products containing narcotic or psychotropic substances falling under the 1961 or the 1971 UN Convention	1961 and 1971 UN Conventions

[1]Directive 2001/83/EC, as amended, on the Community Code Relating to Medicinal Products for Human Use

4.2.2. National Provisions for classification and control

As mentioned above, most countries are Parties of the UN Conventions and thereby agreed to control all psychoactive drugs specified in these Conventions. The UN Conventions are however not self-executing, i.e. do not impact "directly" and the obligations of the Parties thereunder may only be performed pursuant to appropriate national legislation.
In the following subchapters some aspects of the legal framework for classification and control of psychoactive substances is presented for the United States and five Member States of the European Union (France, Germany, Italy, Spain and the United Kingdom). The subchapters are organised in a standardised way to allow easy comparison of some main features of the different systems. The presentation is by no means exhaustive; focus is laid on the same provisions as mentioned in chapter 4.2.1.1.4. This means that e.g. provisions for veterinary products, products for dentists, those for hospital treatment drugs or special provisions for persons on ships or offshore instalments are not considered at all. Likewise, the legislation regarding precursor chemicals are not considered.

4.2.2.1. Classification and control system in United States

4.2.2.1.1 Legal framework relating to controlled substances and preparations

The main legal texts regulating controlled substances in the U.S. are the *Controlled Substances Act* (CSA, 21 U.S.C. 801 et seq.) and the *Controlled Substances Import and Export Act* (CSA, 21 U.S.C. 951 et seq.) which describe the U.S. classification scheme in general terms, the procedure for amending the lists of controlled substances, control measures for manufacturers, distributors and dispensers.[1]

4.2.2.1.2 Classification of controlled substances

According to the CSA, controlled substances in the U.S. are classified based on their abuse potential and medical use into five Schedules:

CI	high abuse potential / without accepted medical use in treatment in the U.S. / lack of accepted safety of use
CII	high abuse potential / with accepted medical use in treatment in the U.S. / abuse of the drug may lead to severe psychological or physical dependence
CIII	less abuse potential than CI, CII drugs / with accepted medical use in treatment in the U.S. / abuse of the drug may lead to moderate or low physical dependence or high psychological dependence
CIV	low abuse potential relative to CIII drugs / with accepted medical use in treatment in the U.S. / abuse of the drug may lead to limited physical dependence or psychological dependence relative to CIII drugs

[1] *Explanatory Note*: All general and permanent laws of the United States are codified by subject matter in the United States Code (U.S.C.), which is divided by broad subjects into 50 titles. References to these legal texts is always made by the reference to the U.S.C.: e.g. the Controlled Substances Act can be found under Title 21 (Chapter 13, Part I) of the United States Code starting with § 801 and thus the CSA is referenced by 21 U.S.C. 801 et seq. Since 1926, the U.S.C. has been published every six years. In between editions, annual cumulative supplements are published.

CV low abuse potential relative to CIV drugs / with accepted medical use in treatment in the U.S. / abuse of the drug may lead to limited physical dependence or psychological dependence relative to CIV drugs

No differentiation is made between substances and preparations controlled as narcotic or psychotropic under the 1961 and 1971 UN Convention, but all drugs are categorized according to their potential for abuse as perceived by the government and also by tradition. Schedules I and II include many widely known street drugs, including heroin, other opiates, and hallucinogenic drugs, such as LSD and marijuana. Schedule III compounds include many stimulants and depressants, analgesics and cough suppressants, the veterinary anaesthetic ketamine, and anabolic steroids. Schedule IV substances cover stimulants and depressants of lower abuse potential, while Schedule V includes therapeutic drug mixtures containing very limited quantities of controlled substances. The most current Schedules are published on an annual basis.

Apart from the classification system based on the strict chemical definition of substances ("by name of the substance") which is foreseen by the 1961 and 1971 UN Conventions, the U.S. classification system includes an "analogue" approach (21 U.S.C. 813, since 1986). Substances are considered as "controlled substance analogues" when they

- have a chemical structure substantially similar to that of a controlled substance in Schedules I or II and
- produce psychoactive effects substantially similar to or greater than that of a substance in Schedules I or II and
- do not include a controlled substance or a substance for which there is an approved new drug application (NDA).

It is important to note that there is no list of "controlled substance analogues". The CSA however provides that criminal sanctions apply manufacture and distribution of "controlled substance analogues" intended for human consumption.

4.2.2.1.3 Terminology

In the U.S. law, the term "narcotic" refers to any of the following:

(A) Opium, opiates, derivatives of opium and opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation. Such term does not include the isoquinoline alkaloids of opium.
(B) Poppy straw and concentrate of poppy straw.
(C) Coca leaves, except coca leaves and extracts of coca leaves from which cocaine, ecgonine, and derivatives of ecgonine or their salts have been removed.
(D) Cocaine, its salts, optical and geometric isomers, and salts of isomers.
(E) Ecgonine, its derivatives, their salts, isomers, and salts of isomers.
(F) Any compound, mixture, or preparation which contains any quantity of any of the substances referred to in subparagraphs (A) through (E).

The term "narcotic" is thus retained in the U.S. law in a similar meaning to that in the 1961 UN Convention, i.e. also including the stimulant cocaine.

4.2.2.1.4 Levels of control

The greater the perceived potential for abuse of a drug, the more severe the limitations on all transactions involving that drug. The following Tables (5A, 5B, and 5C) describe the different levels of control applied to the different Schedules of controlled drugs in the U.S.

According to 21 U.S.C. 811(g), any compound, mixture, or preparation containing a controlled substance may under certain conditions by regulation be exempted from the application of all or any part of the control provisions if it is clear that it does not present any significant risk of abuse. Exemption with regard to import or export will only be granted for certain substances or preparations in Schedules III-V (21 U.S.C. 956(b)).
Based on the 21 U.S.C. 827, extensive record-keeping requirements are foreseen for any transaction involving controlled drugs. Inventories and records must comply with regulations of the DEA and are to be preserved for at least two years. DEA must be provided with periodic reports at such time or times and in such forms as DEA requires.

Under the Food, Drug and Cosmetic (FD&C) Act, the “US Medicines Agency” (Food and Drug Administration, FDA) is responsible for the approval and marketing of medicinal products and for monitoring these products for continued safety after they are in use. This includes controlled substances.
The federal Drug Enforcement Administration (DEA) is the main regulatory agency under the Controlled Substances Act. The DEA, which is part of the Department of Justice, coordinates all licensing procedures. It also heads the interdiction efforts of the government to stem the domestic and international drug trafficking crimes. Undercover operations (as popularised on television) are but a small part of the DEA's agenda.

Table 5A: Different measures in the U.S. regarding control relating to manufacture, domestic and international trade for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
General prohibition		• none	
Authorisation by license required (general)	822(a)[1] 957(a)[2]	• manufacture, distribution, dispensing, import, export to be registered (registration valid for 1-3 years)	CI-CV
Special provision for general authorisation	958(c)[2]	• import/export registration issued <u>if</u> consistent with public interest • import registration issued <u>unless</u> inconsistent with public interest • export registration issued <u>unless</u> inconsistent with public interest	CI, CII CIII-CV CIII-CIV
Authorisation by license required (import)	952	• no import for commercial purposes except in emergency or when insufficient domestic competition exists, limited quantities for scientific, analytical or research purposes allowed (import permit required) • notification, declaration or import permit required for each shipment	CI, CII & narcotic CIII-CV non-narcotic CIII-CV
Authorisation by license required (export)	953(a)[2]	• - export only to Parties of Conventions or those having instituted the same control measures - export permit required for each shipment - permit only issued based on import certificate - from government of importing country - permit only issued for medical or scientific purposes and actual need in import country - no re-export allowed	Narcotic CI-CIV non-narcotic CI-CII
	953(c)[2]	• - export only to countries having instituted the same control measures - export permit required for each shipment - permit only issued based on import certificate from government of importing country - permit only issued for medical or scientific or other legitimate purposes and actual need in import country - no re-export allowed	
	953(e)[2]	• - proof that importation not unlawful in country of destination - export permit, notification or exportation required for each shipment - permit only issued based on import certificate from government of importing country - permit only issued for medical or scientific or other legitimate purposes and actual need in import country - no re-export allowed	non-narcotic CIII-CIV, CV
Manufacturing quota	826[1]	• For each manufacturer/importer: individual quota on absolute amount of drug to be manufactured or imported each year as part of aggregate quota	CI, CII

DEA Drug Enforcement Administration
All paragraphs refer to the respective sections of Title 21 of the U.S.C.
[1] Controlled Substances Act
[2] Controlled Substances Import and Export Act

Table 5B: U.S. provisions for prescriptions / legal classification of supply of controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control	811 (g)(1)	• almost all drugs containing controlled substances are prescription drugs • Any non-narcotic substance that under the FFD&C Act can be lawfully sold over the counter without a prescription will be excluded by regulation of the Attorney General be removed from the Schedules	CII-CV
Form of prescriptions	829(a)	• written prescription, inedible ink to be used, no refill, verbal prescriptions must be confirmed in writing within 72 hours, and may be given only in a genuine emergency some states (e.g. California, Illinois, New York) require a special narcotic prescription form (triplicate forms)	CII
	829(b)	• prescriptions may be oral or written, up to 5 refills permitted (CIII normally do not however carry refills), validity 6 months after date of issue	CIII-IV
	829(c)	• subject to state or local regulation; a prescription may not be required Certain CV may be sold as "exempt narcotic" over the counter: Persons must be over 18 years of age, and must provide name, address and signature for permanent record in a book designated for this purpose. New sale only after at least 48 h.	CV
All paragraphs refer to the respective sections of Title 21 of the U.S.C.			

Table 5C: Further provisions, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Packaging & labelling	825 (a)	• special symbols to be used on label, C-*Schedule No.* or a large "C" with the scheduling class inscribed, e.g. C-II or	CII-CV
	825 (c)	• concise warning on label that it is a crime to transfer the drug to any person other than the patient	CII-CIV
Safe custody	825 (d)	• containers securely sealed as required by regulations of the Attorney General	CI,CII, narcotic CIII, narcotic CIV
Samples		• no information found	
All paragraphs refer to the respective sections of Title 21 of the U.S.C. FFD&CA Federal Food, Drug & Cosmetic Act			

4.2.2.2. Classification and control system in France

4.2.2.2.1 Legal framework relating to controlled substances and preparations

Controlled substances are regulated in France by two main legal texts: the legislative and the regulatory part of the *Code de la Santé Public* (Code of Public Health) in its current version.[1]

4.2.2.2.2 Classification of controlled substances

The French legislative system establishes a concept of "controlled" **substances** that is much broader than that provided by the UN Conventions: The French law has established a category of substances called "poisonous" substances (*substances ou préparations vénéneuses*) under which not only "narcotic" and "psychotropic" substances fall, but also other dangerous substances, and substances inscribed in lists I and II (Art. L.5132-7, Art. R.5149). Lists I and II contain dangerous substances that pose a substantial risk to public health. With the exception of very few substances and preparations, psychotropic substances appear also on List I, whereas narcotic substances are generally only contained on a specific narcotic list.
As far as **medicinal products** are concerned, these are generally classified as List I or List II. Lists I and II cover "medicinal products likely to present a danger for health either directly or indirectly", or "medicinal products for human use containing substances the activity and/or adverse reactions of which require further investigation". The risks associated with list I substances are considered higher than those associated with List II substances. A narcotic status can be given to a medicinal product, if applicable, on top of the List I classification.

France lists psychotropic substances in the annex of "Arrêté du 22 février 1990 modifié fixant la liste des substances psychotropes". This annex is subdivided into 3 parts (here referred to as P1, P2 and P3). Narcotic substances are listed in the "Arrêté du 22 février 1990 modifié fixant la liste des substances classées comme stupéfiants", in 4 Annexes (here referred to as SI, SII, SIII, and SIV).

S I: Narcotic substances such as heroin, cocaine, cannabis methadone, opium etc.
S II : Substances like codeine, propiram etc.
SI and SII correspond to Schedules I, II and IV in 1961UN Convention
S III: psychotropic substances of Schedules I and II of the 1971 UN Convention as well as certain substances of Schedules III and IV of the same Convention
S IV: substances not controlled at international level and certain precursor substances

P1: Part 1 corresponds to Schedules III and IV of the 1971 UN Convention
P2: Part 2 contains certain preparations of "stupéfiants"
P3: Part 3 contains zaleplon, zopiclone (not internationally controlled)

It remains obscure from the reviewed legal texts what if anything at all the different annexes signify in terms of applicable levels of control (see below).

Like the classification system provided by the 1961 and 1971 UN Conventions, the French classification of controlled substances is based on the strict chemical definition of substances ("by name" of the substance), i.e. an "individual list" system applies.

[1] *Explanatory Note*: The Articles of both parts of the Public Health Code are differentiated by an initial L. for "legislative" and an R. for "regulatory", e.g. Art. L.5132-7 is in the legislative part, whereas Art. R.5149 is in the regulatory part of the Code.

4.2.2.2.3 Levels of control

In general, stricter control measures apply to substances classified as narcotics than to those inscribed on list I, and substances on list I fall under a stricter control regimen than substances inscribed on list II. The different measures of control are described in the below Tables (6A, 6B, and 6C).

Table 6A: Different measures of French control relating to manufacture, domestic and international trade for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
General prohibition	R.5179, R.5180, R.5181 Arrêté du 10 Sep 1992	• to produce, put on the market, to use khat, cannabis (plant and resin), tetrahydrocannabinol (THC, except delta 9-tetrahydrocannabinol) and preparations thereof • exceptions may be granted for research purposes • to produce, put on the market, to use certain narcotic and psychotropic substances (e.g. acetorphine, alphamethylfentanyl, para-fluorofentanyl etc.)	khat, cannabis, THC others
Authorisation by license required (general)	R.5171, R.5172, R. 5183	• to produce, put on the market (transport, import, export, storage, offer, acquisition), use and in a general way, all agricultural and industrial operations	stupéfiants psychotropes
Authorisation by license required (import)	R. 5173, R.5186-1	• special import authorisation required for each shipment • customs offices to be involved	stupéfiants psychotropes
Authorisation by license required (export)	R. 5173, R.5186-1	• special export authorisation required for each shipment • customs offices to be involved	stupéfiants psychotropes
Manufacturing quota		no manufacturing quota exist; a declaration of what has been manufactured or destroyed on an annual basis suffices	stupéfiants psychotropes

THC tetrahydrocannabinol

In case that a preparation contains more than one “poisonous” substances, it will be controlled like the ingredient to which the strictest levels of control apply (Art. R.5190).

According to Art. R.5151, certain preparations of narcotic and psychotropic substances can be exempted from parts or all of the control provisions when they contain concentrations that are too weak to pose a substantial risk of abuse.

Based on the French Public Health Code, extensive record-keeping requirements are foreseen for any transaction involving controlled drugs. Special format registers are required for all narcotic drugs (Art. R.5176, R.5177) and registers for all psychotropic substances (Art. R.5186), which have to be preserved for 10 years after the last entry. Statistical returns are provided in general on a yearly basis (Art. R.5178, R. 5187).

Table 6B: French provisions for prescriptions / legal classification of supply of controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control	R.5193	• all control drugs with accepted medical use are prescription-only medicines (unless specifically exempted because of their low concentration, short use)	stupéfiants psychotropes
Form of prescriptions	Arrêté du 01 Jul 1999	• special prescription forms only for narcotic drugs (ordonnance sécurisée), which replace the previously used official format (carnets à souche), numbered and issued specifically for one physician)	stupéfiants
Provisions related to supply on prescription	R.5132-22 R.5132-30 R.5194 R.5208 R.5213 R.5194 R.5214, R.5132-35	• prescription valid for 3 months • total prescription only valid for 24 hours, if presented later only partial prescription to be dispensed • duration of treatment and number of refills to be indicated - duration of treatment covered by one prescription not to exceed 12 months (and can be specifically reduced), dispensed quantity: 1month (except for contraceptives) - duration of treatment covered by one prescription not to exceed 28 days (and can be specifically reduced to 14 or 7 days, dispense may be in fractions) • no refill possible when posology and previous amount dispensed do no not justify a refill at that point in time • preservation of copies of prescriptions (together with official stamp and date of execution): to be retained for 3 years	List I, II stupéfiants psychotropes List I, II stupéfiants stupéfiants, List I, II stupéfiants

Table 6C: Further provisions, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Packaging & labelling	R.5201, R.5206, R.5207	• - skull an crossbones in black, printed on a square orange/yellow field in the upper left part of the label - white space surrounded by a red web to put the name and address of the pharmacist or physician • - St. Andrew's Cross in black, printed on a square orange/yellow field in the upper left part of the label - white space surrounded by a green web to put the name and address of the pharmacist or physician	List I, stupéfiants List II
Safe custody	R.5175	• to keep separate and in locked cabinet or place • to keep separate without free access	stupéfiants, List I List II
Samples	L.5122-10	• No samples of narcotic or psychotropic substances may be distributed	stupéfiants psychotropes

The control of licit commercial trade with controlled substances (manufacture, trade, import, and export) as well as the granting of licenses for scientific purposes is within the purview of the "French Medicines Agency" (*Agence francaise de sécurité sanitaire des produits de santé*, Afssaps). The department in Afssaps that deals with all affairs on concerning controlled drugs is the so-called *Unité stupéfiants et psychotropes* (Unit for narcotic and psychotropic substances).

4.2.2.3. Classification and control system in Germany

4.2.2.3.1 Legal framework relating to controlled substances and preparations

The *Gesetz über den Verkehr mit Betäubungsmitteln*, also known as *Betäubungsmittelgesetz* („Narcotic Drugs Act") or *BtMG*, of 1994 as amended is the central German law on controlled substances. In the German law, the term "narcotic" refers to all psychoactive substances listed in the law irrespective of whether these originate from the 1961 or the 1971 UN Conventions.
On the basis of the BtMG, the Federal Government issued four statutory ordinances regulating the following sectors in detail:

1. prescription of controlled substances by physicians, dentists, veterinarians (*Betäubungsmittel-Verschreibungsverordnung*)
2. domestic trade in controlled substances (*Betäubungsmittel-Binnenhandelsverordnung*)
3. foreign trade in controlled substances (*Betäubungsmittel-Außenhandelsverordnung*)
4. fees chargeable for the various official acts regarding the supervision of licit trade and traffic in controlled substances (*Betäubungsmittel-Kostenverordnung*)

4.2.2.3.2 Classification of controlled substances

Germany lists all substances that are subjected to regulatory control in the annexes of the *Narcotic Drugs Act* (BtMG). No differentiation is made between substances and preparations controlled as narcotic or psychotropic under the 1961 and 1971 UN Convention, but all controlled substances are listed via an "individual list" system in three Schedules, known as Anlage I, Anlage II and Anlage III. The essential criterion for the classification of controlled drugs into one of the three schedules is their respective medical benefit.

Anlage I: Controlled drugs not eligible for trade, nor for medical prescription, i.e. illicit substances with no accepted medical use (e.g. heroin, cannabis, LSD, MDMA)

Anlage II: Controlled drugs eligible for trade but not for medical prescription, i.e. licit substances considered of low therapeutic value which may only be used for scientific purposes (e.g. delta-9-tetrahydrocannabinol, dexamphetamine) or commercially for the manufacture of other products.

Anlage III: Controlled drugs that are eligible for trade and may be prescribed, i.e. substances of established medical value (e.g. codeine, buprenorphine, morphine, methadone)

4.2.2.3.3 Levels of control

In the following Tables (7A, 7B, and 7C), the relevant control measures applicable to controlled substances in Germany are presented.

Table 7A: Different measures of German control relating to manufacture, domestic and international trade for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
General prohibition	§ 3(2)[1]	• of cultivation, manufacture, trade or other traffic in, import, export, dispensing etc. except in exceptional cases specifically authorised for scientific purposes or other purposes of public interest	I
Authorisation by license required (general)	§ 3(1)[1]	• to cultivate, produce, trade or import, export, deliver, sell, otherwise bring them into commercial traffic or acquire them without engaging in their trade etc. • to manufacture exempted preparations	II, III
Authorisation by license required (import)	§ 11[1] and BtMAHV[2]	• import license required for each shipment • license issued as 3 copies: 2 sent to importer, 1 to competent authority in exporting country • specific customs offices to be involved if import from to country outside the EU • in general valid for 3 months	II, III
Authorisation by license required (export)	§ 11[1] and BtMAHV [2]	• export license required for each shipment • license only issued based on import certificate from government of importing country • license issued as 3 copies: 2 sent to importer, 1 to competent authority of importing country • specific customs offices to be involved if export to country outside the EU • in general valid until expiry of import certificate, but not longer than 3 months	II, III
Balancing demand & supply	§ 9(1)[1]	• traffic limited to certain annual limits which are estimates based on previous years (raise of limits may be applied for without much difficulty)	II, III

[1] *Betäubungsmittelgesetz* of 01 Mar 1994, as amended
[2] *Betäubungsmittel-Außenhandelsverordnung* of 16 Dec 1981, as amended

Certain preparations of substances mentioned in Anlage I to III may be exempted for domestic marketing at least from parts of the control provisions (i.e. so-called exempted preparations, e.g. benzodiazepines).

Based on the German Narcotic Drug Law and its subordinate legislation, extensive record-keeping requirements are foreseen for any transaction involving controlled drugs. Special format registers in accordance with the specimen provided by the "German Medicines Agency" (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) are required for all controlled drugs unless these are specifically exempted from these provisions. Preservation of records is 3 years after last entry. Statistical returns are to be provided in general on a 6-monthly basis (§18 BtMG).

Table 7B: German provisions for prescriptions / legal classification of supply of controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control	§ 1[1]	• all control drugs with accepted medical use are prescription only medicines; only preparations of substances in Anlage III may be lawfully prescribed	III
Form of prescriptions	§ 8[1]	• special prescription • official format: "Betäubungsmittelrezept", to be ordered from BfArM (numbered and issued specifically for one physician) • consists of 3 parts: I, II for pharmacist, III to be retained by physician; • inedible ink to be used	III
Provisions related to supply on prescription	§ 2, 8[1]	• amounts for 30 days not to exceed fixed maximum amounts • number of controlled substances to be prescribed within the same period of time limited • exceptions for chronic therapy possible, physician to indicate "A" • preservation: to be retained for 3 years	III

[1] *Betäubungsmittel-Verschreibungsverordnung* of 20 Jan 1981, as amended

Table 7C: Further provisions, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Packaging & labelling	§ 10, 11[1]	• no special requirements for medicinal products containing controlled drugs	III
Safe custody	§ 15[2]	• to keep controlled drug separate and in secure place	II, III
Samples	§ 47(3)[1]	• No samples may be distributed for substances controlled the German Narcotic Drug law	III

[1] *German Drugs law: Gesetz über den Verkehr mit Arzneimitteln – Arzneimittelgesetz (AMG)*, latest amendment 2005

[2] *Betäubungsmittelgesetz* of 01 Mar 1994, as amended

The control of licit commercial trade with controlled substances (manufacture, trade, import, and export) as well as the granting of licenses for scientific purposes is within the purview of the BfArM. The department within BfArM that deals with issues concerning narcotic substances is the so-called "Bundesopiumstelle".

4.2.2.4. Classification and control system in Italy

4.2.2.4.1 Legal framework relating to controlled substances and preparations

The Presidential Decree (*Decreto del Presidente della Repubblica*) n° 309/90 of October 1990 (DPR 309/90) forms the legal framework for licit trade with controlled substances in Italy. It contains all rules for classification, production, import/export, prescription, controls, prevention, care and rehabilitation. Although currently under review (personal communication), this law is still in force.

4.2.2.4.2 Classification of controlled substances

In Italy, substances and preparations controlled as narcotic or psychotropic under the 1961 and 1971 UN Convention are not regulated separately. Substances and preparations are rather classified via an "individual list" system that distinguishes 6 listings/tables. The most current Schedules are included in the Italian Pharmacopoeia:

List /Table I includes opioids (e.g. morphine, fentanyl, oxycodone), cocaine derivatives, and amphetamines:
- a) Opium and all substances that can be extracted from opium poppy; alkaloids, with narcotic and analgesic activity, entities chemically related to opium
- b) Coca and alkaloids with stimulating action on the CNS and substances with similar action
- c) amphetamine-like substances with stimulating action on the CNS
- d) Each substance able to produce effects on the CNS or able to produce physical or psychic dependence in the same way or in a stronger way in comparison with the products indicated above
- e) Indol-derivatives: tryptamine derivatives, lysergic acid derivatives, phenyl-ethylamine derivatives, with hallucinogenic effects or able to produce disorders
- f) Medicinal products containing the above-mentioned substances

List /Table II cannabis
- a) cannabis (leaves, flowers, resin, oils)
- b) medicinal products containing the above-mentioned substances

List /Table III highly addictive barbiturates and hypnotic sedatives
- a) barbiturates able to produce high physic or psychic dependence and substances with hypnotic/sedative effects like barbiturates. Long-acting barbiturates with antiepileptic activity and short-acting barbiturates (used as general anaesthetics) are excluded.
- b) medicinal products containing the above-mentioned substances

List /Table IV medical substances
- a) substances for which physic and psychic dependence is known but for which the dependence is smaller than for substances contained in table I & III
- b) medicinal products containing the above-mentioned substances

List /Table V special preparations
- a) Medicinal products containing the substances of the tables I, II, III, IV when the products are not able to produce physic or psychic dependence, due to their qualitative and quantitative composition or pharmaceutical form
- b) benzodiazepines
- c) Finished products of tramadol
- d) Barbiturates associated with other active ingredients.

List /Table VI stimulants (e.g. etizolam, meprobamate)

4.2.2.4.3 Levels of control

Like in many other countries, the strictness of control measures is proportional to the medical and social danger associated with a drug. In the following Tables (8A, 8B, and 8C), the relevant control measures applicable to controlled substances in Italy are presented.

Table 8A: Different measures of Italian control relating to manufacture, domestic and international trade for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
General prohibition		• none	
Authorisation by license required	Art 17 - 71[1]	• to cultivate, manufacture, import, export, transit, distribute, trade, scientific research (responsible body: Ministry of Health) • license to be renewed every 2 years	From list I to list VI
Import & export And transit	Art. 50 - 59[1]	• Specific authorisation required for each batch imported or exported the validity of the authorization is 6 months • customs office involved (only if import from /export to country outside the EU)	From List I to list V
Manufacturing quota	Art. 31[1]	• MoH defines the quantity of active substances can be manufactured each year. The list is published in the Italian Official Journal. Exceeding quantity of 10% can be allowed on specific notification	From list I to list V

[1]DRP 309/90: Presidential Decree (*Decreto del Presidente della Repubblica*) n° 309/90 of October 1990

Based on the DPR 309/90 (Art. 17 - 71), extensive record-keeping requirements are foreseen for any transaction involving controlled drugs. Special format registries in accordance with the specimen provided by the Ministry of Health: to be utilised by manufacturer and wholesalers for medicinal products included in list I to V (pharmacists have to use this register for medicinal product in list I to IV). Records have to be preserved for 2 years. Information on the transactions must be given any time on demand of the Ministry of Health and regularly after certain specified periods of time. Statistical returns are provided on quarterly (DPR309/90, Art. 66 for manufacturers) and/or an annual basis (DPR 309/90, Art. 69 for manufacturers, wholesalers).

Table 8B: Italian provisions for prescriptions / legal classification of supply of controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control	Art. 43[1] It. Ph.	• medical prescriptions required	I to V
Form of prescriptions	Leg.ve Decree n. 539 / 1992 Art 71[1]	• normal (renewable) prescription, valid for up to 3 months	V: benzo-diazepines
		• normal (non renewable) prescription , valid for up to 30 days	IV, V

	Art. 43[1] It. Ph.	• special form, called "yellow form" 3 parts (1 for the physician, 1 for the pharmacist, 1 for local health authorities), valid for 10 days (*)
		  • limited to 8 days of therapy
		  • may only contain one strength or pharmaceutical form of a substance
			I, II, III

	Decree 04 April 2003	• for chronic pain therapy: special prescription form, called "3 copies form" (since April 2003), valid for 30 days
		  • limited to 1 month of therapy
		  • may contain two different strengths or pharmaceutical forms of the same substance or even two different medicinal products
			I, IV: morphine, fentanyl, codeine, oxycodone, hydromorphone, methadone, codeine combinations, buprenorphine

		• forms are available from the local health authorities.	
		(*) available from Physician Order	

[1]DRP 309/90: Presidential Decree (*Decreto del Presidente della Repubblica*) n° 309/90 of October 1990
It. Ph. Italian Pharmacopoeia

Table 8C: Further provisions, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Labelling an Packaging	It. Ph.	• "medicinal product under DPR 309/90 with the indication of the list	From I to VI
Safe custody	It.Ph.	• to be kept in locked receptacles or cabinets	From I to IV
Samples	Legislative Decree 541/92	• Is it not allowed to provide free samples of controlled substances	From List I to VI

It. Ph. Italian Pharmacopoeia

The control of licit commercial trade with controlled substances (manufacture, trade, import, and export) as well as the granting of licenses for scientific purposes is within the purview of the Italian Ministry of Health. The central unit in the Ministry of Health dealing with controlled drugs is the Central Office for Narcotic Drugs (*Ufficio Centrale Stupefacenti*). All authorisations required under the Controlled Substances Law in Italy are issued by this body.

4.2.2.5. Classification and control system in Spain

4.2.2.5.1 Legal framework relating to controlled substances and preparations

With respect to regulating controlled substances in Spain, there are two main legal texts:
the *Ley* ("Law") 17/1967 implementing the UN Convention of 1961 on narcotic drugs and the *Real Decreto* ("Royal Decree") 2829/1977, implementing the UN Convention of 1971 on psychotropic substances.

4.2.2.5.2 Classification of controlled substances

In Spain, substances and preparations controlled as narcotic or psychotropic under the 1961 and 1971 UN Convention are regulated separately. Accordingly, the Spanish law differentiates between "narcotics" (= estupefacientes) and "psychotropics" (= psicotrópicos). In fact, the Spanish law places drugs under control exactly as in the 1961 and 1971 UN Conventions. As a consequence only the “individual List” system applies in Spain.

The annexes of the 1961 UN Convention are mirrored in the annexes to "*ORDEN 31 de julio de 1967, que enmienda las Listas anexas al Convenio de 1961*". These annexes will be referred to as EI, EII, EIII, and EIV throughout this master thesis, E being the abbreviation for “estupefacientes”. The regulatory control of narcotic substances is established by *Ley* 17/1967. The classification and measures of control as foreseen by the 1961 UN Convention do apply.

Psychotropic substances are listed in the *Real decreto* 2829/1977. Annex 1 of this Royal Decree is subdivided in 4 lists I, II, III, IV, specified as PI, PII, PIII and PIV hereafter, P being the abbreviation for “psicotrópico”. The *Real Decreto* 2829/1977 not only provides for a classification of psychotropic substances but also for their regulatory control.

4.2.2.5.3 Levels of control

In the following Tables (9A, 9B, and 9C), the relevant control measures applicable to controlled substances in Spain are presented.

Table 9A: Different measures of Spanish control relating to manufacture, domestic and international trade for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
General prohibition	Art.2[1,2]	• of cultivation, manufacture, trade or traffic in, possession and use, except for scientific research (responsible for issuing special authorisations: Ministry of Health & Interior) • of manufacture, import, export, transit, trade in, distribution, storage etc. except in exceptional cases specifically authorised for scientific purposes (responsible body for special authorisations: Ministry of Health)	EIV PI
Authorisation (notification*) required **Authorisation and registration required**	Art.8, 12, 16, 17[1] Art.6, 14[2]	• for cultivation, manufacture, import, export, transit and transport* • for manufacture and trafficking	EI, EII, EIII PII, PIII, PIV
Import & export	Art.10, 19[2] Art.16[1], Real Decreto[3]	• Authorisation and permit for every transaction required • Involvement of customs offices	EI, EII, EIII, PII, PIII, PIV
Manufacturing quota	Art.12[1]	• fixed quantities per period	EI, EII

[1] *Ley* 17/1967
[2] *Real decreto* 2829/1977
[3] *Real Decreto* 1573/93 of 10 Sep 1993

In case that a preparation contains more than one substance mentioned in lists PI to PIV of the *Real Decreto* 2829/1977, the preparation will be controlled as the substance to which the strictest rules apply (Art. 3). The psychoactive substances mentioned in Annex 2 of the *Real Decreto* 2829/1977 but do not appear in PI to PIV of Annex 1 are exempted from regulatory control: as depicted in the Table 9C, they must, however, be labelled according to the provisions of *Real Decreto* 2829/1977 (Art. 13) and are only available on medical prescription (Art. 16).
Extensive record-keeping requirements are foreseen for any transaction involving controlled drugs. Record-keeping is more formalised, i.e. special registries are to be used (libro de contabilidad). Preservation of documentation/copies is 2 years. Manufacturers have to provide annual returns of all transactions.

Within the Spanish Ministry of Health and Consumptions the functions related to controlled substances (such as issuance of licenses and authorisations) are co-ordinated by one of the five subdirectorates of the Spanish Medicines and Medical Devices Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS)*: This is the *División de Estupefacientes y Psicotropos* belonging to the *Subdirección general de Inspección y Control.*

Table 9B: Spanish provisions for prescriptions / legal classification of supply of controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control		• only available upon medical prescription	EI, EII, EIII PII, PIII, PIV, not in PI to PIV but in P2
		• normal prescription	PII, PIII, PIV, not in PI to PIV but in P2
		• special medical prescription (This means physicians issue a normal prescription + special narcotic prescription (2- copy form + doctor´s record). Before the patient can get his prescription in the pharmacy he/she has to go to a special site that issue authorization = " Sello de inspección ")	EI, EII, EIII
Form of prescriptions		• special narcotic form: triplicate	EI, EII, EIII
		• no special form	PII, PIII, PIV, not in PI to PIV but in P2
Provisions related to supply on prescription	Art. 17[2]	• only 1 product to be specified	PII, PIII, PIV, not in PI to PIV but in P2
	Art.19[1]	• only 1, no maximum therapeutic doses, no. of prescriptions described per time	EI, EII

[1] *Ley* 17/1967
[2] *Real decreto* 2829/1977.

Table 9C: Further provisions, including reference to the relevant legal basis

Labelling an Packaging	Art. 5, 13[2]	• medicinal products to carry a specific symbol on the outer carton and the package leaflet: ◑	not PI to PIV but in P2
		• medicinal products to carry a specific symbol on the outer carton and the package leaflet: ◐	PII, PIII, PIV,
		• medicinal products to carry a specific symbol on the outer carton and the package leaflet: ●	EI, EII, EIII
Safe custody	Art.21[1]	• to avoid diversion and misuse	EI, EII
Samples	Ley[3]	• No samples may be distributed for narcotic or psychotropic substances or preparations thereof	EI to EIV, PI to PIV

[1] *Ley* 17/1967
[2] *Real decreto* 2829/1977
[3] *Ley* 25/1990 Spanish Pharmaceutical Law

4.2.2.6. Classification and control system in the United Kingdom

4.2.2.6.1 Legal framework relating to controlled substances and preparations

The main law regulating controlled substances in the United Kingdom (UK) is the *Misuse of Drugs Act* 1971 (MDA), as amended. It is through this act that the UK fulfills its obligations under the 1961 and 1971 UN Conventions. The associated secondary legislation (see sections 7, 10, 22 and 31 of the MDA), above all the *Misuse of Drugs Regulations* 2001, include more detailed provisions regarding the control of dangerous substances and preparations, specifically regarding their import, export, manufacture, supply, prescription, possession and possession with intent to supply. Other legislation covers safe custody (*Misuse of Drugs (Safe Custody) Regulations* 1973, as amended), the supply to addicts *(Misuse of Drugs (Supply to Addicts) Regulations 1997*) and licence fees (*Misuse of Drugs (Licence Fees) Regulations, 1986*).

4.2.2.6.2 Classification of controlled substances

In the UK, substances and preparations controlled as narcotic or psychotropic under the 1961 and 1971 UN Conventions are not regulated separately. Two different classification systems are used for different purposes:

- The MDA distinguishes three classes of controlled substances (A, B, C), based on the level of harm they may cause, with A being the most dangerous:
  Class A e.g. cocaine, methadone, morphine, MDMA, LSD, heroin
  Class B e.g. codeine, some amphetamines
  Class C: e.g. amphetamines, cannabis, benzodiazepines, buprenorphine
  The MDA prohibits import, export, supply etc. of controlled drugs unless these transactions have been specifically authorised. The severity of penalties imposed under the criminal law for an infringement of the MDA depends upon the classification of the substance involved. Offences involving e.g. heroin attract the highest penalties (up to lifetime imprisonment) whereas maximum penalties are less severe for offences involving Class B or C drugs.

- The *Misuse of Drugs Regulations* 2001 distinguish five Schedules:
  Schedule 1: includes cannabis and hallucinogens. Schedule 1 reproduces the drugs listed in the *Misuse of Drugs (Designation) Order 2001*, which may not be used for medicinal purposes, their production and possession being limited to special purposes e.g. research.
  Schedule 2: In practical terms this is the most important of the five schedules. These drugs cover pharmaceutical opioids and amphetamines in medical use, but also other stimulants, such as e.g. cocaine.
  Schedule 3: includes the most of the barbiturates and a small number of minor stimulant drugs which are not thought so likely to be misused as those drugs in Schedule 2, nor to be so harmful if they are misused. In addition, some barbiturates and buprenorphine are listed here.
  Schedule 4: This Schedule is split into two parts: Part I contains most of the benzodiazepines, Part 2 most of the anabolic and androgenic steroids, together with growth hormones.
  Schedule 5: contains low concentration preparations of certain controlled drugs which are exempt from full control (not for injection)

> Depending on the respective Schedule of a controlled substance or a preparation thereof, different regimes of regulatory control apply: Substances and preparations included in Schedule 1 have no acknowledged therapeutic use and are most tightly regulated. The substances in the other Schedules do have medical uses and are subject to less control, with those in Schedule 4 and 5 being least regulated. These Regulations ensure that legitimate activities are exempted from the relevant offence provisions of the MDA. What the Act prohibits, the Regulations allow.

It is important to note that the UK have implemented a generic system into the "individual listing" system This means that the listings do not only contain individual chemical substances and preparations thereof but in some cases refer in a generic way to a compound and a whole array of derivatives, allowing the whole family of substances to be controlled without the need to list every member of the family specifically.

4.2.2.6.3 Levels of control

The *Misuse of Drugs Regulations* 2001 and parallel regulations such as e.g. the *Misuse of Drugs (Safe Custody) Regulations* 1973, as amended, include detailed provisions regarding the control of "dangerous" substances. The main control measures regarding licit traffic and supply of controlled substance are summarised in the tabular overview below (Table 10A, 10B, and 10C). In the case of the control measures implemented in the UK, there are however some aspects, such as details on authority licenses for domestic trade, import, export as well as on providing annual returns on all transactions, that are not regulated explicitly in the available legal texts: Regulation 5 of the *Misuse of Drugs Regulations* 2001 specifies that manufacture, supply, offer etc. of controlled drugs is not unlawful when a license has been issued by the Secretary of State. This section, however, does not specify which different types of licenses exist nor does it refer to import and export of controlled drugs. Likewise, Reg. 26 of the *Misuse of Drugs Regulations* 2001 requires manufacturers, importers/exporters, wholesalers and other persons involved in the manufacture, trade in and supply of controlled substances to furnish information on demand of the Secretary of State or personnel authorised by him, but it does not specify that annual returns should be made for all transactions involving controlled drugs so that the UK can fulfil its legal obligations under the UN Conventions. The *Misuse of Drugs Regulations* 2001 likewise does not make reference to subordinate legal provisions. Information on relevant licenses and requirements for annual returns are however available from the Home Office (see their website: http://www.homeoffice.gov.uk/).

Table 10A: Different measures in the UK for control relating to manufacture, domestic and international trade for controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
General prohibition		none known	
Authorisation by license required (domestic)	Reg. 5[1]	• to produce, supply, offer to supply or have in his possession controlled drugs (CD)	1, 2, 3, 4, 5
Authorisation by license required (import)	Sec.3[2], Reg.4[1],	• domestic license to possess drugs under MDA required (see above) • customs to be involved (if import from to country outside the EU • import license required for each consignment • import license to be surrendered to the Customs Officer • import certificate to be sent consignor abroad for submission to his government	1, 2, 3, 4*
Authorisation by license required (export)	Sec.3[2], Reg.4[1],	• domestic license to possess drugs under MDA required (see above) • customs to be involved if import from to country outside the EU • import certificate from government of importing country required • export license required for each consignment	1, 2, 3, 4* 1, 2 1, 2, 3, 4*
Manufacturing quota		*not known*	

[1] The *Misuse of Drugs Regulations* 2001, as amended

[2] The *Misuse of Drugs Act* 1971, as amended

* Schedule 4 drugs may be lawfully possessed by anyone, even without a prescription, provided they are in the form of medicinal products. The drugs in Part I may also be lawfully imported or exported if they are in the form of such products for self-administration. The drugs in Part II may be freely imported or exported whether they are in the form of medicinal products or not (Reg. 4 of the *Misuse of Drugs Regulations* 2001)

Certain products can be exempted from parts or all of the control measures if they are not likely to pose a significant risk to public health because of e.g. their strength or route of administration (Reg. 2 of the *Misuse of Drugs Regulations* 2001, as amended).

Based on the *Misuse of Drugs Regulations* 2001, extensive record-keeping requirements are foreseen for any transaction involving controlled drugs. Record-keeping is more formalised for Schedule 1 & 2 controlled drugs (special CD registers) than for Schedule 3, 4, 5 drugs. Preservation of documentation/copies is for 2 years. Information on the transactions must be given any time on demand made by the Secretary of State or by any person authorised in writing by the Secretary of State on that behalf. Statistical returns are provided on an annual basis. These are provided on separate forms for substances controlled by the 1961 and 1971 UN Conventions.

Table 10B: UK provisions for prescriptions / legal classification of supply of controlled drugs, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Prescription control	Sec.58[2] + *secondary legislation*	• all CD with medical use are prescription only medicines POM (except those exempt because of maximum strength/dose)	2, 3, 4, 5
Form of prescriptions	Reg. 15[1]	• same prescription form as for other medicines but • indelible ink to be used • signed and dated by the person issuing it • specify address of the person issuing it • specify the name and address of the person for whose treatment it is issued (handwritten by issuing person) • specify the dose, pharmaceutical form and total quantity to be supplied (handwritten by issuing person), • direction specifying the amount of the instalments of the total amount which may be supplied and the intervals to be observed when supplying (if applicable)	2, 3
Provisions related to supply on prescription	Reg. 16, 23[1]	• not valid before date specified on prescription • only valid for 13 weeks from date specified on prescription • to be retained at premises from which drug is supplied for two years • no repeats allowed	2, 3

[1] The *Misuse of Drugs Regulations* 2001
[2] The *Medicines Act* 1968

Table 10C: Further provisions, including reference to the relevant legal basis

Control	Ref.	Explanation	Schedules
Packaging & labelling	Reg. 18[1]	• no special legal requirements for medicinal product, but any bottle and other container must be marked with the amount of CD contained (voluntary marking "CD" possible)	1, 2, 3
Safe custody	Reg. 3[2]	• to keep controlled drug in a locked safe, cabinet or room to prevent unauthorised access to the controlled drug • to comply with specifications for such secure places	1, 2 & 3 (only partly)
Samples	Reg. 19[3]	• No samples may be distributed for substances controlled by the 1961 and 1971 UN Conventions	1961 and 1971 UN Conven-tions

[1] The *Misuse of Drugs Regulations* 2001
[2] The *Misuse of Drugs (Safe Custody) Regulations* 1973, as amended
[3] The *Medicines (Advertising) Regulations* 1994

Unlike in many other European Countries, the "UK Medicines Agency" (Medicines and Healthcare Products Regulatory Agency, MHRA) or the Ministry of Health are not involved in control measures. The control of the licit commercial trade with controlled substances (manufacture, trade, import, and export) as well as the granting of licenses for scientific purposes is within the purview of the Home Office.

4.2.3. Summary & Conclusion

The UN Conventions are not self-executing: To be able to enforce them the Parties have to transpose the Conventions and any amendment thereof into their domestic legislative systems. The UN Conventions only require the Parties to meet certain broad obligations, but leave some freedom as to how precisely those obligations are to be implemented by the country concerned. In this respect, it should be mentioned that both Conventions allow the application of stricter domestic control measures than those required by the international framework (Art. 39 of the 1961 UN Convention and Art. 23 of 1971 UN Convention). The comparative analysis of the classification and control systems implemented in the U.S. and several EU countries revealed the following:

- Within their national legislations, some countries distinguish between narcotic and psychotropic substances, in an analogous way to the 1961 and 1971 UN Conventions (e.g. Spain). Others combine the two in one list that subclassifies substances and preparations thereof only according to the level of structural similarity, medical value and/or potential harm (e.g. U.S., Germany, Italy, and United Kingdom). France is a little bit further set aside as it uses the terminology of "narcotic" and "psychotropic" substances and keeps separate lists, but the "narcotic" Schedules also include substances that are listed in the 1961 and 1971 UN Conventions as well as purely nationally controlled substances and the "psychotropic" Schedules only include Schedules III and IV of the 1971 UN Conventions.
- The number of schedules established in the different countries also varies considerably and with that usually the refinement of different levels of control applicable to different substances. In Germany, for example, there are only three categories: illicit substances, substances available for trade but not for medical prescription, and those that may be prescribed. In UK and the U.S., five different levels of control exist. In Italy, substances are classified in six schedules.
- There is much divergence in the control of prescription. Some countries such as Germany require special prescription using official triplicate forms for all controlled substances eligible for medical use (unless these are exempt) and have laid down by law maximum amounts that may be prescribed in a certain period of time, others (e.g. U.S. or UK) do not generally require use of special prescription forms but do allow or prohibit refills for certain categories of controlled substances.
- Although the U.S. are very lenient with regard to prescription control, they are very strict regarding export and import requirements. The U.S. require for some categories of controlled substances that a confirmation is given that the exported substances are not re-exported again from the country of destination. This gives the impression that the U.S. do not trust other countries to apply the same levels of control to the traffic of controlled substances as themselves, which is kind of strange considering that it is the U.S. that suffer from a considerable amount of diversion and abuse (see Appendix I). The

prohibition imposed on re-export of controlled substances from the country of destination makes it difficult to conduct multi-national clinical studies with certain controlled study medications when these are manufactured in the U.S. This is because regional warehouses are often used to distribute the study medication across national borders to the various trial sites in that region. As for import of controlled substances in Schedules CI and CII, and of narcotic controlled substances in CIII-CV, the U.S. only allow import into their territory for commercial purposes under very special circumstances. This means that e.g. medicinal products containing these substances have to be manufactured in the U.S. in order to be sold in the U.S. which could be interpreted as kind of a protective measure.

What most of the classification systems do however have in common, is that they rely almost exclusively on an "individual list" system, consisting of a listing of chemically defined substances or preparations thereof. Only substances contained in one of the schedules are controlled. Any derivative (except for some salts, esters, ethers etc.) being chemically distinct from the listed compound is not within the scope of the legislation and thus *per se* not controlled. Listings have the advantage that there is no doubt about which substances fall within their scope and which do not, but they often have the disadvantage of being rather static and slow as far as changes are concerned because the updating mechanisms may involve parliamental or ministerial decrees.

Of the countries investigated here only two have implemented a second approach on top of the "individual list" system. The additional approach was implemented in these countries to keep pace with the appearance on the market of new synthetic drugs that are often deliberately designed to circumvent the international Conventions' provisions. For amphetamine-type stimulants, it is for example quite easily possible to obtain a large number of structures altered in a way that the basic structure of the amphetamine and thus the amphetamine-type effect is unchanged. The new molecules are however sufficiently dissimilar in structure to ensure that the substance is outside the scope of any control measures.

The U.S. have implemented a so-called "analogue approach": Substances are considered as "controlled substance analogues". This approach is however restricted to similarities to Schedule I and II substances. The U.S. *Controlled Substances Act* provides that criminal sanctions apply to the manufacture and distribution of "controlled substance analogues" intended for human consumption and the Drug Enforcement Administration has attributed the decrease in the production and distribution of analogues to the introduction of the "analogue approach" into its legislation in 1986. Of the European countries investigated here, the UK has implemented a so-called "generic approach" which means that in addition to the "individual list" system, the UK has introduced the use of generic definitions for various families of drugs. They hereby catch at least some new synthetic drugs which do not appear on the "individual list". A disadvantage of a generic system is however the fact that it may offer some room for interpretation: In response to a scheduling action of the European Union (for explanation see Chapters 4.3.3.1, 4.3.3.8) on 4-MTA, for example, there was debate in the UK about whether or not 4-MTA was already classified under the generic system, and this debate could only be solved after more than two years by specifically listing 4-MTA as a new substance. The generic approach is not very common in the EU. Of the "old" EU-15 Member States, only UK and Ireland have implemented this approach. A generic system was also discussed for implementation in Germany; the idea was however refused in the end. To tackle the problem of the emergence of new synthetic drugs, Germany and some other Member States have implemented an "emergency list approach",

which is an urgency procedure by which certain new drugs can be controlled on a provisional basis (also see Chapters 4.2.2., 4.3.3.4.1).

In conclusion, the adoption of the UN Conventions has led to a considerable variability in the scheduling systems and control measures at national level (Appendix III provides a comparative overview on the classification of opioids in the different territories discussed in this master thesis). This is because the transposition of international provisions in national law inevitably involves a certain amount of interpretation. Often the political climate, constitutional/legal considerations as well as traditions and other principles set the context within which resulting proposals for national drug policy are considered.
The various national classification and control systems have to be kept in mind when international marketing concepts for medicinal products containing controlled substances are developed. Furthermore, there are some countries (e.g. U.S.) that have implemented control measures that may also impact on earlier strategic decisions, such as for example location of manufacturing sites.

4.3. Control of new substances with abuse potential

As is described in chapter 4.2.2 most scheduling systems (at national and international level) do not work by drug classes but on a more or less purely individual naming scheme. This means that any new psychoactive substance, be it structurally derived from a substance already on the list or an entirely new compound, is not subject to any regulatory control. As new substances with abuse potential appear on the market place (e.g. designer drugs or new substances developed by pharmaceutical industry), the "individual lists" need updating, i.e. scheduling actions must be initiated and scheduling decisions be taken.

In the following sections, the legal basis and procedural aspects of scheduling actions are looked into in more detail, both on an international as well as on a national level (i.e. in the territories which are in the focus of this thesis). Where possible the general legal provisions are presented followed by a description how a new psychoactive substance for which a national marketing authorisation is sought is put under control. For the EU, in a second step, the interlinkage between supra-national marketing authorisation procedures and national scheduling actions is discussed.

4.3.1. International scheduling actions

4.3.1.1. General legal provisions

The 1961 and 1971 UN Conventions both establish a mechanism to expand and modify the schedules. They designate the UN Commission on Narcotic Drugs (CND) as the body authorised to adopt decisions on amendments of the schedules (Art. 3 of 1961 and Art. 2 of 1971 UN Conventions). As a specialised agency of the United Nations system, WHO is responsible for conducting the medicinal and scientific evaluation of abuse-liable drugs and making recommendations to CND concerning the level of international control to be applied. Within WHO, the WHO *Expert Committee on Drug Dependence* (ECDD) has been entrusted with this task. Assessments and recommendations provided by the ECDD may pertain, as the case may be, to substances not yet under international control and to already controlled substances (by amending existing schedules including the deletion of substances from the schedules). It is important to

note that no substance can be controlled internationally without first being evaluated by WHO. The ECDD is appointed (or called for) approximately every two years by the WHO. The time schedule for any review procedure is adapted to the meeting scheduled of CND and procedural requirements.
The WHO review of abuse-liable substances for international control includes routine collection of information by the Secretariat and the so-called pre-reviews and critical reviews conducted by the ECDD. The pre-review may be the first step in the evaluation intended to select drugs for the potential second step, the critical review. A critical review can also be directly triggered by the ECDD in any of the following cases:

(1) notification by a Party to the 1961 or the 1971 UN Convention concerning the scheduling of a substance
(2) explicit request by CND to review a substance
(3) information on clandestine manufacture of a substance posing an especially serious risk to public health and having no recognised therapeutic value in any of the Member State.

4.3.1.2. International scheduling criteria

In order to ensure consistency in its review process, WHO has developed formal procedures for the review of abuse-liable, psychoactive substances. The current review procedure follows the guidelines that were adopted by the Executive Board of WHO in 2000 (*Guidelines for the WHO review of dependence-producing psychoactive substances for international control*, WHO/EDN/QSM/2000.5). The scheduling criteria described in these guidelines are based on the relevant provisions of the 1961 and 1971 UN Conventions and additional guiding principles worked out by the ECDD.
The criterion used for scheduling decisions of narcotic drugs is the similarity in terms of abuse and undesirable/ill effects to substances already controlled. In accordance with the 1961 UN Convention, the ECDD, when deciding whether to recommend international control, first determines whether the substance under review has morphine-like, cocaine-like, or cannabis-like effects or is convertible into a scheduled substance having such effects. If so, the Committee determines whether or not the substance is liable to similar abuse and produces similar undesirable effects as substances in Schedule I or Schedule II, or confirms that it is convertible into substances already in one of these schedules.
For psychotropic substances, two levels of scheduling criteria apply. At the first level, the similarity to scheduled substances, the dependence liability, and the psychotropic effects are assessed. To put a new psychoactive substance under control, it is sufficient to confirm that the substance in question has dependence liability and can produce "central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function, thinking, behaviour, perception or mood". This criterion has enabled the scheduling of new types of dependence-producing psychotropic substances that are not similar to substances already scheduled. The scheduling criteria for psychotropic substances, unlike those for narcotic drugs, have however an additional requirement for "evidence that the substance is being or is likely to be abused so as to constitute a significant public health and social problem warranting the placing the substance under international control"(Art. 2, 4(b) of 1971 UN Convention). This provision actually deters the ECDD from proposing "preventive" controls for psychoactive substances.
As is outlined in Tables 1 and 2, the classification to one or another Schedule within one of the UN Conventions will ultimately depend on the balance between the risk to public health associated the substance and its therapeutic usefulness. In cases were the criteria do not allow

proper classification to one or another schedule, the recommendation should normally be made with a higher regard to the risk to public health than to therapeutic value.

No specific guidance is given in the *Guidelines for the WHO review of dependence-producing psychoactive substances for international control* as to how similar to the original drug a substance must be for it to be considered as morphine-like, cocaine-like, or cannabis-like. The lack of specific guidance on this matter poses considerable difficulty for the ECDD when the drug under review has some similarity, for example, with both a narcotic drug and a psychotropic substance. As could be expected, the 1961 Convention does not give any indication how to decide between the two Conventions, as at the time it was agreed on, the other convention did not exist yet. However, 1971 Convention does not provide for a mechanism for a choice either. As such, the decision as to whether to control e.g. analgesic and stimulant drugs under the 1961 or 1971 UN Conventions is a major problem. Recent attempts to develop additional guidelines to solve the problem have failed because of the opposition of several Parties (see corresponding minutes on this item of the 114th and 115th meeting of the Executive Board) as these guidelines could have led to the reclassification of a considerable number of substances between the two Conventions.

As guidelines are missing that provide for a decision-making based on scientific principles, there is a substantial risk of international scheduling actions to be political rather than purely rational decisions.

4.3.1.3. Procedure for scheduling new psychoactive substances

Requests for the introduction of a new psychoactive substance into the Schedules of the 1961 or 1971 UN Convention can be made by any Party to the UN Conventions or the WHO (Art. 3 of 1961 UN Convention, Art. 2 of 1971 UN Convention). All requests have to be addressed to the Secretary General who is responsible for informing the Member States, the WHO and the CND. The requests should be accompanied by all relevant supporting documentation. As described above, the scientific review of the drug is performed by the ECDD. According to the *Procedure to be followed by CND in matters of scheduling of narcotic drugs and psychotropic substances* (1982), WHO has to inform the CND in a timely manner on the period within which it intends to carry out the review. CND then decides at which session, the WHO review is discussed. WHO's recommendations and assessments have to be forwarded to the Secretary-General at least three months prior to the CND session at which the recommendation or assessment is to be considered. Any decision of the CND is communicated by the Secretary-General to all member states of the United Nations, to non-member states parties of the Conventions, to the WHO and the INCB. The decision is effective with respect to each party on the date of receipt of the communication. The parties then have to take such action as may be required to implement the decision nationally. The 1971 UN Convention limits the timeframe for national implementation to 180 days.
Decisions of CND may be reviewed by the *Economic and Social Council* of the United Nations upon request of any Party. This request must be filed within 90 days from receipt of the notification about the decision. Copies of a request for review are transmitted to CND, to the WHO, and to all Parties by the Secretary-General. The Council may confirm, alter, or reverse the CND decision. The Council decision is final. During the time the review is pending, the original decision remains in effect.

Most of the countries of the world are Parties to the 1961 or 1971 UN Conventions, respectively. When the decision is taken to put a new psychoactive substance under international control, the regulatory measures defined by the international schedules have to be implemented in all countries being Party to these Conventions. These countries have to add an internationally scheduled drug to the appropriate national schedule, i.e. the national schedule should reflect as far as possible the extent of control set by the United Nations for the respective drug.

4.3.1.4. Consequences for pharmaceutical industry

Because of their public responsibility and product liability, pharmaceutical companies have to judge whether or not a new psychoactive drug developed by them should be subjected to regulatory control before marketing. If regulatory control is considered necessary to protect public health, the new drug has to be included into the relevant national schedules in a timely manner to prevent any delay in marketing of the product in the respective countries.
As described above, the initiation of an international scheduling action, although attractive at first sight, is no viable approach to achieve this goal. The several are:

- Considering the total time the UN need to come to a scheduling decision (usually several years) and the time subsequently needed by the Parties to the UN Conventions to implement these decisions nationally (~ 180 days, but can also be longer), a scheduling action triggered via the UN can be expected to impede fast market access. An international scheduling action can also not be started at an early stage of development (to make up for the time needed by UN), as it is not clear at such a stage whether the development will be continued. Furthermore, some of the required data to judge the abuse liability may not yet be available or may be considered too confidential to be distributed to UN bodies.
- It is not clear from the available legal provisions, how a pharmaceutical company could start an international scheduling action and which kind of data they would need to provide.
- For psychoactive substances, the absence of actual epidemiologic abuse data may deter ECDD from taking a “preventive” scheduling decision regarding new psychoactive substance developed by pharmaceutical industry or at least delay such decision.

4.3.2. Scheduling actions in the United States

4.3.2.1. General legal provisions

In the U.S., amendments to the lists of controlled substances require a respective ruling by the Attorney General. Scheduling decisions can be taken by the Attorney General on his own motion, at the request of the Secretary of Health and Human Services (HHS) or on petition of any interested party (§ 811 Controlled Substances Act, CSA). Such decision of the Attorney General must be based on a medical and scientific evaluation and recommendation from the Secretary of HHS (§812 CSA). The evaluation and recommendation by Secretary of HHS has to be based on a so-called “eight-factor analysis” (§ 812(c) CSA):

(1) The new product’s and continued drug substance's actual or relative potential for abuse.
(2) Scientific evidence of its pharmacological effect, if known.
(3) The state of the current scientific knowledge regarding the product.
(4) Its history or current pattern of abuse.

(5) The scope, duration, and significance of abuse.
(6) What, if any, risk there is to the public health.
(7) Its psychic or physiological dependence liability.
(8) Whether the drug substance contained in the product is an immediate precursor of a substance already controlled under the CSA.

The evaluation/recommendation by the Secretary of HHS is binding on the Attorney General to such an extent that if the Secretary recommends that a substance or schedule should not be controlled, the Attorney General cannot control it.

To avoid imminent hazard the Attorney General may schedule a substance without prior consultation with HHS on a temporary basis (1 year) in Schedule I on condition that the substance is not yet scheduled or not an approved medicinal product. A notification of that order must be published 30 days ahead.

In the event that the 1961 UN Convention is amended, the Attorney General can issue an order to control such substance under the Schedule he deems most appropriate. In this case there is no need for prior consultation of the Department of HHS (§ 811(d)(1)). In the event that the 1971 UN Convention is amended, the Secretary of HHS after consultation with the Attorney General will first determine whether existing controls meet the specified requirements. If this is not the case, the Secretary of HHS is expected to take the following actions: (1) recommend a scheduling action (which may or may not include more stringent measures than required by the UN Convention) or (2) request the Secretary of State to transmit a written notice to the UN (pursuant to paragraph 7 of Art. 2 of the 1971 Conventions) explaining that the U.S. will not be able to apply all provisions to that substance or preparation or ask for review of the UN scheduling action by the Economic and Social Council of the UN (§ 811(d)(3)).

The U.S. position on international scheduling issues is developed by the Controlled Substances Staff (CSS), a special division within FDA, in collaboration with the Department of State, the DEA and the National Institute on Drug addiction (NIDA).

4.3.2.2. Control of new psychoactive substances for which a marketing authorisation application has been submitted

Within FDA, the CSS is the focal point for all activities regarding scheduling, abuse, and dependence of substances, including international scheduling and control. The *Manual of Policies and Procedures* MAPP 4200.3 establishes the responsibilities and procedures in the Center for Drug Evaluation and Review (CDER) for consulting CSS regarding the evaluation of abuse liability, drug dependence, risk management and drug scheduling.

Upon submission of a New Drug Application (NDA) for a CNS-active medicinal product with a known or potential risk for abuse (e.g. a new pain medication containing a new opioid substance), the responsible review division at CDER (e.g. the Division of Anaesthesia, Analgesia and Rheumatology Products), is required to complete a consult request form (FDA 3291) which is to be forwarded together with supporting documents (i.e. the sections of the NDA related to abuse liability, letters from the sponsor on abuse liability issues and any other information pertinent to the abuse liability of the medicinal product) to the CSS coordinator. According to FDA's *Guidance for Review Staff and Industry on Good Review Management Principles and Practices for PDUFA Products* (April 2005), consult of CSS must be requested within 30 (for priority status reviews) and 45 days (for normal status reviews) of submission. The CSS must be informed by the responsible CDER review division about the desired

completion date for the review, any pertinent internal or industry meetings, Advisory Committee meetings, and meetings with other groups.
The CSS coordinator notifies the DEA, about the submission of a marketing authorisation application for new drug that appears to have abuse liability and assigns a reviewer for the medicinal product in question.
The CSS reviewer has to analyse the documents, attend meetings as requested by either the responsible review division or the CSS, request abuse-related data if necessary or available from external (e.g. Substance Abuse and Mental Health Services Administration (SAMHSA), NIDA, DEA) or internal sources (e.g. Division of Surveillance, Research and Communication Support DSRCS, ODS). When drawing up the scientific statement, CSS will take the eight factors as required by the CSA into account (for details see above).
In addition to the CSS, the Office of Drug Safety (ODS) has to be involved by the CDER division to assess and discuss any proposal of a RiskMAP submitted by the applicant. The responsible CDER division has to request consult from CSS, ODS and the Division of Drug Marketing, Advertising and Communication (DDMAC) to evaluate the proposed trade name, product information, package labelling.

The CSS will coordinate with the Office Chief Counsel, CDER, FDA, and the Department of HHS, the transmission of the scientific assessment and the scheduling recommendations to the DEA. Based on the recommendations provided by FDA, a scheduling decision is eventually made by the DEA (for the Attorney General).

The time needed by FDA/DHHS to draw up the scientific recommendations on the abuse potential and scheduling of a new medicinal product and by DEA to issue a scheduling decision is in general several months. The national scheduling process is planned to run in parallel to the general review and approval process of the medicinal product.

4.3.2.3. Consequences for pharmaceutical industry

The US drug scheduling process for new psychoactive is very transparent and can be easily understood from the available legal provisions as well as guidance documents and other publications from the relevant agencies (e.g. MAPP 4200.3, *Guidance for Review Staff and Industry on Good Review Management Principles and Practices for PDUFA Products* (April 2005), homepage of the Controlled Substances Staff). Due to the intensive interlinkage between marketing authorisation procedures and scheduling procedures and due to the existence of standardised procedures, pharmaceutical companies do not have to worry about how to ensure that scheduling actions are taken in a timely manner: The scheduling of a new psychoactive drug is clear at the time the marketing authorisation is issued.

4.3.3. Scheduling actions in the European Union

4.3.3.1. Scheduling actions triggered by the European Union

Despite the lack of a harmonised European classification system and of harmonised European control measures, the European Union can nonetheless trigger scheduling actions and assure that these are implemented at a national level. The European Union first obtained competence in this area by the Joint Action 97/396/JHA: This Joint Action introduced an early warning mechanism with the aim to enable new synthetic drugs of abuse not currently listed in the schedules of the 1971 UN Conventions to be reported and banned quickly after they appeared on the market. Based in Joint Action 97/396/JHA, Europol and the EMCDDA collected information from

Member States on the production, traffic and use of new synthetic drugs with an abuse potential comparable to substances listed in Schedules I and II of the 1971 UN Convention. This information was to be shared with the other Member States, the Commission, and the European Medicines Agency (EMEA). At the request of one of the Member States or the Commission, the EMCDDA had to convene a special meeting under the auspices of its Scientific Committee (with representatives of the Commission, Europol and the EMEA). The Committee's duty was to assess the possible risks, including the health and social risks, caused by the new synthetic drugs, and discuss possible consequences of prohibition. This risk assessment was to be carried out on the basis of information provided by the Member States, the Commission, the EMCDDA, Europol, the EMEA and had to take into account all factors which, according to the 1971 UN Convention, would warrant the placing of a substance under international control. On completion of the risk assessment, a report was drawn up on the findings. The Council could, within a month from the date of this report, adopt an unanimous decision that the new synthetic drug should be made subject to national control by the Member States of the EU. The Member States had to implement the decision taken by the Council, within such delay as that decision specified (usually 90 days).

The early warning system was introduced to address the growing concern that national legislation constantly lagged behind the emergence of new synthetic drugs of abuse on the market. It was thought that this could only be remedied by some concerted action of the European Union. Meanwhile, the Joint Action 97/396/JHA has been replaced by the Council Decision 2005/387/JHA *on Information Exchange, Risk Assessment and Control of New Psychoactive Substances*, which retains the basic principles of 97/396/JHA, but redefines its main objective, the clarity of its procedures and definitions, the transparency of its operation, and last but not least its scope. The deadline to implement the necessary national measures once the Council decides to submit a new psychoactive substance to control measures has been extended to one year (from previously 90 days). More importantly, in addition to new psychotropic substances in the meaning of the 1971 UN Convention, Decision 2005/387/JHA now also covers new narcotic substances in the meaning of the 1961 UN Convention. It is important to note that human medicinal products (as defined in Directive 2001/83/EC, as amended) are now also within the scope of the decision. However any decision taken under the provisions of Decision 2005/387/JHA must not result in any deterioration of human health care and substances of established and acknowledged medical value are excluded from control measures triggered by Decision 2005/387/JHA. It seems somehow contradictory to include medicinal products into the initial assessment but to exclude these products from any control measures. Neither does it make much sense to reinforce the exchange of information and appropriate cooperation with EMEA, by making use of information obtained under the pharmacovigilance systems as defined in Directive 2001/83/EC, but to exclude medicinal products from any control measures provided for by Decision 2005/387/JHA. According to Decision 2005/387/JHA, where the information on abuse concerns an approved medicinal product, the Commission, on the basis of data collected by EMCDDA and Europol, shall assess with the EMEA the need for further action, in close cooperation with the EMCDDA and in accordance with the mandate and procedures of the EMEA. It is not quite clear what this provision really means as EMEA does not have a real mandate to require Member States to put psychoactive substances under regulatory control. Interestingly Paragraph 32 of the "Preamble" of Directive 2001/83/EC, as amended, states in this respect that it is considered important especially with regard to the Community marketing authorisation procedure (Centralised Procedure, CP) to harmonise the basic principles applicable to the classification for the supply of medicinal products in the European Union by taking as a starting point the principles already established on this subject by the Council of Europe as well

as the work of harmonisation completed within the framework of the United Nations, concerning narcotic and psychotropic substances, but neither Directive 2001/83/EC nor Regulation (EC) 726/2004 install measures apart from special prescription control that would ensure or initiate such harmonisation.

4.3.3.2. Consequences for pharmaceutical industry

Although Decision 2005/387/JHA provides the possibility for harmonised European scheduling actions, it currently cannot be used for new psychoactive substances of therapeutic value for which a marketing authorisation is submitted. It is also unclear whether a scheduling action under Decision 2005/387/JHA could be initiated by a pharmaceutical company. Nonetheless, Decision 2005/387/JHA is definitely a step towards a more coherent approach within the European Union. Pharmaceutical companies developing new psychoactive substances should stay alert with respect to future developments in this field.

4.3.3.3. Scheduling actions in France

4.3.3.3.1 General legal provisions in France

According to Art. L. 5132-7 and R. 5132-88 of the *Code de la Santé Public*, any amendment to the narcotic and psychotropic lists require a ministerial decree (so-called *arrêté*) which is to be signed by the Minister of Health. The Minister takes his decision upon proposition of the General Director of Afssaps after consultation with the National Commission on Narcotics and Psychotropics (*Commission nationale des stupéfiants et des psychotropes*). According to Article R.5132-103, the duties of the *Commission nationale des stupéfiants et des psychotropes* comprise the evaluation of the dependence and abuse potential of substances, plants, medicinal or other products and of their potential effects on public health, and the recommendation of control measures to prevent drug dependence and abuse.

Under the French law on controlled substances, a national evaluation system for drug dependence is established which includes Afssaps, the above-mentioned National Commission, Drug Dependence Evaluation and Information Centres (*Centres d'évaluation et d'information sur la pharmacodépendance,* CEIP), healthcare professionals and pharmaceutical industry. Healthcare professionals and pharmaceutical industry are required to notify severe cases of abuse or dependence to CEIP or Afssaps, respectively. Afssaps is responsible for coordinating all evaluation activities regarding drug dependence and all actions of the different bodies involved in the national evaluation system (Article R.5132-100). As described in its Activities Report 1999, Afssaps has the duty to control the licit use, i.e. the licit production and placing on the market, of narcotics and psychotropic substances. It is the central body of administration of controlled substances with regard to the 1961 and 1971 UN Conventions. Together with the General Division of Health it fulfils the function of developing and application of control measures for narcotics and psychotropic substances, independently of whether these constitute medicinal products or not.
Afssaps does not only ensure the application of the Conventions through its General Director but also furnishes EMEA, the INCB and WHO with all relevant information on drug dependence (Article R.5132-102).

⇒ In France, approval by a Minister is necessary to alter the list of controlled substances and the Afssaps is involved in all scheduling recommendations.

4.3.3.3.2 Control of new psychoactive substances for which a national marketing authorisation application has been submitted to Afssaps

No information is publicly available on this issue from Afssaps. According to personal communcication, when a marketing authorisation application is submitted for a medicinal product containing a new psychoactive substance, the committee concerned with the scientific assessment of the application gives advice on the whether or not a marketing authorisation will be granted and in parallel asks the National Commission on Narcotics and Psychotropics (Commission nationale des stupéfiants et des psychotropes) for its advice on the classification of the medicinal product. There are no strict timelines for this process. As marketing authorisation procedures may easily take up several years (current average 22 months) in France, the scheduling decision can be expected to be obtained in parallel to the decision on the marketing authorisation application. The information on the scheduling will be officialised in Appendix II of the licence (Appendix I contains the approved Summary of Product Characteristics; Appendix III the leaflet and labelling). When the marketing authorisation application is submitted through a Mutual Recognition Procedure (MRP), the advice of the narcotic committee will only be given after Day 90 of the procedure, i.e. during the time when the national marketing authorisation is issued. In this case a delay in the issuance of the marketing authorisation could occur, as this process currently takes only 6 months on average.

4.3.3.4. Scheduling actions in Germany

4.3.3.4.1 General legal provisions in Germany

In Germany, amendments to the Schedules (Anlagen I to III) of controlled substances require statutory orders that have the force of law. These statutory orders are called "*Betäubungsmittelrechts-Änderungsverordnungen*" and are numbered consecutively. They are issued by the Federal Government. In general, a scheduling decision can only be taken after experts have been heard and the Bundesrat has consented (§ 1(1) BtMG). However, where the update concerns the transposition of a UN scheduling action, the Ministry of Health and Social Security does not need to hear experts nor does it need the consent of the Bundesrat (§ 1(4) BtMG).

To get the opinion of experts, the Federal Ministry of Health and Social Security has established the so-called Expert Committee on Narcotic Drugs (*Sachverständigenausschuss für Betäubungsmittel*). This Expert Committee meets on a regular basis. Its activities are lead by BfArM. The Head of the *Bundesopiumstelle*, i.e. the Division on Narcotic Drugs in BfArM, also heads the Expert Committee. The Expert Committee discusses requests to amend the schedules of the BtMG, and gives a scientific recommendation to the legislator. On the basis of the vote of the Expert Committee, a draft ordinance is prepared and published for comments (Blasius *et al.*, 1997).

In urgent cases, the Federal Ministry of Health and Social Security has the authorisation to temporarily (for the period of one year) include substances and preparations (which are not medicinal products) in the appropriate schedules if this is necessary due to the extent of abuse and actual danger of health ("emergency" system).

Scheduling actions initiated by the European Union (Council Decision), follow the normal route of amendments, i.e. a hearing of experts and the consent from the Bundesrat are required.

As a consequence of the involvement of the Bundesrat, the decision-making process can be rather lengthy and the time from the meeting of the Expert Committee until the coming into effect of the ordinance may easily take several months.

⇒ In Germany, approval by the Federal Government is normally needed to alter the list of controlled substances. BfArM is involved via its Division on Narcotic Drugs (Bundesopiumstelle) in the Expert Committee on Narcotic Drugs (*Sachverständigenausschuss für Betäubungsmittel*) and thus in scheduling recommendations.

4.3.3.4.2 Control of new psychoactive substances for which a national marketing authorisation application has been submitted

When a marketing authorisation for a medicinal product containing a new psychoactive substance is submitted, the relevant clinical or preclinical assessor would normally contact the "Bundesopiumstelle". Once this cooperation has been set up, all necessary actions can be such that decisions on whether or not to put this substance and preparations thereof under control are taken in a timely manner. A close interaction between the *Sachverständigenausschuss* and the assessors of the marketing authorisation application is necessary to determine the scheduling class. Introduction in Anlage III is *per se* only possible when it is clear that the marketing authorisation will ultimately be granted. Considering the feedback received from BfArM (personal communication), there does not seem to be a standard process ensure that marketing authorisation procedures and scheduling procedures are well-coordinated. It is thus highly recommended that the applicant makes sure that the "Bundesopiumstelle" is being informed on the submission of the marketing authorisation application of a new psychoactive drug. Through the information exchange between the scientific assessors of the marketing authorisation application, the applicant, the "Bundesopiumstelle" and the *Sachverständigenausschuss* scheduling decisions and the granting of a marketing authorisation are coupled at least to some extent. It should however be kept in mind that the scheduling decisions must be approved by the Federal Government and the Bundesrat. It is not likely that these bodies would oppose a scheduling recommendation from the *Sachverständigenausschuss*, but depending on other matters that may be included in the same scheduling action (decisions on other substances, change of regulatory provisions), a scheduling decision might become delayed. Taking into account the fact that national marketing authorisation procedures may take up to 24 months (current average) in Germany, it would seem however likely that the scheduling decision could be taken in that timeframe. In the case that a scheduling decision was delayed, the granting of the marketing authorisation would most probably be delayed. Alternatively, a conditional approval might be issued (prohibiting the marketing until a scheduling decision has been taken), or the approval might be granted with transitional provisions to be taken by the applicant regarding trade and dispensing of the product (as e.g. identified in a risk management plan). As the abuse liability assessment can be considered an important component of the overall risk-benefit analysis (§ 25(2) No.5 of the *Arzneimittelgesetz*), it is highly unlikely that the marketing authorisation would be granted without any restriction before the scheduling decision was granted.

When the marketing authorisation application for a medicinal product containing a new psychoactive substance was submitted through a Mutual Recognition Procedure (MRP), the time that is normally needed for the MRP and the issuance of the marketing authorisation (~ 6 months) might not suffice for a scheduling decision to be taken.

It should be noted in this respect that according to § 25 (2) No.7, the granting of a marketing authorisation for a medicinal product must be denied if its trade was in contrast to domestic legal

provisions or a regulation or decision of the Council or Commission of the European Union, e.g. when the product was classified in Anlage I.

4.3.3.5. Scheduling actions in Italy

4.3.3.5.1 General legal provisions

In Italy, according to Section 13 of DPR 309/90, any amendments to the Tables (Schedules) containing the lists of all controlled substances require a decree signed by the Minister of Health, jointly with the Minister of Justice. A central body in the Ministry of Health, the *Ufficio Centrale Stupefacenti* (Central Office of Narcotic Drugs), prepares the decision together with the *Istituto Superiore di Sanità* (Italian Health Institute) after positive judgement by the *Consiglio Superiore di Sanità* (Health Superior Council).
According to DPR 309/90, a national scheduling action has to be triggered when amendments are made to the annexes of the UN Conventions or when a Council Decision is taken with regard to the control of substances in the European Union. Likewise, the Tables should also be updated whenever new scientific evidence becomes available.

The inclusion of a specific drug into an appropriate Schedule is made based on the classification criteria described in Chapter 4.2.2.4.2.

⇒ In Italy, approval by two Ministers is necessary to alter the list of controlled substances.

4.3.3.5.2 Control of new psychoactive substances for which a national marketing authorisation application has been submitted

When a marketing authorisation is issued for a new psychoactive substance with potential for abuse, i.e. when the corresponding decree is published in the Italian Official Journal, the Table under which this new substance falls (if any at all) is already indicated. This means that the marketing authorisation procedure and the scheduling procedure, although separate procedures, one managed by the "Italian Medicines Agency" (*Agenzia Italiana del Farmaco*, AIFA), the other by the Central Office of Narcotic Drugs in the Ministry of Health, are interlinked.
The information on the need to schedule a new active substance can either be passed on to the Ministry of Health by the scientific assessors of the marketing authorisation application or by the pharmaceutical company who can directly submit a proposal for classification. Any submission by a pharmaceutical company should be accompanied by a documentation package adequately supporting its request. The pharmaceutical company is given the possibility to ask for an appointment to discuss the issue in person with some official representative from the Ministry.
Before AIFA was established in July 2004, the interface between regulatory actions and scheduling actions was even more elaborate as these actions were administered by the same division in the Ministry of Health. The future will show whether or not the above processes will still run smoothly after this re-organisations made within the Italian Ministry of Health. Taking into account the fact that national marketing authorisation procedures may take up to 23 months (current average) in Italy, it would seem however likely that the scheduling decision could still be taken parallel to the marketing authorisation procedure. Considering the fact that the issuance of a national marketing procedure after successful conclusion of an MRP takes 18 months on average in Italy, there should also be no delay in market access when the marketing authorisation was submitted via an MRP.
It should also be noted that in former times, the procedure for scheduling could be started already with the evaluation of clinical trials investigating new chemical entities displaying abuse

potential. The ministerial assessor of those trials informed the *Ufficio Centrale Stupefacenti* about the new substance and thus could trigger an evaluation procedure on the necessity of scheduling actions. As the Ministry of Health is not involved in the evaluation of most studies any longer, the procedure for scheduling will now most probably be only started with the submission of the marketing authorisation procedure.

4.3.3.6. Scheduling actions in Spain

4.3.3.6.1 General legal provisions

In Spain, any amendment to the list of controlled substances is published in the Spanish Official Journal. This Official Journal is updated by the department in the AEMPS that deals with controlled substances (*División de Estupefacientes y Psicotropos* in the *Subdirección general de Inspección y Control*). This is generally only done after international scheduling activities (i.e. scheduling actions by the relevant UN bodies) but can also take place upon Council Decisions by the European Union.

Any change in the annexes of the1961 UN Convention is transposed into national law via orders or resolutions (*Ordenes*), issued by the *Dirección general de Farmacia y Productos Sanitarios* in the Spanish Ministry of Health. Likewise, changes to the Annexes of the Real Decreto 2829-1977 require resolutions by the Dirección General de Ordenación Farmacéutica. This means that amendments require signature of one Minister.

When a purely national scheduling action is required, the Spanish Ministry of Health prepares additional legislation through *Ordenes* which permit inclusion of these substances into Annex I. The Spanish Health Ministry will transmit this information to WHO through the *Dirección general de Farmacia y Productos Sanitarios*.

⇒ In Spain, approval by a Minister will suffice to alter the list of controlled substances.

4.3.3.6.2 Control of new psychoactive substances for which a national marketing authorisation application has been submitted

No information has been obtained so far on the exact procedure to put a medicinal product containing a new psychoactive substance under national control. AEMPS can in any case decide that some national control measures are applied e.g. a prescription control analogous to that of narcotic or psychotropic substances. According to the Real Decreto, there should also be measures to submit new psychotropic substances under national control. However, with the Spanish scheduling system mirroring the UN system, the degree of national flexibility and freedom to act seems to be more restricted than in other European countries. This is also reflected in some preliminary feedback by AEMPS indicating that this matter is regarded as highly complex.

4.3.3.7. Scheduling actions in the United Kingdom

4.3.3.7.1 General legal provisions

Any amendment to the Schedules of the MDA requires an Order in Council by Her Majesty, the Queen of England. These orders are issued after approval of both houses of Parliament and are called "*The Misuse of Drugs Act 1971 Modification Orders*". An Order in Council may be varied or revoked by a subsequent Order in Council. Any amendment to Schedules 1 to 5 of the *Misuse of Drugs Regulations* 2001 are made by the Secretary of State in exercise of the powers

conferred to him by sections 7, 10, 22 and 31 of the MDA. These amendments are called "*The Misuse of Drugs (Amendment) Regulations*".

It should be mentioned that in the UK, due to the fact that some substances are classified under the generic system (i.e. definitions applying to a family of substances), less scheduling actions are required than in most countries worldwide that only rely on the "individual list" system. On the other hand, the generic system may sometimes cause quite some a debate on whether or not a new substance is already classified under the generic system.
In the amendment processes of both the MDA and *Misuse of Drugs Regulations* 2001, the so-called *Advisory Council on the Misuse of Drugs*, also known as the ACMD or the *Advisory Council*, plays a key role: No amendment to the legal provisions can be made without prior consultation of the ACMD. The Advisory Council has been established under Section 1 of the MDA and constitutes a statutory and non-executive, independent expert body that advises the British Government on all drug-related issues. According to Sec. 1(1) of the MDA, ACMD's duty is to keep under review the misuse of drugs in the UK and to advise any one or more of the Ministers, i.e. the Secretary of State for the Home Office, the Secretaries of State concerned with health and/or the Secretary of State concerned with education, on measures (which may or may not involve a change of law) to prevent misuse and to deal with the social problems caused by such misuse. ACMD considers any substance which is being or appears to be misused and which is or appears to be capable of having harmful effects sufficient to cause social problems. Much of the Advisory Council's work is taken forward in its Committees and Working Groups.
As defined in Section 1(3) of the MDA, ACMD has to take action on any matter referred to them by the Ministers or any communication referred to them via the Secretary of State by any organisation or authority established by or under any treaty, convention or other agreement to which the British Government is a party. As such, the ACMD e.g. works closely together with the "British Medicines Agency" (Medicines and Healthcare Products Regulatory Agency (MHRA)), bodies of the European Union and the UN CND.

⇒ In the United Kingdom approval of parliament (including signature of the Secretary of State) is needed to modify the lists of controlled substances annexed to the *Misuse of Drugs Act* 1971, as amended. For subsequent changes in the Schedules annexed to the *Misuse of Drugs Regulations* 2001, the signature of the Secretary of State or an authorised person will suffice. The MHRA is not directly involved in scheduling recommendations.

4.3.3.7.2 *Control of new psychoactive substances for which a national marketing authorisation application has been submitted*

No information is publicly available on the coupling of marketing authorisation and scheduling procedures. According to feedback from MHRA, MHRA mainly assess applications using quality, safety and efficacy criteria. MHRA would consider the in-use potential abuse and implications for patients. However, it is the Home Office in the UK that deals with the Misuse of Drugs Regulations and determine whether a particular drug should be placed on the controlled drug list. From the feedback received to date it seems that MHRA would not take any active role in coordinating marketing authorisation and scheduling procedures. This would leave it to the applicant to make sure that a scheduling action is triggered in a timely manner.

4.3.3.8. Timeliness of implementing international scheduling actions (including those triggered by EMCDDA) in the European Union

Art. 2.7 of the 1971 UN Convention on Psychotropic Substances request a decision of the Commission on Narcotic Drugs to put a substance under control to become effective within 180 days of its communication to the Parties. EU Council Decisions to control substances similarly give a deadline for their implementation, which used to be 90 days.

Between 2000 and 2004, a survey was conducted by EMCDDA in order to evaluate the timeliness of implementing an international scheduling decision. The survey compared theoretical estimates for implementation times as provided by the 15 "old" Member States of the European Union (see Table 11) with the situation in practice. To consider the situation in practice, the national scheduling of four substances requested to be controlled by CND or the EU Council were tracked. The actual number of days between the international request and the actual implementation (real-life experience) of national control is given in Table 12.

Table 11: Estimates of the time it takes to put a substance under control after a corresponding decision has been taken either by CND or the EU Council

Member state	Time estimate
Austria	no estimate available
Belgium	≥ 6 months
Denmark	~ 10 days
Germany	1-2 months
Greece	1-2 months
Finland	2 weeks
France	≥ 2 months
Ireland	~ 1.5 months (generic system may be applicable)
Italy	1-2 months after scientific results are made available
Luxembourg	1-2 months
the Netherlands	~ 1 month
Portugal	1-6 months
Spain	~ 4.5 months
Sweden	if UN ⇒ automatic, otherwise - ~1 month
United Kingdom	1.5-2 months (generic system may be applicable)

Note: *Figures are not fully comparable, as some countries may have included the period for scientific evaluations, or the time between final approval of the law and its official publication.*

(Source: modified from EMCDDA report *Legal response to new synthetic drugs 2000-2004* of Jul 2004)

Table 12: Number of days between international request and actual control of a substance

Substance / Member state	4-MTA (EU: 90 days)	GHB (UN: 180 days)	2-CB (UN: 180 days)	PMMA (EU: 90 days)
Austria	568	932	not controlled	not controlled
Belgium	60	n.a.	323	54
Denmark	81	n.a.	10	70
Germany	n.a.	263	n.a.	n.a.
Greece	n.a.	n.a.	n.a.	n.a.
Finland	76	173	173	not controlled
France	1040	407	407	57
Ireland	not controlled	n.a.	n.a.	n.a.
Italy	54	n.a.	n.a.	279
Luxembourg	80	not controlled	186	53
the Netherlands	138	498	n.a.	229
Portugal	351	1065	1065	533
Spain	145	269	269	142
Sweden	75	n.a.	385	116
United Kingdom	868	750	n.a.	n.a.

4-MTA: 4-methylthioamphetamine, GHB gammahydroxybutyric acid, 2-CB: 4-Bromo-2,5-dimethoxyphenetyl-amin, PMMA: N-methyl-1-(4-methoxyphenyl)-2-aminopropane

"n.a." indicates that the substance was already controlled in that country

(Source: EMCDDA report *Legal response to new synthetic drugs 2000-2004* of Jul 2004)

Curiously, many countries predict an average estimate of 1-2 months to implement control measures on a national basis, but were actually not able to comply with these estimates. Some countries take a year or more to put a substance under control. If scheduling actions triggered by supra-national agreements (where the issue of scheduling itself should not be debatable) may already take up several months, one may wonder how long national scheduling decisions might take when there is no external trigger, e.g. in the case that a marketing authorisation application is submitted for a new psychoactive substance with abuse potential. It can only be hoped that future developments in this field will take further steps towards a more harmonised European approach, preferably installing a pan-European classification and control system.

4.3.4. Comparison of scheduling actions in different countries and their impact on marketing authorisations granted under different procedures

For pharmaceutical companies developing new psychoactive substances the "individual list" system that is established in most countries can have both advantages and disadvantages depending on the substance under development. It may be considered advantageous in those cases where the new substance or preparation can be demonstrated to have a low potential for abuse. The control measures simply do not apply to the new drug and thus no efforts will be needed to get an exemption from control as purely generic system may require. When the new psychoactive substance is however suspected to have a considerable abuse liability, a pharmaceutical company would probably want, for reasons of public responsibility and liability, to have the substance placed under regulatory control before marketing. With the increasing

regulatory emphasis on prospective risk assessment and minimisation, a clear position will be expected from pharmaceutical companies towards the necessity of regulatory control and other actions to minimise risks.

When new psychoactive drugs need to be put under regulatory control, it is essential to understand how regulatory control can be achieved in a timely manner such as not to delay the marketing of these products. The above review of scheduling procedures has shown that not only do the classification systems of controlled substances vary considerably between countries, but also the legal procedures involved in putting a new substance under control differ from country to country. The following conclusions can be drawn:

- International scheduling actions are far too slow to be an attractive option for pharmaceutical companies to put new psychoactive drugs for which marketing authorisations (MAs) are sought under national control. International scheduling actions can easily take several years and it will take further months (or even years) to have the scheduling decisions implemented at the national basis. To have an international scheduling decision nationally implemented at the time the first MAs are obtained would require starting the scheduling action at a time point when a final decision on the further development of a candidate drug may not even have been taken; to say nothing of the fact that at that point in time there would probably be so few data available on the abuse liability of a substance that no rational decision-making could occur.
- For some countries, like the U.S. who have established highly standardised and interrelated procedures for MA and scheduling there is not too much to worry about from the perspective of pharmaceutical industry. New drug applications for medicinal products containing new psychoactive substances will automatically involve consult from the relevant department at the FDA (the Controlled Substances Staff) and the DEA and thus ensure that a scheduling decision is taken at the time the MA is granted.
- As for national MA procedures in countries of the European Union, scheduling and marketing authorisation procedures are coupled in most countries at least to some extent, even though the processes are not as tightly interwoven as in the U.S. In contrast to the situation in the U.S., it seems, however, advisable for pharmaceutical companies to ensure that the respective national bodies involved in scheduling decisions get all relevant information in a timely manner such that the scheduling decision can be taken before or at the time the MA is granted. With national MA procedures taking one to two years on average, there should be enough time to obtain a national scheduling decision even in cases where national schedules can only be amended by approval of parliament.
- As far as the situation in Europe is concerned, it has however to be kept in mind that the importance of national MA procedures and thus the involvement of national “Medicines Agencies” in the evaluation process of medicinal products has been decreasing since the introduction of the Mutual Recognition Procedure (MRP), the Centralised Procedure (CP) and more recently the Decentralised Procedure (DCP). When the national “Medicines Agencies” become less and less involved in the evaluation of MA applications, including those for medicinal products containing new psychoactive substances, the delicate coupling between the MA procedures and scheduling decisions may come off balance, as information may not be passed on to the relevant national bodies for scheduling actions as timely as this would be necessary:

- *MRP*: The MA application (MAA) (for a medicinal product containing a new psychoactive substance) is first submitted in one Member State only. This Member States, the Reference Member State (RMS), is performing a full evaluation of the submitted dossier which may take the above-mentioned average of one to two years. This timeframe will most probably suffice to also obtain a national scheduling decision for the new psychoactive substance and the preparation thereof. MAs in further Member States (Concerned Member States, CMS) are obtained by mutual recognition of the marketing authorisation issued by the RMS. With 3 months overall duration, the MRP is much shorter than a national marketing authorisation procedure. Taking into account the discussion of chapter 4.3.3.8, this timeframe is unlikely suffice to obtain scheduling decisions in the CMS. This may at best result in a delay in the issuance of national MAs, which currently already takes 3 to 6 months on average for "normal" products that do not require any scheduling decision. Considering that the abuse liability assessment is an important component of the risk-benefit evaluation of an authority, a lack of scheduling could also be interpreted as a serious risk to public health and even impede the European phase of the MRP.
  There are several MRPs with opioid-containing medicinal products. In almost all cases however the scheduling decision had been taken well before the MAAs had been submitted via the MRP (i.e. the MAAs where for medicinal products with known active substances). There is however one exception: In June 1996, an MRP was started with the medicinal product Ultiva® which is a powder for solution for injection containing the hydrochloride salt of the opioid remifentanil. Germany was RMS, and Austria, Belgium, Denmark, Finland, France, Greece, Italy, Luxembourg, the Netherlands, Portugal, and Spain were CMS. In the case of remifentanil the international scheduling action was only initiated in 1999. Before that national scheduling actions in some countries, e.g. in Germany (20 Jan 1998) and in France (29 Nov 1996), but only in France the MA was issued after the scheduling decision so that the available example again is not really adequate as the discussion/concern about remifentanil's abuse potential was obviously initiated after its marketing.
- *CP*: Here MAs are granted by the European Commission and not by single Member States anymore. The national "Medicines Agencies" are still involved to some extent in the evaluation of the application dossier, but while this involvement may still be considerable where a country has a leading function in the assessment (e.g. rapporteur or co-rapporteur), the involvement is much more reduced in the other Member States. In this case the information exchange with the relevant national bodies for scheduling actions may not take place or at least not take place in a timely fashion. According to Art. 9 of Regulation (EC) 726/2004 *laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, EMEA is required to annex the following details to a favourable opinion on a marketing authorisation application: any conditions or restrictions which should be imposed on the supply or use of the medicinal product, including the conditions under which the medicinal product may be made available to patients. (see Title VI of Directive 2001/83/EC, regulating different categories of prescription) and any recommended conditions or

restrictions with regard to the safe and effective use of the medicinal product. The same Regulation does not however confer any rights to EMEA to enforce any recommendation that a medicinal product containing a new psychoactive substance should be classified according to the relevant national provisions regulating controlled substances. It is not quite clear to what extent the issuance of a Community authorisation would be affected when safe use would require control of the medicinal product under the controlled substances law. Would the granting be delayed until adequate control was established in all Member States, would the Community authorisation be conditional, i.e. only coming into effect in a country once adequate control was established or would appropriate risk minimisation provisions by the applicant suffice until adequate control was established by the Member States? Feedback form EMEA confirmed that this is a complex question. EMEA would expect the applicant to identify the risk and propose suitable risk minimisation member in the form of an EU-RMP. In the end, it is considered both the responsibility of the company and the MS to make sure there proper measures are taken regarding the classification.

Currently there are only two examples of opioid-containing medicinal products authorised via the CP. These are Orlaam® (authorised: 01 Jul 1997 / 16 Mar1998, suspended in 2001, withdrawn in 2002) and Ionsys® (authorised: 24 Jan 2006). The active moieties of both products (levoacetylmethadol and fentanyl, respectively) had been controlled on an international level well before the central MAA was submitted. This means these two products cannot be considered adequate examples of how scheduling actions may be initiated on a European level. It is however worth mentioning, that although the active substance in Orlaam® was already scheduled in Germany, it was scheduled in Anlage I at the time the first central MA (01 Jul 1997) was received. It was only between the first and the second marketing authorisation for Orlaam® (20 Jan 1998) that the relevant isomer contained in Orlaam® was moved to Anlage III and thus eligible for marketing and prescription. This at least shows that the central MA does consider local market restrictions and that local adaptations to the European provisions occur, albeit this may happen relatively slowly

- The newly established decentralised procedure (DCP) could offer some advantages in this respect. Here, one of the Member States takes the lead in the evaluation process (RMS). In contrast to the MRP, however, the CMS are already involved in the evaluation process from the very beginning. With 120 days for the initial assessment, a clock-off period of several months and another 90 days of procedure, the level of involvement of Member States and the timeframe may allow national scheduling decisions to be taken in a timely manner.

It seems that the classification of medicinal products containing new psychoactive substances and the implementation of necessary control measures would require some kind of harmonised European approach. However, to date, the matter has not appeared on the agenda of the *Coordination Group for Mutual Recognition and Decentralised Procedures* (CMD), or its precedent, the *Mutual Recognition Facilitation Group* (MRFG) (personal communication by two CMD members). This is not too surprising as the number of medicinal products containing new psychoactive substances has been rather limited during the past years. Bearing the above-said in mind, it is imperative for pharmaceutical companies that develop medicinal products with new psychoactive

substances to get detailed knowledge on both how scheduling actions work in all countries of the European Union and which bodies participate in decision-making. To the extent that this is possible, these bodies should be contacted and informed about any future submission of a marketing authorisation procedure for these compounds well in advance so as to avoid any potential delays in the national scheduling actions. It may also be worthwhile to address the issue during the development phase at scientific advice meetings either with EMEA or national authorities and/or during pre-submission meetings.

Conclusion: Regarding the coupling between MA and scheduling procedures, the situation is more complex in the European Union than in the U.S. This is in part due to the fact that MA procedures can be conducted on a supranational level in the European Union whereas the scheduling actions are still mainly national procedures. In the U.S. both procedures are national. Furthermore, the transparency of procedures and involved bodies is much higher in the U.S. than in the European Union. Much of the procedural uncertainty in Europe also seems to be due to the fact that scheduling actions for new pharmaceutical ingredients are not very common and have thus only happened scarcely since the introduction of obligatory supra-national procedures (MRP, CP in 1995).
From the analysis performed here, it is clear that the potential scheduling of new psychoactive drugs requires pharmaceutical companies not only to develop a worldwide registration strategy but also a scheduling strategy. It is important to understand in this respect that these strategies may mutually influence each other.

4.4. Impact of scheduling on the therapeutic use of a substance

Theoretically, therapeutic use of a drug should not be limited by scheduling. The intention of scheduling is to implement control measures to limit the use of such drugs for illegitimate purposes without unduly restricting their use for medical and scientific purposes.

However, practice has shown that scheduling may very well interfere with the legitimate use of such drugs (also see Mansbach *et al.*, 2003):

It is known that many healthcare providers e.g. underprescribe opioid pain relievers such as morphine and codeine, because they overestimate the potential for patients to become addicted to these drugs. Misunderstandings regarding the nature and occurrence of addiction have historically been barriers to the appropriate treatment of pain and have stigmatised the medical use of opioids (Savage *et al*., 2003). This fear of prescribing opioid pain medications is known as "opiophobia". Although it is true that opioid-containing drugs carry a risk for addiction and physicians should watch for signs of abuse in their patients, the likelihood of patients with chronic pain to become addicted to opioids is relatively low (with the exception of those with a personal or family history of drug abuse or mental illness). The adverse drug reaction reports from WHO Collaborating Centre for International Drug Monitoring at Uppsala, Sweden confirm that only modest numbers of drug dependence cases have been associated with the use of opioids analgesics. More research is however needed to better understand what factors predispose people to addiction and what can be done to prevent addiction among those at risk.

Apart from exaggerated fears of addiction, the administrative burden of regulatory requirements or overly restrictive national drug control policies may also be a reason for limited use of scheduled substances in therapy. Despite several WHO initiatives, consumption of e.g. opioids

remains extremely low in comparison to the medical need, and many national governments have yet to address this important deficit. In many countries, especially third world countries, opioids are not available or only in limited quantities or places, or are available but underused. Data gathered by the INCB (INCB report 2004) showed that there is great cultural variation in the medical use of opioids, particularly in pain management: In 2003, 6 countries together accounted for 79 % of global consumption of morphine, while developing countries, representing about 80 % of the world's population, accounted for only about 6 % of global consumption of morphine.

That scheduling is considered to limit the therapeutic use of substances can also be illustrated by resistance of organisations or governments against international attempts to apply stricter controls on some substances. In the *Resolution on the Availability and Control of Buprenorphine* drawn up by the *College on Problems of Drug Dependence* (CPDD) regarding recent activities (2002-2006) at WHO to transfer buprenorphine from the 1961 to the 1971 UN Convention, CPDD expressed their fear that if the international attempts to re-schedule buprenorphine were successful, the net result would be a major setback for addiction treatment in both in the United States and internationally. CPDD went so far as to describe a potential re-scheduling of buprenorphine as "a disaster to humane, effective, and safe therapy for these millions of individuals". Similarly, the Austrian Government reacted to the international activities to re-schedule buprenorphine by emphasising that buprenorphine is considered an important alternative to methadone for the treatment of opioid dependence around the world, and offers several advantages over methadone treatment. Like CPDD, the Austrian Government expressed their concern about the impact of any change in the current control regime of buprenorphine.

It can thus be concluded, that while not intended, the regulatory control of medicinal products is considered to have a major impact on the extent of their use in therapy. As such, the global healthcare problem of unrelieved pain (see position papers from the International Association for the Study of Pain, ISAP and WHO, 2000. *Narcotic and Psychotropic drugs: Achieving balance in national opioids control policy.* WHO/EDM/QSM/2000.4) can be considered a direct consequence of the scheduling of many analgesics.

4.5. Current perspectives in the development of medicinal products containing psychoactive substances

As is shown in Appendix I, the magnitude of abuse of prescription drugs in the U.S. rivals that of illicit drug abuse. With the U.S. market being the biggest market for pharmaceutical products and psychoactive substances offering relief for many patients suffering from neurological and psychiatric disorders, such as e.g. pain, anxiety, and depression, pharmaceutical industry is currently searching for new ways to get the problem of abuse of prescription medicines under control.

One approach to tackle the problem could be to devote time to searching for new psychoactive substances that display the same efficacy as existing drugs but do not have their abuse potential. In the recent years, there has not however been much progress in this field. It can also be expected that at least in some cases the reinforcing properties of drugs are tightly coupled to the intended psychoactive effects, such that attempts to reduce the abuse-liability would also disrupt the effectiveness of the substance in its intended indication.

There is however increasing evidence (Beardsley and Balster, 2005) that the pharmacokinetic profile of a formulation (i.e. the rate of onset and offset of a psychoactive substance's effect) is an important variable determining its abuse liability, although evaluation on how the formulation can influence the abuse-liability have not received much study so far (Mansbach, 2005). Formulations slowing down the rate of onset and offset of a psychoactive substance's effects are thought to have a lower abuse potential. This can for example be concluded from the fact that especially prolonged-release formulations of narcotic analgesics, stimulants and depressants are frequently sought, examined and tampered with, thereby compromising the intended slow release of the active substance: To allow for intravenous or intranasal abuse, the prolonged-release oral formulations are crushed into a powder. Orally, they may simply be chewed to allow for rapid release of the entire dose, thus producing enhanced psychoactive effects, and in the case of narcotic analgesics a powerful morhine-like high and possibly respiratory depression or death. The Internet provides broad and varied guidance on tampering methods that are specific to drug classes and special formulations (Cone, 2005).

Taking the above said into account, an alternative approach to tackle the problem of prescription drug abuse could therefore be to try to develop formulations of existing or new psychoactive substances that decrease their likelihood of abuse by creating "barriers" to tampering and misuse. Such "tamper-resistant" or "abuse-deterrent" formulations could be expected to reduce abuse and attendant adverse health consequences even if the product is diverted (Sapienza, 2005). It is certainly of critical importance in the development of abuse-deterrent formulations that it is considered how, to what extent and by whom products containing the targeted psychoactive substance are abused. In this respect all potential types of abuse including abuse "as is", abuse of multiple doses, and abuse by alternate routes of administration, by physical or chemical separation of the active substance need to be taken into account. Pharmaceutical industry needs to be aware of the extent and ingenuity of tampering practices and the formulation barriers that must be achieved to effectively reduce misuse of pharmaceuticals. Further development and refinement of benchtop tamper testing to become a valid, relevant, comprehensive, reproducible and evaluable tool would help to direct subsequent animal or human testing or establish that such testing is not essential (Goliber and Wright, 2005).

One way to decrease abuse liability is the combination of psychoactive substances with secondary ingredients: The combination of the opioid dephenoxylate with atropine is an example for this type of formulation, the combination of opioid agonists with antagonists is another. Atropine and the opioid antagonists do not affect safe use when the medication is taken as intended. When the preparation is tampered with or taken in non-intended ways, the release of these secondary ingredients may cause unpleasant effects, prevent a high, or even cause precipitated withdrawal in opioid-tolerant subjects. Another option for an abuse-deterrent formulation could be to increase its mechanical stability such that it is virtually impossible to crush or chew it (Dupont and Lande, 2005; Friedman *et al.*, 2005; Bartholomäus *et al.*, 2005). Alternatively or additionally drug formulations can be designed in way to make them form viscous gels when dissolved in different solutions. Altered mechanical or physical properties could help to reduce intravenous abuse and oral abuse by chewing, they could however not be expected to reduce the abuse in subjects that misuse the medication as is. Similarly, development of pro-drugs that need to be cleaved by enzymes in the intestine to release the psychoactive substance could be a further option to deter abuse. Whereas the approach of combining psychoactive substances with secondary ingredients has been realised in several medicinal products (e.g. Subuxone®: buprenorphine/naloxone or Lomotil®: diphenoxylate and atropine),

the others have not until now and contribution of these formulations to reduce or prevent abuse in “real life”still awaits demonstration.

In summary, there is currently some activity around the investigation of the impact of formulation on the abuse liability of medicinal products. The future will have to show whether these activities will be successful as a mitigation strategy for the problem of prescription drug abuse. What is certainly still needed is the development of more sensitive methods to better predict the relative abuse potential of new formulations. With the increasing regulatory emphasis on prospective risk assessment and minimisation, the development of formulations that might deter or reduce abuse will be important in protecting the public interest while simultaneously providing efficacious medicines to all who need them. Incentives for pharmaceutical industry could be less restrictive risk management plans, less restrictive scheduling and an improved corporate image.

5. Summary

Many substances suitable to treat neurological and psychiatric disorders have stimulant, depressant or hallucinogenic effects on the higher functions of the central nervous system and thus may have an inherent tendency to promote abuse and dependence. In many cases special measures of control are necessary to prevent abuse and diversion of these products.

Control measures for psychoactive substances have been established at international level with the *Single Convention on Narcotic Drugs* 1961and the *Convention on Psychotropic Substances* 1971. The UN Conventions and any amendment thereof are not self-executing: To be able to enforce them the Parties to the Conventions, to which most countries belong worldwide, have to transpose them into their national legislative systems. The need for national adoption of the UN Conventions has led to a considerable variability in national classification and control systems. Most of the classification systems rely almost exclusively on an "individual list" system, i.e. they list (schedule) chemically defined substances or preparations thereof. As a consequence, only substances explicitly mentioned in one of the national schedules are controlled. Any derivative (except for some salts, esters, ethers etc.) being chemically distinct from the listed compound is outside the scope of the legislation and thus *per se* not controlled. "Individual list" systems do have the advantage that there is no doubt about substances falling within their scope, but they often have the disadvantage of being rather static and slow as far as updates are concerned.

When pharmaceutical companies develop new psychoactive substances, they must bear in mind that these substances may require control. To be able to assess the abuse liability of new psychoactive drugs, additional studies (animal and/or human) are necessary and may be required by regulatory agencies. The procedures for putting a new substance under control ("scheduling actions") are generally separate from the actual marketing authorisation procedures. Therefore, pharmaceutical companies need to have an intimate knowledge of the national classification systems and the legal provisions regulating national scheduling actions. It is also important for them to know that global registration strategies must be supplemented by scheduling strategies to ensure that scheduling decisions are taken in a timely manner and do not delay or prevent marketing of the products. Pharmaceutical companies must bear in mind that their global registration strategy might be influenced by the need for scheduling actions.

From a marketing perspective, it is furthermore important to understand that the scheduling of drugs may have an impact on their availability and patient access, and thus ultimately on revenues that may be expected.

This master thesis analyses the additional data requirements for psychoactive substances, the classification and control systems, as well as scheduling actions and their relation to marketing authorisation procedures in the U.S. and five European Member States. The situation in the U.S. was found to be very transparent whereas, it seems more complex in the European Union. This may be due to the fact that the EU is a conglomerate of 25 Member States and that the legislation on controlled substances is governed almost exclusively by national law whereas marketing authorisation procedures may be run at a supra-national level. This thesis has revealed a clear need for a harmonisation of classification and control systems in the European Union.
Considering its territorial restriction, the current master thesis can naturally only be a starting point for a broader analysis of all aspects to be considered when new abuse-liable drugs are developed.

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IT : Agenzia Italiana del Farmaco, AIFA, http://www.agenziafarmaco.it/aifa

UK: Home Office, http://www.homeoffice.gov.uk/

UK: Medicines and Healthcare Products Regulatory Agency, MHRA, http://www.mhra.gov.uk/

U.S.: Drug Abuse Warning Network, DAWN, http://dawninfo.samhsa.gov/

U.S.: Substance Abuse and Mental Health Services Administration (SAMHSA), http://www.samhsa.gov/

U.S.: National Institute of Drug Abuse, NIDA, http://www.nida.nih.gov/

U.S.: Drug Enforcement Administration, DEA, http://www.dea.gov/

UN: List of Narcotic Drugs, 'Yellow List', http://www.incb.org/pdf/e/list/yellow.pdf

UN: List of Psychotropic Drugs 'Green List' http://www.incb.org/pdf/e/list/green.pdf

UN: International Narcotic Control Board, INCB, http://www.incb.org/incb/index.html

UN: Commission on Narcotic Drugs, CND, http://www.unodc.org/unodc/cnd.html

UN: United Nations Office on Drugs and Crime, UNODC, http://www.unodc.org/unodc/index.html

WHO: Expert Committee on Drug Dependence, ECDD, http://www.who.int/substance_abuse/right_committee/en/index.html

Appendix I: Worldwide abuse of illicit and licit substances

I.1. Collection of data on drug abuse

To be able to estimate the size of the problem of drug abuse and to effectively prevent health problems and other consequences related to drug abuse (drugs being used as defined in the glossary as substances and preparations that may or may not be of medical value), reliable information on the prevalence, characteristics and patterns of abuse is required. During the 1990s, drug abuse surveillance systems have been instituted throughout the world. Surveys of the general population have helped to judge the extent of drug abuse and to act as a sort of early warning system, perhaps not of newly emergent drugs but certainly of new trends. Most drug surveys have been applying any, some or all of the three most widely used recall periods which are

- lifetime use (ever);
- last year use (last 12 months)
- last month use (last 30 days).

At the international level, the INCB, is collecting data on the domestic drug abuse situation from all Parties to the UN Conventions. The WHO has been providing technical assistance in the systematic collection of this information for some years (*Guide to Drug Abuse Epidemiology* 2000, WHO/MSD/MSB/00.3). The WHO publications review drug epidemiology methods in general and the use of these methods in specific populations. They describe how these methods can be used to collect information necessary for the planning, implementation and evaluation of prevention and treatment programmes and should thus help ensure comparability of results obtained both on international and on national level.
In the EU, the EMCDDA has been performing cross-national comparative analyses of national survey results on drug abuse. In order to make comparative analyses of national surveys possible, instruments and guidelines to improve quality and comparability of general population surveys on drugs in the European Union were developed in the late 1990s (Coordination of an expert working group to develop instruments and guidelines to improve quality and comparability of general population surveys on drugs in the European Union CT.97.EP.09). One result is a European Model Questionnaire in which core items, core variables and model questions are defined. The core items, core variables and model questions are to be taken as a minimum standard for country-specific questionnaires. The EU Model Questionnaire is based on questionnaires from the WHO and includes questions on the use of illicit drugs, especially cannabis, ecstasy, amphetamines, heroin, cocaine, relevin (optional), LSD and on the use of tobacco and alcohol.

I.2. International surveys on drug abuse

The *United Nations Office on Drugs and Crime* (UNODC) estimates that about 200 million people consumed illicit drugs in 2001/2002 (annual prevalence). As shown in Table 13, this includes about 163 million for cannabis, 34 million for amphetamines, 8 million for ecstasy, 14 million for cocaine, and 15 million for opioids (of which 10 million for heroin). The numbers should be treated with some caution, as there are large gaps in the prevalence data reported to the United Nations. The United States (U.S.) are the world's largest single market for illicit drugs (2004 INCB report, E/INCB/2004/1). In 2001, more than 20 million people in the U.S. reported

to have used LSD, more than 8 million people to have used Ecstasy, and more than 1.6 million people to have injected and more than 3 million people to have misused heroin via other routes at least once in their lifetime (SAMSHA, Office of Applied Studies, National Household Survey on Drug Abuse, 2001).

Table 13: Extent of drug abuse (annual prevalence) - estimates 2000-2001

	Illicit drugs of which:	Cannabis	Amphetamine-type stimulants		Cocaine	Opioids	of which heroin
			Amphe-tamines	Ecstasy			
GLOBAL (million people)	200.0	162.8	34.3	7.7	14.1	14.9	9.5
in % of global population	3.4%	2.7%	0.6%	0.1%	0.2%	0.3%	0.16%

Sources: UNDCP, Annual Reports Questionnaire data, various Govt. reports, reports of regional bodies, UNDCP estimates.

In the context of the global situation on drug abuse, it is also important to assess the impact of illicit drug use. One way of impact assessment is to define the category of "problem drugs". Problem drugs are those drugs whose use induces high treatment demand. As such, the term does not necessarily relate to the size of the population consuming these drugs. Cannabis, for example, although being the most widely consumed illicit drug worldwide, is only in Africa the main problem drug for which people seek treatment (61% of treatment demand). Interestingly, some of the least prevalent drugs of abuse, namely, opioids are responsible for most treatment demand worldwide. On average 70% of all treatment demand in Asia, 64% in Europe and 62% in Australia is related to opioid abuse. In the Americas, cocaine is still the main problem drug accounting for 58% of treatment demand in South America and around 40% in North America. In the U.S., however, the number of people admitted to treatment institutions for heroin abuse has started to exceed the number of people admitted for cocaine abuse (1999 and 2000).

I.2.1. Abuse of prescription opioids

As far as abuse of prescription opioids is concerned, only sporadic information is available in most countries. According to the 2004 INCB report (E/INCB/2004/1), despite the very large quantities of drugs and the large number of transactions involved, no cases involving the diversion of opioid-containing drugs from licit international trade into illicit channels were detected. However, the diversion of pharmaceutical products containing opioids from national distribution channels and the abuse of such products continue to be problems not only in developing countries, but also in some developed countries. In the United States, a nationwide survey indicated that the extent of non-medical use of prescription opioids among young people was second only to the extent of cannabis abuse. According to the survey, among persons in their final year of secondary school (ages 17-18), the abuse of hydrocodone was more than double the abuse of cocaine, ecstasy or methamphetamine.

Cases involving the diversion and abuse of opioids, in particular methadone and buprenorphine, when prescribed for substitution treatment have been identified in other countries. Abuse of and/or seizures of buprenorphine have been reported by countries in Europe (Denmark, Finland, France, Norway, Portugal, and Spain), Western Asia (Iran) and South East Asia (Japan). In Austria, for example, the diversion of slow-release oral morphine tablets used for substitution treatment is a matter of national concern.

Based on the little available data, global trends in the area of prescription opioid abuse are not easy to predict. However, in its Resolution 2005/26 *Demand for and Supply of Opiates Used to Meet Medical and Scientific Needs*, the Economic and Social Council expressed deep concern at the level of licit global production of opiate raw materials and the significant accumulation of stocks over the past few years. This oversupply is considered to have the potential to upset the delicate balance between the licit supply of and demand for opiates for medical and scientific purposes.

I.3. U.S. surveys on drug abuse

The United States (U.S.) is not only a major partner in international drug control efforts, in particular in the area of law enforcement, but unfortunately, also is the world's largest single market for illicit drugs (2004 INCB report, E/INCB/2004/1). Abuse data for the U.S. are summarised in Table 14. In 2001, more than 20 million people in the U.S. reported to have used LSD, more than 8 million people to have used Ecstasy, and more than 1.6 million people to have injected and more than 3 million people to have misused heroin via other routes at least once in their lifetime (SAMSHA, Office of Applied Studies, National Household Survey on Drug Abuse, 2001).

Table 14: Estimated numbers of lifetime users of specific hallucinogens, heroin, cocaine, specific pain relievers, tranquilizers (i.e. persons who have used the below drugs nonmedically at least once in their lifetime)

	Total			
Drug / Drug Class	**2000**	**2001**	**2002**	**2003**
Hallucinogens				
LSD	19,642,000	20,202,000	n.a	n.a
"Extasy"	6,482,000	8,131,000	n.a	n.a
Mescaline	7,728,000	7,804,000	n.a	n.a
Heroin (i.v.)	**1,170,000**	**1,656,000**	**n.a**	**n.a**
Heroin (other)	**2,779,000**	**3,091,000**	**n.a**	**n.a**
Cocaine (i.v.)	**1,555,000**	**1,826,000**	**n.a**	**n.a**
Pain relievers				
Morphine	1,536,000	1,640,000	2,100,000	n.a
Oxycontin®	399,000	957,000	1,900,000	2,800,000
Methadone	819,000	732,000	n.a.	n.a
Codeine	4,442,000	5,131,000	6,900,000	n.a
Vicodin®; Lortab®, or Lorcet®	6,708,000	9,453,000	13,100,000	n.a
Percocet®, Percodan®, or Tylox®	6,402,000	7,780,000	9,700,000	n.a
Demerol®	2,151,000	2,219,000	2,900,000	n.a
Tranquilizers				

Table 14: Estimated numbers of lifetime users of specific hallucinogens, heroin, cocaine, specific pain relievers, tranquilizers (i.e. persons who have used the below drugs nonmedically at least once in their lifetime)

	Total			
Drug / Drug Class	**2000**	**2001**	**2002**	**2003**
Valium® or Diazepam	10,325,000	10,570,000	n.a	n.a
Klonopin® or Clonazepam	1,223,000	1,618,000	n.a	n.a
Stimulants				
Metamphetamine, Desoxyn®, or Methedrine	8,843,000	n.a	9,600,000	n.a
Ritalin® or Methylphenidate	2,761,000	n.a	3,4442,000	n.a
Dexedrine®	1,982,000	n.a	2,72,000	n.a
Dextroamphetamine	634,000	n.a	494,000	n.a
Preludin®	671,000	n.a	597,000	n.a

n.a. = no data found
Source: SAMSHA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000 and 2001

I.3.1. Abuse of prescription opioids

Unlike many other countries, the U.S. report high and increasing levels of abuse of several medicinal products containing opioids. In recent years, the abuse of opioid pain relievers has been recognised as a serious and growing public health problem and has also received much media attention.

According to the National Institutes of Health (NIH), the occurrence of opioid abuse has risen over the past decade. Recent estimates from the Drug Abuse and Warning Network (DAWN) confirmed that drug abuse-related emergency department (ED) visits involving opioid pain relievers have been increasing since 1994. Two pain relievers, oxycodone and hydrocodone, account for a substantial proportion of this increase (1994: Oxycodone ~ 4,000 mentions, hydrocodone ~ 9,300 mentions; 2002: Oxycodone: ~ 22,000 mentions, hydrocodone: ~ 25,000 mention). In 2002, opioid pain relievers accounted for more than 100,000 ED mentions, or 15 % of the entire drug mentions in abuse-related ED visits. Oxycodone (marketed under the brand names OxyContin® and Percocet®) and hydrocodone (marketed under the brand name Vicodin® (hydrocodone + acetaminophen)), were the most frequently named pain relievers, accounting for 40% of the opioid pain relievers involved in these ED visits. Taken together, opioid pain relievers were as frequent as heroin or marijuana in ED visits related to drug abuse, but less frequent than cocaine or alcohol. In a survey carried out by National Institute on Drug Abuse (NIDA) in 2004, it was revealed that 9.3% of the 17 year olds reported using Abbott's Vicodin® without prescription in the past year and 5% using Purdue's OxyContin®, resulting in these two medications being the most abused prescription drugs among adolescents.

The majority of prescription drugs abused in the U.S. are diverted from the licit market and obtained through Internet pharmacies. In January 2003, the U.S. Medicines Agency (*Food and Drug Administration*, FDA) and SAMHSA launched a joint prescription drug abuse prevention education effort, with the primary goal of preventing and reducing prescription the abuse of prescription drugs, especially narcotic opiate pain relievers by teens and young adults. The campaign included brochures and posters, as well as print and television educational advertising highlighting the risks (especially the potentially lethal risks) of prescription opioid abuse. FDA is

also working with professional agencies, including the American Medical Association (AMA), to help develop educational programs for physicians regarding sound use of potent opioid analgesics. This effort includes education about the risks of overdose, misuse, abuse, and diversion of scheduled substances as well as ways to manage the risks while ensuring proper treatment of patients with pain. According to a testimony by the Director of the Office of Drug Evaluation II of FDA before the Subcommittee on Regulatory Affairs of the U.S. House of representatives in September 2005, FDA is continuing to meet with the Drug Enforcement Administration (DEA), SAMHSA, the NIDA, the Office of National Drug Control Policy (ONDCP), the Centers for Disease Control and Prevention, the American Medical Society (AMA), and industry to share information and insights needed to address the problem of prescription drug abuse.

I.4. European surveys on drug abuse

According to the 2004 INCB report (E/INCB/2004/1) and the 2005 EMCDDA annual report, cannabis is the most widely abused illicit drug in the European Union. A tentative and probably conservative extrapolation from recent surveys suggests that over 40 million people in the EU have used cannabis (about 16 percent of the population age 15 to 64) at least once in their lifetime. The lowest prevalence rates of lifetime use are found in Malta (3.5 %), Portugal (7.6 %) and Poland (7.7 %) and the highest in France (26.2 %), the United Kingdom (30.8 %) and Denmark (31.3).

As is described in the 2005 EMCDDA report, Europe remains a major market for stimulant drugs, and indicators suggest that for Europe as a whole the trend in amphetamine, ecstasy and cocaine use continues to be upwards: Cocaine abuse appears to be increasing in the United Kingdom and, to a lesser extent, in Denmark, Germany, the Netherlands, Spain and Switzerland. According to recent national population surveys, between 0.5 % and 6 % of the adult population report having tried cocaine at least once (i.e. lifetime prevalence), with Italy (4.6 %), Spain (4.9 %) and the United Kingdom (6.8 %) being at the upper end of this range.

Public concern about so-called "synthetic drugs" rose over the 1990s in response to the adoption of ecstasy and related drugs within a mass recreational and music youth culture known as "rave", "techno," or "dance". Although most attention has been focused on ecstasy, other synthetic drugs such as the amphetamines and LSD have also been involved. The dominant trend is a long-term and continuing rise in the availability and use of amphetamines, although prevalence in the general population remains low. According to recent surveys, among all adults (15–64 years), lifetime experience of amphetamine use in EU Member States ranges from 0.1 % to 6 %, except in the United Kingdom, where the figure is as high as 12 %.

Although the prevalence of heroin use in the EU population is low, it clearly represents the illicit drug associated with the most serious health and social problems such as mortality, morbidity, and drug-related crime across most of the EU. Opiate users have an overall mortality that is up to 20 times or higher than that of the general population of the same age. This increased mortality is particularly high among injectors. Causes of mortality among opiate users include not only overdoses, but also AIDS and other infectious diseases, and external causes of death (accidents, violence, suicides, etc.). The level of heavy opiate use or dependence (mainly heroin) appears relatively stable across the EU. The average age of known users (30 years, range = 24 to 33) continues to slowly increase which may reflect partly the expansion of substitution treatment. The total number of "problematic opiate users" is estimated to be as high as 1.5 million people (4

per 1,000 population) in the EU; of these, about 1 million (2.7 per 1,000 population) probably meet the criteria for dependence.

I.3.2. Abuse of prescription opioids in the European Union

As a natural consequence of the EU Model Questionnaire, which does not include questions on misuse of prescription opioids, and its national implementation, there is not much information available on abuse of these products. This may not necessarily mean that there is no such problem. Population surveys are however not the only source available on prescription opioid abuse. According to Directive 2001/83/EC, as amended, Member States are required to operate a pharmacovigilance system which shall also take into account any available information on misuse and abuse of medicinal products. No immediate actions have been taken so far in respect of misuse/abuse of opioid-containing medicines, suggesting that prescription opioid abuse is in fact not very prevalent in the European Union. This is also confirmed by interviews with key opinion leaders in the field of pain treatment as well as with payers in France, Germany, Spain and the UK (personal communication): while it is known to constitute a major problem in the U.S., the abuse of prescription opioids, especially of oxycodone, is considered only of low relevance in the European Union). Street markets for opioids exist, but mainly for heroin. There are sporadic reports on diversion of other opioids (both licit and illicit drugs): Fentanyl, illicitly manufactured in the Ukraine, was illicitly supplied to the Baltic States and to Scandinavian countries (INCB report 2004, E/INCB/2004/1). Seizures of fentanyl and methylfentanyl were reported repeatedly in Estonia, while Latvia reported its first seizure of 3-methylfentanyl in 2003 and Austria its first seizure of fentanyl in January 2004. Obviously, in Estonia, the poor quality of the heroin available on the local market has been compensated for since 2002 by the introduction of these two synthetic opiates, under the names ‘white Chinese’, ‘white Persian’ or ‘synthetic heroin’ (Reitox national reports, 2004). Recent studies of illicit drug users have furthermore reported the use of non-prescribed Temgesic® and Subutex® tablets in the EU (see EMCDDA Annual Report 2005 - selected issues: Buprenorphine). Data on buprenorphine misuse remain however scarce and not harmonised at European level. In 2004, out of 17 countries where buprenorphine treatment was available, 12 reported some misuse of buprenorphine. The two countries where the problem was most visible were Finland and France. In Finland, 28 % of persons entering drug treatment and 90 % of opioid users reported that they had buprenorphine as a primary drug leading to treatment; in France the corresponding figures were 5.8 % and 8.3 %. Elsewhere, the number of buprenorphine misusers is much lower. Information on the availability of buprenorphine on the black market is also very limited. Diversion of buprenorphine to the illegal market is reported in Austria (where it is very rare), the Czech Republic, Estonia, France and Finland. An element which may have contributed to the increase in buprenorphine demand and availability is the low cost of the drug as compared to heroin in the illegal market. In Finland, a decrease in the availability of heroin, resulting from a reduction in heroin production in Afghanistan, may have been a crucial factor in the increase in buprenorphine availability in the illegal market (Nordic studies on alcohol and drugs, 2004).

Appendix II: Important organisations, networks and programme

To get a clearer picture and a better understanding of the field abuse liable substances, a brief description of some important international and organisations, networks and programmes is given in this chapter.

II.1. Commission on Narcotic Drugs (international)

The CND was established in 1946 by the Economic and Social Council of the United Nations. It is the central policy-making body within the United Nation system for dealing with all drug-related matters. The Commission analyses the world drug abuse situation and develops proposals to strengthen international drug control. As a functional Commission of the Economic and Social Council, the CND assists the Council in supervising the application of international conventions and agreements dealing with controlled substances. It also advises the Council on all matters pertaining to the control of psychoactive substances and their precursors. The CND is also a decision organ to place, remove or transfer psychoactive substances under international control.

II.2. International Narcotics Control Board (international)

The INCB is the independent and quasi-judicial control body for the implementation of the United Nations Conventions on controlled substances. It was established in 1968 on the basis of the 1961 UN Convention. INCB is independent of governments as well as of the United Nations, its 13 members serve in their personal capacity.

II.3. United Nations Office on Drugs and Crime (international)

UNODC is a global leader in the fight against illicit drugs and international crime. Established in 1997, it is mandated to assist member states in their struggle against drugs, crime and terrorism.

II.4. World Health Organisation (international)

The WHO is the UN agency whose primary responsibility is in the sphere of public health.

II.5. WHO Programme for International Drug Monitoring (international)

The main function of this WHO Programme is to provide early warnings of drug-related problems, including drug abuse, dependence and withdrawal syndrome. Since the initiation of the Uppsala Monitoring Centre (UMC), nearly three million reports of adverse drug reactions have been received from health care professionals from 69 different countries. Reports are sent as text and then coded to provide medically useful terms. Unfortunately, the terms used by reporters can be imprecise or contained within the large body of text. To enable the programme to provide early warnings, any terms that can possibly have a value as a pointer to dependence are coded as “dependence” to ensure that early signals are not missed. There is a need for

caution in the interpretation of the UMC data as health care professionals currently do not use terminology related to drug abuse and dependence in a consistent manner.

II.6. International Epidemiology Work Group (international)

IEWG is a network of drug abuse researchers from various countries, regions, and international organisations. The IEWG is an outgrowth of efforts to establish a global drug abuse surveillance network. It is based on recognition of the essential need to coordinate and share the most timely and accurate information about the changing dynamics of drug abuse worldwide. The IEWG meets annually and provides a forum for the representatives of different nations and regions of the world to exchange information about current drug abuse patterns and trends, emerging drugs of abuse, risk factors, vulnerable populations, consequences of use, and methods of collecting, analysing, and reporting data/information.

II.7. European Monitoring Centre for Drugs and Drug Addiction (EU)

EMCDDA is located in Lisbon. It became operational in 1995 and works together with Europol (see below) to collect, analyse and disseminate objective and reliable data on drug abuse. The Centre has developed a network known as Reitox (European Information Network on Drugs and Drug Addiction), which allows information to be exchanged rapidly between Member State governments, the Commission, non-governmental organisations and the Centre itself. For the purpose of analysis and comparison of these data, the epidemiological indicators in the different member states, such as the prevalence of drug use and its impact on health, have to be harmonised throughout the EU. The EMCDDA issues annual reports on the drugs situation in the EU. The Centre also publishes scientific studies of specific subjects such as epidemiological trends, synthetic drugs and demand reduction. EMCDDA thus provides regional epidemiologic surveillance in Europe.

II.8. European Police Office (EU)

Europol, which became operational on July 1999, is responsible for combating illicit drug trafficking within the European Union and works to improve police and customs cooperation between the Member States. Designed as a police service to structure cross-border investigations and police cooperation between member states, Europol is intended to streamline efforts to combat and prevent international organised crime, including terrorism and money laundering.

II.9. National Institute on Drug Abuse (United States)

NIDA was established in 1974, and in October 1992 it became part of the National Institutes of Health which belong to the U.S. Government (Department of Health and Human Services). NIDA is organised into 4 divisions: Epidemiology, Basic Neurosciences & Behaviour Research, Clinical Neurosciences & Behaviour Research, Pharmacotherapies & Medical Consequences of Drug Abuse. It supports scientific research in the area of drug abuse and addiction to promote understanding in this area. According to NIDA, the Institute supports over 85% of the world's research on the health aspects of drug abuse and addiction, ranging from molecule to managed care, and from DNA to community outreach research. NIDA is also working to ensure that

scientific data is rapidly and effectively transferred to policy makers, drug abuse practitioners, other health care practitioners, and the general public.

II.10. Office of National Drug Control Policy (United States)

The White House ONDCP is a component of the Executive Office of the President of the U.S. and was established by the Anti-Drug Abuse Act 1988. Its principal purpose is to establish policies, priorities, and objectives for the Nation·s drug control program. The goals of the program are to reduce illicit drug use, manufacturing, and trafficking, drug-related crime and violence, and drug-related health consequences. To achieve these goals, the Director of ONDCP is charged with mapping the National Drug Control Strategy.

II.11. Drug Abuse and Warning Network (United States)

DAWN is a U.S. public health surveillance system that monitors drug abuse-related emergency department (ED) visits and drug abuse-related deaths reviewed by medical examiners and coroners. Data on ED visits are collected from a national probability sample of non-Federal, short-stay hospitals, with oversampling in 21 metropolitan areas. Data from the sample are used to generate estimates for the coterminous U.S. and the 21 metropolitan areas. ED are reportable to DAWN if a patient between the ages of 6 and 97 was treated for a condition associated with intentional drug abuse, including recreational use, dependence, or suicide attempt. Visits involving chronic health conditions resulting from drug abuse are reportable.

Appendix III: Classification of opioids

Classification of opioids according to UN and severe national legal provisions

Substance	**UN 61/72**	**UN 71**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**USA**
	Class	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***
3-methylfentanyl	I	-	SI	I	I	EI, IV	A, 1	I
3-methylthiofentanyl	I	-	SI	I	I	EI, IV	?	I
Acetorphine	I, IV	-	SI	I	I	EI	A, 2	I
Acetyl-alpha-methylfentanyl	IV	-	SI	I	I	EI, IV	A,c1	I
Acetyldihydrocodeine *(Acetylcodone)*	II	-	SII	I	I	EII	B,2/5[8]	I
Acetylmethadol *(Methadyl acetate)*	I	-	SI	I		EI	A, ?	I
Alfentanil (Alfenta)	I	-	SI	III	I	EI	A, 2	II
Allylprodine	-	-	-	III	-	-	A, 2	I
Alphacetylmethadol (LAAM)	I	-	SI	I	I	EI	A, 2	I
Levo-alphacetylmethadol	s.a.	-	-	III	s.a.	s.a.	s.a.	II
Alphameprodine				I			A, 2	I
Alphamethadol	I	-	SI	I	I	EI	A, 2	I
Alpha-methylfentanyl *(China White)*	I,IV	-	SI	I	I	EI, IV	A, 1	I
Alpha-methylthiofentanyl *(China White)*	I,IV	-	SI	I	I	EI, IV	?	I
Alphaprodine				I			A, 2	I
Anileridine (Leritine)	I	-	SI	I	I	EI	A, 2	II
Benzethidine				I			A, 2	I
Benzylfentanyl				I			?	
Benzylmorphine	I	-	SI	I	I	EI	A, 2	I
Betacetylmethadol	I	-	SI	I	I	EI	A, 2	I
Beta-hydroxy-3-methylfentanyl *(China White)*	I, IV	-	SI	I	I	EI, IV	A, 1	I
Beta-hydroxyfentanyl *(China White)*	I, IV	-	SI	I	I	EI, IV	A, 1	I
Betameprodine				I			A, 2	I
Betamethadol				I			A, 2	I
Betaprodine				I			A, 2	I
Bezitramide				I			A, 2	II
Buprenorphine	-	III	P1	III	IV	PIII , P2	C, 3	III
Carfentanil				I			A, 2	II
Clonitazene	I	-	SI	I	I	EI	A, 2	I
Codeine *(Morphine methyl ester, methyl morphine)*	II	-	SII	III	I	EII	B, 2/5[8]	II (III,V)[1]
Codeine methylbromide	-	-	?	I	-	-	-	I
Codeine-N-oxide	-	-	?	I	-	-	-	I
Codoxime	I	-	SI	I	I	EI	Not known	-
Concentrate of poppy straw	I	-	SI	II	I	EI	A, 1	II

Classification of opioids according to UN and severe national legal provisions

Substance	**UN 61/72**	**UN 71**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**USA**
	Class	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***
Cyprenorphine								I
Desomorphine	I, IV	-	SI	I	I	EI, IV	A, 2	I
Dextromoramide	I	-	SI	II	I	EI	A, 2	I
Dextropropoxyphene	II	-	SII	II	IV	EII	C, 2/5[9]	IV (Bulk: II)
Diacetylmorphine							?, 2	
Diamorphine							A, 2	
Diampromide	I	-	SI	I	I	EI	A, 2	I
Diethylthiambutene	I	-	SI	I	I	EI	A, 2	I
Difenoxin	I	-	SI	II	I	EI	A, 2/5[10]	I (w/ atropine: IV, V)
Dihydrocodeine	II	-	SII	III	I	EII	B, 2/5[8]	II (III,V)[2]
Dihydrocodeine-1-0-carboxyme							A, 2	
Dihydroetorphine	I	-	SI	I	I	EI	?, 2	II
Dihydromorphine	I	-	SI	II	I	EI	A, 2	I
Dihydrothebain				II			-	
Dimenoxadol	I	-	SI	I	I	EI	A, 2	I
Dimepheptanol	I	-	SI	I	I	EI	A, 2	I
Dimethylthiambutene	I	-	SI	I	I	EI	A, 2	I
Dioxaphetyl butyrate	I	-	SI	I	I	EI	A, 2	I
Diphenoxylate	I	-	SI	II	I	EI	A, 2/5[11]	II (V)[3]
Diprenorphine								II
Dipipanone	I	-	SI	I	I	EI	A, 2	I
Ethylmethylthiambutene	I	-	SI	I	I	EI	A, 2	I
Ethylmorphine	II	-	SII	II	I	EII	B, 2[8]	II (III,V)[4]
Etonitazene	I	-	SI	I	I	EI	A, 2	I
Etorphine (HCl)	I, IV	-	SI	III	I	EI	A, 2	I (II)
Etoxeridine	I	-	SI	I	I	EI	A, 2	I
Fentanyl	I	-	SI	III	I	EI	A, 2	II
Furethidine	I	-	SI	I	I	EI	A, 2	I
Heroin	I, IV	-	SI	I	I	EI, IV	A, 2	I
Hydrocodone	I	-	SI	III	I	EI	A, 2	II, III[5]
Hydromorphinol	I	-	SI	I	I	EI	A, 2	I
Hydromorphone	I	-	SI	III	I	EI	A, 2	II
Hydroxypethidine	I	-	SI	I	I	EI	A, 2	I
Isocodeine	-	-	-	II	-	-	-	-
Isomethadone	I	-	SI	II	I	EI	A, 2	II
Ketobemidone	I, IV	-	SI	II	I	EI, IV	A, 2	I
Lefetamine	-	IV	P1	I	IV	PIV	B, 2	-
Levomethorphan	I	-	SI	I	I	EI	A	II
Levomoramide	I	-	SI	II	I	EI	A, 2	I
Levophenacylmorphan	I	-	SI	I	I	EI	A, 2	I
Levorphanol	I	-	SI	II	I	EI	A, 2	II
Lofentanil				I			2	
Metazocine	I	-	SI	I	I	EI	A, 2	II
Methadone	I	-	SI	III	I	EI	A, 2	II
Methadone intermediate	I	-	SI	II	I	EI	A, ?	II

Classification of opioids according to UN and severe national legal provisions

Substance	**UN 61/72**	**UN 71**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**USA**
	Class	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***
Methadyl acetate							A, 2	
Methyldesorphine	I	-	SI	I	I	EI	A, 2	I
Methyldihydromorphine	I	-	SI	I	I	EI	A, 2	I
Metopon	I	-	SI	I	I	EI	A, 2	II
Moramide intermediate	I	-	SI	II		EI	A, ?	II
Morpheridine	I	-	SI	I	I	EI	A, 2	I
Morphine	I	-	SI	III	I	EI	A, 2/5[12]	II, III[6]
Morphine methylbromide	I	-	SI		I	EI	A, 2	I
Morphine methylsulfonate	-	-	-	-	-	-	-	I
Morphine-N -oxide	I	-	SI	I	I	EI	A, 2	I
MPPP (1-Methyl-4-phenyl-4-4propionoxypiperidine, synthetic heroin)	I, IV	-	SI	I	I	EI, IV	A, ?	I
Myrophine	I	-	SI	I	I	EI	A, 2	I
Nalorphine				-				III
Nicocodine	II	-	SII	II	I	EII	B, 2/5[8]	I
Nicodicodine	II	-	SII	II	I	EII	B, 2/5[8]	
Nicomorphine	I	-	SI	I	I	EI	A, 2	I
Noracymethadol	I	-	SI	I	I	EI	A, 2	I
Norcodeine	II	-	SII	I	I	EII	B, 2/5[8]	
Norlevorphanol	I	-	SI	I	I	EI	A, 2	I
Normethadone	I	-	SI	III	I	EI	A, 2	I
Normorphine	I	-	SI	I	I	EI	A, 2	I
Norpipanone	I	-	SI	I	I	EI	A, 2	I
Opium	I	-	SI	III	I	EI	A, 1/2/5[13]	II,III,V[7]
Oxycodone	I	-	SI	III	I	EI	A, 2	II
Oxymorphone	I	-	SI	I	I	EI	A, 2	II
Para-fluorofentanyl (China White)	I, IV	-	SI	I	I	EI, IV	A, 1	I
Pentazocine	-	III	SIII	III	IV	PIII	B, 3	IV
PEPAP (1-(2-Phenylethyl)-4-phenyl-4-acteoxypiperidine, synthetic heroin)	I, IV	-	SI	I	I	EI, IV	Not known	I
Pethidine (meperidine)	I	-	SI	III	I	EI	A, 3	II
Pethidine intermediate A	I	-	SI	II	I	EI	A, ?	II
Pethidine intermediate B	I	-	SI	II	I	EI	A, ?	II
Pethidine intermediate C	I	-	SI	II	I	EI	A, ?	II
Phenadoxone	I	-	SI	I	I	EI	A, 2	I
Phenampromide	I	-	SI	I	I	EI	A, 2	I
Phenazocine	I	-	SI	I	I	EI	A, 2	II
Phenomorphan	I	-	SI		I	EI	A, 2	I
Phenoperidine	I	-	SI	I	I	EI	A, 2	I
Pholcodine	II	-	SII	II	I	EII	B, 2/5[8]	I
Piminodine	I	-	SI	I	I	EI	A, 2	II
Piritramide	I	-	SI	III	I	EI	A, 2	I
Proheptazine	I	-	SI	I	I	EI	A, 2	I
Properidine	I	-	SI	I	I	EI	A, 2	I
Propiram	II	-	SII	II	I	EII	B, 2/5[14]	I
Racemethorphan	I	-	SI	I	I	EI	A, 2	II
Racemoramide	I	-	SI	II	I	EI	A, 2	I
Racemorphan	I	-	SI	II	I	EI	A, 2	II

Classification of opioids according to UN and severe national legal provisions

Substance	**UN 61/72**	**UN 71**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**USA**
	Class	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***	***Class***
Remifentanil	I	-	SI	III	I	EI	- , 2	II
Sufentanil	I	-	SI	III	I	EI	A, 2	II
Thebacon	I	-	SI	II	I	EI	A, 2	I
Thenylfentanyl				I				
Thebaine	I	-	SI	II	I	EI	A, 2	II
Thiofentanyl *(China White)*	I, IV	-	SI	I	I	EI, IV	Not known	I
Tilidine	I	-	SI	II / III	I	EI , P2	A, 2	I
Tramadol	-	-	-	-	IV		-	-
Trimeperidine	I	-	SI	I	I	EI	A, 2	I

(Sources: U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section, List of: Scheduling Actions, Controlled Substances, Regulated Chemicals, April 2005, ELLD - EU-Substances and classifications 26 July 2002)

w/ with

s.a. see above

[1] Codeine & isoquinoline alkaloid 90 mg/du: III, Codeine combination product 90 mg/du: III, Codeine preparations - 200 mg/100 ml or 100gm: V

[2] Dihydrocodeine combination product 90 mg/du: III,Dihydrocodeine preparations - 10 mg/100 ml or 100gm: V

[3] Diphenoxylate preparations 2.5 mg/25 µg $AtSO_4$

[4] Ethylmorphine combination product 15 mg/du: III, Ethylmorphine preparations - 100 mg/100 ml or 100gm: V

[5] Hydrocodone & isoquinoline alkaloid <15 mg/du: III, Hydrocodone combination product <15 mg/du: III

[6] Morphine combination product 50 mg/ 100 ml or gm: III

7 Opium combination product 25 mg/du: III, Opium extracts, fluid extract, poppy, tincture, granulated, powdered, raw: II, Opium preparations - 100 mg/100 ml or /100gm: V

8 Falls within Schedule 5 if in a preparation either alone or with one or more of the drugs referring to this note not being a preparation designed for administration by injection, when compounded with one or more active or inert ingredients and containing a total of not more than 100 mg of the substance or substances (calculated as base) per dosage unit or with a total of not more than 2.5% (calculated as base) in undivided preparations.

[9] Falls within Schedule 5 if in a preparation designed for oral administration, containing not more than 135 mg of dextropropoxyphene (calculated as base) per dosage unit or with a concentration of not more than 2.5% (calculated as base) in undivided preparations.

[10] Falls within Schedule 5 if in any preparation of difenoxin containing, per dosage unit, not more than 0.5 mg of difenoxin and a quantity of atropine sulphate equivalent to at least 5% of the dose of difenoxin.

[11] Falls within Schedule 5 if in any preparation of diphenoxylate containing, per dosage unit, not more than 2.5 mg of diphenoxylate calculated as base, and a quantity of atropine sulphate equivalent to at least 1% of the dose of diphenoxylate.

[12] Falls within Schedule 5 if in a preparation of medicinal opium or morphine containing (in either case) not more than 0.2% of morphine calculated as anhydrous morphine base, being a preparation compounded with one or more other active or inert ingredients in such a way that the opium or, as the case may be, the morphine, cannot be recovered by readily applicable means or in a yield which would constitute a risk to health.

[13] raw: 1, prepared or medicinal: 2 or 5 if in a preparation of medicinal opium or morphine containing (in either case) not more than 0.2% of morphine calculated as anhydrous morphine base, being a preparation compounded with one or more other active or inert ingredients in such a way that the opium or, as the case may be, the morphine, cannot be recovered by readily applicable means or in a yield which would constitute a risk to health or if in any powder comprising 10% opium

[14] Falls within Schedule 5 if in a preparation containing, per dosage unit, not more than 100 mg of propiram calculated as base and compounded with at least the same amount (by weight) of methylcellulose.

Appendix IV: Scheduling actions involving opioids

Overview on opioids affected by scheduling actions by WHO or national governments during the past 20 years (1985-2005)

Substance	**WHO**	**DE**	**ES**	**FR**	**IT***	**UK**	**U.S.**
dextropro-poxyphene	*(1981) (< 2.5% or 135 mg/du w/o other controlled substances) → III (UN 1961) (1980) II (UN 1961)*	(2005) exempted preparations deleted from II (1992) (II) exempted preparations modified *(1984) III → II + exempted*	*(1982) EII*	[1990: SII]		*(1983) C*	*(1980) du: IV bulk: IV→ II (1977) IV*
dihydroetorphine	(1999) I - UN 1961	(2001) I	(2000) EI	(2000) SI		(2003) A, 2	(2000) II
remifentanil	(1999) I - UN 1961	(2001) III	(2000) EI	(2000) SI		(2003) A, 2	(1996) II
buprenorphine	(1989) III – UN 1971	*(1984) III*	(1989) PIII (1986) P2	[1990: PI]		(1989) C, 3	(2002) V → III (1985) II → V
isocodeine	-	(2001) II	-	-	-	-	-
Etryptamine		(1994) I				(1998) A, 1	(1994) I
LAAM, ORLAAM (*l*-alphaacteyl-methadol)	I - UN 1961	(1998) III	EI	[1990: SI]		*A, 2*	(1993) I → II
oxycodone		(1998) II → III (1992) III → II		[1990: SI]		*(1971) A*	
codeine		(1998) II → III (1994) (II) exempted preparations modified (1992) (II) exempted preparations modified (1991) (II) exempted preparations modified		[1990: SII]		*(1971) B*	
dihydrocodeine		(1998) II → III (1992) (II) exempted preparations modified		[1990: SII]		*(1971) B*	
butorphanol	-	-	-	-	-	-	(1997) IV (1992) II → -/-
methadone		(1994) II → III		[1990: SI]		*(1971) A*	
morphine		(1994) (III) exempted preparations modified		[1990: SI]		*(1971) A*	

Overview on opioids affected by scheduling actions by WHO or national governments during the past 20 years (1985-2005)

Substance	**WHO**	**DE**	**ES**	**FR**	**IT***	**UK**	**U.S.**
etryptamine		(1994) I	(1995) PI	(2000) SIII		(1998) A, 1	
difenoxin	*(1974)* *I* *III (< 0.5 mg/du + > 5% atropine sulfate)*	(1992) (II) exempted preparations modified	*(1975)* *EI* *EIII (< 0.5 mg/du + > 5% atropine sulfate)*	[1990: SI]		*(1975)* *A*	*(1975)* *I* *(1978) w/ atropine:* *I → IV*
diphenoxylate	*(1973)* *(< 2.5 mg/du + > 1% atropine sulfate) → III*	(1992) (II) exempted preparations modified	*(1975)* *(< 2.5 mg/du + > 1% atropine sulfate) → EIII*	[1990: SI]		?	
ethylmorphine		(1992) (II) exempted preparations modified		[1990: SII]		*(1971)* *B*	
propiram	*(1975)* *(< 100 mg/du + 100 mg metylcellulose) → III* *(1971)* *II*	(1992) (II) exempted preparations deleted	*(1975)* *(< 100 mg/du + 100 mg metylcellulose) → E III* *(1971)* *II*	[1990: SII]		*(1973)* *B*	*(1972)* *I*
dextromoramide		(1992) II		[1990: SI]		*(1971)* *A*	
sufentanil	*(1980)* *I (UN 1961)*	(1992) I → III	*(1981)* *EI*	[1990: SI]		*(1983)* *A*	*(1984)* *I → II*
benzylfentanyl		(1992) I		-		(1986) A	(1985) I *expired*
carfentanil		(1992) I		-		(1986) A	(1988) II
lofentanil		(1992) I		-		(1986) A	
thenylfentanyl		(1992) I		-		(1986) A	(1985) I *expired*
acetyl-α-methyl-fentanyl	(1988) I,IV	(1991) I	(1988) EI,IV	[1990: SI]		(1986) A	(1987) I (1986) I (1985) I
α-methyl-fentanyl	(1988) I,IV	(1991) I	(1988) EI,IV	[1990: SI]		(1986) A	(1986) I *(1980)* *I*
α-methylthio-fentanyl	(1990) I,IV	(1991) I	(1990) EI,IV	[1990: SI]		(1986) A	(1987) I (1986) I (1985) I

Overview on opioids affected by scheduling actions by WHO or national governments during the past 20 years (1985-2005)

Substance	**WHO**	**DE**	**ES**	**FR**	**IT***	**UK**	**U.S.**
β-hydroxy-fentanyl	(1990) I,IV	(1991) I	(1990) EI,IV	[1990: SI]		(1986) A	(1987) I (1986) I (1985) I
β-hydroxy(-3)-methylfentanyl	(1990) I,IV	(1991) I	(1990) EI,IV	[1990: SI]		(1986) A	(1988) I (1986) I *expired* (1985) I
Mefentanyl / 3-methylfentanyl	(1988) I,IV	(1991) I	(1988) EI,IV	[1990: SI]		(1986) A	(1986) I (1985) I
MPPP	(1988) I,IV	(1991) I	(1988) EI,IV	[1990: SI]			(1987) I (1986) I (1985) I
Methylthio-fentanyl	(1990) I,IV	(1991) I	(1990) EI,IV	[1990: SI]		(1986) A	(1987) I (1985) I
para-fluoro-fentanyl	(1990) I,IV	(1991) I	(1990) EI,IV	[1990: SI]		(1986) A	(1987) I (1986) I
PEPAP	(1988) I,IV	(1991) I	(1988) EI,IV	[1990: SI]			(1987) I (1986) I (1985) I
thiofentanyl	(1990) I,IV	(1991) I	(1990) EI,IV	-		(1986) A	(1987) I (1986) I (1985) I
alfentanil	*(1984)* *I*	*(1984)* *III*	*(1984)* *EI*	[1990: SI]		*(1984)* *A*	(1987) I → II *(1984)* *I*
thebacon		(1987) III → II		-		*(1971)* *A*	
papaver bracteatum		(1987) (II) exempted preparations modified *(1984)* *(II) exempted preparations modified*		-		*?*	
opium		(1987) (III) exempted preparations modified		[1990: SI]		*(1971)* *A*	

Overview on opioids affected by scheduling actions by WHO or national governments during the past 20 years (1985-2005)

Substance	**WHO**	**DE**	**ES**	**FR**	**IT***	**UK**	**U.S.**
papaver somniferum		(1987) (III) exempted preparations modified *(1984)* II → III		-		*(1971)* *A*	
nalmefene		–		–		-	(1985) II → -/-
etorphine	*(1968)* *I,IV*	*(1984)* *I → III*	*(1968)* *EI,IV*	[1990: SI]		*(1971)* *A*	*(1974)* *I → II*
pentazocine		*(1984)* *III*	*(1984)* *PIII*	(2000) SIII		*(1985)* *B*	*(1980)* *IV*

* for Italy information is available by a comparative analysis of the different versions of the Italian Pharmacopoeia which was not done for time reasons

Hiermit erkläre ich, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Aachen, den 14. März 2006

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Lebenslauf

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