The Prescription Status and Its Implications for Pharmaceutical Companies

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List of Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AMG	Arzneimittelgesetz
AM-RL	Arzneimittel-Richtlinie
AMVerkRV	Verordnung über apothekenpflichtige und freiverkäufliche Arzneimittel
AMVV	Arzneimittelverschreibungsverordnung
API	Active Pharmaceutical Ingredient
BAH	Bundesverband der Arzneimittelhersteller
BfArM	Bundesministerium für Arzneimittel und Medizinprodukte
BtMAHV	Betäubungsmittel-Außenhandelsverordnung
BtMBinHV	Betäubungsmittel-Binnenhandelsverordnung
BtMG	Betäubungsmittelgesetz
BtMVV	Betäubungsmittel-Verschreibungsverordnung
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
CP	Centralized procedure
DCP	Decentralized Procedure
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GSL	General Sales List
GÜG	Grundstoffüberwachungsgesetz
HTA	Health Technology Assessment
HWG	Gesetz über die Werbung auf dem Gebiete des Heilwesens
IE	Republic of Ireland

INN	International Nonproprietary Name
MHRA	Medicines and Healthcare Products Regulatory Agency
MRP	Mutual Recognition Procedure
NICE	National Institute for Health and Care Excellence
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
NHS	National Health Service
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-Counter
PIL	Patient Information Leaflet
POM	Prescription-Only Medicine
PPRS	Pharmaceutical Price Regulation Scheme 2014
RMS	Reference Member State
SGB V	Fünftes Buch Sozialgesetzbuch – Gesetzliche Krankenversicherung
SmPC	Summary of Product Characteristics
TFEU	Treaty on the Functioning of the European Union
UK	United Kingdom
WHO	World Health Organization

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Abstract

The prescription status is a powerful tool to restrict patients' access to pharmaceutical products dependent on the products' safety profile, abuse and misuse potential as well as sufficient marketing experience. It differentiates between prescription drugs and non-prescription drugs; any pharmaceutical product is assigned upon registration to one of the sub-categories of free sale drugs or pharmacy-only drugs for non-prescription, as well as common, special and restricted prescription drugs.

However, the status does not only affect patients but also has a sizable effect on pharmaceutical companies. Legal implications set the boundaries for advertisement, distribution channels and customer target groups as well as pricing and drug reimbursement by the public healthcare system. But eventually the most important question for pharmaceutical companies is to what extent the prescription status impacts turnover, unit sales and market share.

This thesis provides an overview on the legal background of the prescription status in the EU and compares the respective implementation into German and British law. Options to influence the legal status by choosing the optimal registration strategy or initiating a switch are discussed. Real-life case studies illustrate each topic, underlining the practical relevance of the problem and providing examples on how existing regulations were applied and made use of. In the end, recommendations for pharmaceutical companies are derived from the insights and strategies analyzed before, taking into account how to adapt pricing and customer target groups in relation to the prescription status and ultimately maximizing profit for a pharmaceutical product.

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I. Introduction: Drug Abuse, Misuse and Safety

"Dosis sola venenum facit" [1] – Already Paracelsus (1493-1541) knew that all substances can be harmful if they are consumed in a wrong dose or in a wrong way. Most drugs are potent substances that interact with the patient's body functions and thus may potentially do more harm than other substances the patient usually gets in contact with. While a released medical drug has a proven positive benefit-risk ratio in its approved dose and indication, the benefit-risk ratio might turn negative if the product is used in a wrong dose or under wrong circumstances. Therefore, medical drugs are released under certain legal statuses in order to restrict and control access to these substances. Some very potent drugs may even have dangerous adverse effects if used in the correct way and thus require not only a restricted access, but also a close surveillance in their administration by healthcare professionals. In accordance with the varying potential risk of harm of different drugs to the patient, there have been introduced different graded prescription statuses.

Prescription statuses counter the wrong use of medicinal products. However, there are different terms and classifications of incorrect use, misuse and abuse that are not always defined unambiguously:

Incorrect use is when a medicinal product is unintentionally used in a different way than prescribed. Often, this is a result of lack in medical education and non-consultation of the patient information leaflet. Only one out of four patients read the complete patient information leaflet prior to first use of a medicinal product. [2] The ill-informed situation leads to incorrect dosing, incorrect administration (e.g. chewing a retard capsule resulting in an immediate release of the substance) or harmful interactions with other substances (e.g. drinking alcohol while on medication). A special case of incorrect use takes place if patients stop taking their medicine although they need it. To counter it, the compliance of the patient needs monitoring in cases of serious diseases; especially if the symptoms of the condition appear less deterrent to the patient than the side effects of the drug (e.g. antidiabetics may lead to acute nausea while treating a condition that only has long-term effects on the patient). However, patients in these situations should be supplied with an ongoing contact to healthcare professionals to consult with them the continuation of an administration, or even to obtain treatment of side effects.

If a drug is intentionally used in a different way or dose than the product was prescribed, this is a case of **drug misuse**. Such persons may hope to increase the effect of a drug by taking increased doses, thereby ignoring the also increasing prevalence of side effects. Passing on personally prescribed pharmaceutical products to friends that suffer from the (apparent) same condition is also regarded as drug misuse. [3] A third form is present in the chronic self-administered use of a drug that leads to tolerance and increased side effects (e.g. painkillers, sleeping pills).

Drug abuse is the intentional use of a drug for other reasons than treating a medical condition. Drug abusers take drugs in order to get desired physiological or psychological effects. Examples are the use of opioids to get high or the use of laxatives for weight reduction. [4] Also drugs that cause euphoric or sedating side effects are more likely to be abused. Whether a drug has abuse potential can be checked by structure comparison in silico, in animal studies that assess self-administration patterns or from clinical trials and post-marketing experience, when patients request higher or more frequent doses than necessary on medical grounds. Prolonged drug abuse often appears in connection with **addictions**; therefore, psychoactive drugs have the highest potential for addictions resulting from physical and psychological dependence. Addicted patients deprived of their substance show withdrawal symptoms and craving. Thus, these patients continue the use of the drug even if negative effects are recognized. [5]

Drug abuse and misuse are dangerous to the patient because authorities granted marketing authorization for a drug based on a positive benefit-risk ratio for approved doses and predefined indications. The benefit-risk ration for a divergent drug use might be much worse and not acceptable. However, the abuse potential of different drugs varies in a wide range and is mainly dependent on two characteristics: the possibly desired adverse reactions and the addictive potential. According to the German Federal Medical Council, about 4.3 % of the German population are at risk of becoming or are already addicted to pharmaceutical drugs. [6] While 4-5 % of all drugs have a serious potential for abuse or misuse, [7] only few of them are addictive. About 80 % of all addictions are caused by benzodiazepines, a group of sedative, hypnotic and anxiolytic drugs. [6] Many drugs of this class are classified as narcotics – the most restricted prescription status – unless the prescribed doses are very low (Annex III BtMG).

The intention of this thesis is to provide an overview of the different prescription statuses assigned by authorities and their balance through national and international regulations by the

legislators in the EU with special focus on the situation in Germany and the UK. Furthermore, the effects of prescription statuses on the marketing, reimbursement and sales of drugs by the pharmaceutical industry are assessed as well as a pharmaceutical company's scope of influence on the assignment of prescription statuses. In doing so, this thesis questions whether a less restricting prescription status will always present the most optimal choice to market a drug, taking into account the different prescription statuses' impact on pricing options and customer target groups as well as margin and distribution restrictions.

II. Classification of the Prescription Status

1. Overview

Prescription statuses have been established by the national and international authorities as a system of differently graded access controls for medicinal products in order to deal with the risks of incorrect use, misuse, abuse and addiction. Access control for medicinal products not only slows down the availability of drugs to patients, but also requires a more complicated distribution process. Therefore, risks originating from a drug have to be balanced against the drawbacks of an access restriction. Generally speaking, most cases of incorrect use and misuse can be managed with the supervision from a healthcare professional like an apothecary at the point of sale or a doctor for prescription, depending on the risk profile of the drug. Drugs with abusive and addictive potential however usually need special tracking and distribution restrictions. These different requirements are reflected by the established prescription statuses.

2. Non-Prescription Drugs

2.1. Free Sale Drugs

Non-prescription drugs, also called OTC ("over the counter") medicinal products are sold directly to the customer without a prescription. It can be assumed that they can be used in a safe way without the extensive supervision of a healthcare professional. OTC products can be divided into free sale drugs and pharmacy-only drugs. [8]

Free sale drugs are freely available for sale outside of pharmacies, e.g. in drugstores or supermarkets. In the UK, this category is called GSL ("General Sales List"). In Germany, these products are described in § 44 AMG and further defined in § 1 et seq. AMVerkRV. Free sale drugs are regarded as generally safe even without supervision by a healthcare professional and are generally intended to treat minor ailments (§ 6 AMVerkRV). In Germany most of these drugs are traditional remedies of herbal origin (cf. § 1 (1-2) AMVerkRV), but some chemical drugs are also freely available. In UK even common painkillers like ibuprofen or paracetamol can be bought outside pharmacies.

Free sale medicinal products have in common that they are suitable for self-medication and that even if used incorrectly, they only pose a very small risk for the patient's health. This is quite important because the patient usually treats himself based on non-professional self-diagnostics, without obtaining advice from a healthcare professional before using these products. In fact, some of these medicinal products are regarded as common food (e.g. some tea types such as peppermint and chamomile) by many customers and only classified as medicinal product because of their health claim. All of these products are well-established and have a well-examined risk profile.

These free sale drugs can be sold outside of pharmacies without the assistance of a pharmacist. Handling of these Products in the EU is different - while in Germany a special training is necessary to sell these products (§ 50 AMG), in UK those products can be sold by any person that is inside of a closed room (Human Medicines Regulations 2012, s221(2)).

In pharmacies, free sale products may be placed in the self-service areas in contrast to pharmacy-only drugs which can only be sold being handed to the customer "over the counter" within the original meaning of OTC.

2.2. Pharmacy-Only Drugs

Pharmacy-only drugs can only be sold in pharmacies under administration of a studied pharmacist. The drugs are stored out of reach of the customers and are provided "over the counter" by the pharmacist. This restriction should ensure that the customer gets proper advice by the pharmacist and cannot buy excessive amounts of a drug for potential misuse. The pharmacy-only status is analogous to the classification "P" (pharmacy-only) in the UK. Among these OTC

products are mostly products for short-term treatment that are not likely to persist and do not require a complex diagnosis. [9] Examples are products for pain relief, against the common cold or laxatives.

Pharmacy-only OTC drugs are mostly used for self-medication and are regarded as generally safe even without prior examination and treatment by a healthcare professional. Nevertheless they are only safe if they are used as intended and many of them can be harmful if misused or overdosed. [10] Accordingly, pharmacy-only drugs are not as safe as free sale drugs and a professional consultation is advisable when using these products. The pharmacist's duty is to scrutinize the patient's self-diagnostics and request for the pharmaceutical product. The pharmacist should assess the patient's symptoms in characteristics, duration and frequency in order to evaluate if the requested product is suitable, [11] and in cases of doubt recommend alternatives. However, this ideal concept is not always used in practice and especially in online pharmacies, counselling standards are usually not met. [12]

While the pharmacy-only status may help to provide better consultation and prevent incorrect use, it does hardly impede intentional misuse. With the help of multiple resident pharmacies or online pharmacies, a patient will always be able to get an excessive amount of the desired pharmaceutical product.

3. Prescription Drugs

3.1. Prescription-Only Drugs

A prescription drug has to be prescribed by a physician to get legally dispersed in pharmacies. Prescription drugs are often abbreviated with "Rx" (from Latin "recipe", the imperative to "take"). In UK, this classification is called "POM" (Prescription-Only Medicine). In some countries, not only physicians but also pharmacists or nurses are authorized to prescribe certain prescription drugs (Human Medicines Regulations 2012, s214(3)).

Prescription drugs usually bear the risk of significant side effects or are new substances that may have unknown side effects. [13] Therefore they should only be administered under professional supervision as part of a healthcare treatment.

The prescriber is a healthcare professional who explains the correct use of the product to the patient, monitors drug interactions, adverse side effects and the patient's compliance. This leads to a much safer use of the drug product and reduces the related risks of the drug. The prescription-only status is suitable to reduce the risk of incorrect use and also reduces the risk of intentional misuse by restricting drug access to patients with the indication the drug is intended for, as well as by restricting drug access to appropriate amounts.

In the EEA, the criteria for prescription drugs are defined in Article 71 Directive 2001/83/EC, leading to a quite similar implementation in the different member states. Generally speaking, medical prescription should be required either for products that pose health risks to patients even under correct use and should therefore not be administered without medical supervision, or for products that are likely to present a risk because they are often used incorrectly or for new substances that require further investigation. Additionally, products that are administered parenterally (e.g. infusions) are assigned to the prescription-only status because their administration route cannot be applied securely by laypersons.

In Germany, prescriptions are regulated according to § 48 AMG. A complete list [14] of all substances requiring a prescription is given in Annex 1 of the AMVV.

3.2. Restricted Prescription

Restricted prescription according to Article 70 (2c) 2001/83/EC or § 48 2(6) AMG in Germany is a sub-category of prescription drugs. Pharmaceutical products falling into this category cannot be prescribed by all doctors, but only by special professionals or doctors working in certain institutions such as hospitals. This status is used for products that are only used in the treatment of conditions that require a hospital or other special institutions with specialized facilities for diagnosis and treatment. [13] It is also used for products with very serious side effects. Many of the drugs with this restricted prescription status are related to the treatment of cancer.

This prescription status is very suitable to prevent misuse, not only by patients but also by overconfident general practitioners. It prevents that patients are treated by persons that cannot sufficiently diagnose the condition or deal with the possibly severe side effects of the treatment.

Not all products with the restricted prescription status have the same restrictions. Depending on the indication and risk profile, the set of allowed prescribers can be defined individually.

3.3. Narcotics

The prescription status “controlled drug”, “narcotic” or “special prescription” according to Article 70 (2b) 2001/83/EC describes a pharmaceutical product that is available for legal prescription. In different contexts, the term “narcotics” also refers to illegal drugs or medical anesthetics; however, these substances will not be in the scope of this master thesis. Narcotics are a sub-category of prescription drugs.

The legal status of a narcotic is mainly given to substances that have a high potential for addiction (§ 1 (2) BtMG); they are not necessarily narcotic or sedating. Also medicinal products that may be used as precursor for such dangerous substances are also strongly regulated in their trade and prescription (Article 3 et seq. of Regulation 111/2005).

The classification of pharmaceuticals as narcotics is suitable to prevent misuse, but is mostly intended to prevent abuse. This most restricted prescription status and its severe restrictions for prescription and distribution are necessary to ward off the massive efforts invested by addicts and criminal dealers into the procurement of the drug. However, this also imposes impediments for the supplying pharmaceutical companies.

In Germany, narcotics are regulated by the narcotics law (Betäubungsmittelgesetz – “BtMG”). There is no universal definition of narcotics; instead, all substances regarded as narcotic are listed in Annex I-III BtMG. Thereof, the narcotics that are available for legal prescription are listed in Annex III BtMG.

In the EEA, the classification criteria for narcotics are largely harmonized according to Article 71 (2) of Directive 2001/83/EC. However, the national laws are not always applied uniformly. The main reasons for narcotic status are risk for abuse, addictive potential or potential to be used for illegal purposes (e.g. synthesis of illegal substances). The status may also be assigned to new substances as precautionary measure if there is a certain addictive potential or risk of abuse. As an additional formal reason, substances that are classified as narcotic or psychotropic according to the United Nations Conventions of 1961 and 1971 [15] [16] are also regarded as special prescription drug. Products can be classified as narcotic and restricted prescription at the same time. [13]

3.4. Renewable and Non-Renewable Prescription

A much neglected prescription detail is the option to make a prescription renewable. By this, a product can be dispensed multiple times at different points in time with only one prescription. This status is mostly used for medicines in the treatment of chronic diseases that do not require permanent monitoring by a healthcare professional for well-adjusted patients (e.g. hypertension). Obviously, this status is not applicable for products that are potentially addictive, i.e. most narcotics are ruled out. It is also not applicable for products that can be harmful during prolonged use (e.g. cortisone). [17]

The option to deliver a medicinal product by renewable prescription is described in Article 70 (2) of Directive 2001/83/EC. However, it is neither implemented nor harmonized in all EU member states. Even for centrally registered products, this option is not explicitly mentioned in the commission decision for granting the marketing authorization, thereby enabling all member states to implement this option in accordance with their national law. [13] Therefore, the availability of this prescription attribute is depending on national preferences and only binding to the respective country.

In Germany, renewable prescription has not been introduced, thus all prescriptions can only be used once (§ 4 (3) AMVV). In the UK, renewable prescription has been implemented by The National Health Service (General Medical Services Contracts) Regulations 2004, s6 (38).

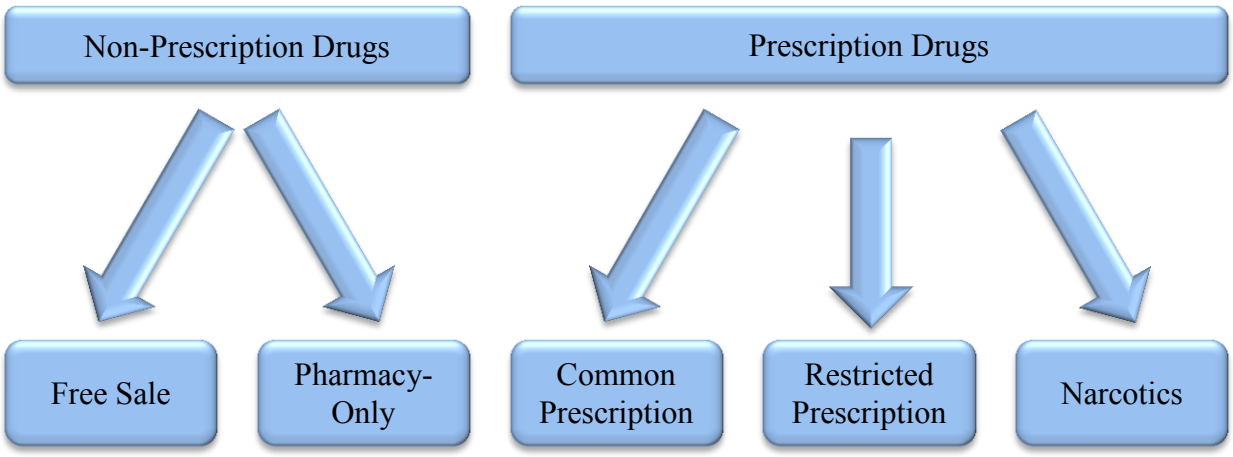

Figure 1: Visualization of the main and sub-categories of the legal status.
Source: Own design.

III. National and International Regulations for Prescription Status

1. The Legislative Framework of the EEA

Big efforts have been made to harmonize the differentiation criteria between prescription and non-prescription drugs in the EEA. The harmonization was partly successful, establishing an extensive catalogue of criteria to differentiate these products. Nevertheless different national authorities can still come to different decisions about the legal status of a product. The differentiation of sub-categories of the prescription status is much less harmonized. To define the status of substances as narcotics, there are basic agreements based on the United Nations conventions [15] [16]. The classification of subcategories like pharmacy-only and free-sale drugs is hardly harmonized at all. And for the difference between renewable and non-renewable prescription there are not even basic rules to come to a mutual understanding.

The regulations with regard to prescription status are widely harmonized within the EEA through Articles 70-75 of Directive 2001/83/EC. Still, individual member states often come to divergent decisions about prescription status classifications, especially for national registered products. These different classification decisions are result of divergent consideration of the following factors: [18]

(1) mentalities (e.g. emphasizing the patient's self-responsibility in the UK),
(2) traditions (e.g. initial prescription status of the innovator with same API),
(3) ideas of morality (e.g. religious reservations about emergency contraceptives in PL),
(4) health policies (e.g. handling of antibiotics) or
(5) national regulations for reimbursement (e.g. cost savings after granting OTC status).

Differences can be cultivated by member states because the Directive 2001/83/EC only offers a quite short description of the classification criteria. According to Article 71(1), medicinal products should be given a prescription-only status if they:

- are dangerous even when used correctly,
- are frequently used incorrectly and can therefore result in a danger to human health,
- contain substances that require further investigation (especially in case of new medicinal products) or

- are either normally prescribed by a doctor or administered parenterally.

Even though intended to harmonize the basic principles for the prescription of medicinal products (Recital 32 of Directive 2001/83/EC), these criteria partly missed their goal due to divergent national implementation of the directive.

Therefore the EMA issued the "Guideline on changing the classification for the supply of a medicinal product for human use" [19] that – despite its name – also provides detailed advice for the initial classification of a medicinal product. This guideline should be used by EU member states also for their national decisions. However, it covers differentiation into prescription and non-prescription medicine according to Article 70 of Directive 2001/83/EC only. Therefore especially the differentiation between subcategories (e.g. free sale vs. pharmacy-only) is handled differently in the EU member states.

To be classified as non-prescription medicine according to this guideline, a product must meet certain criteria. There are 4 main criteria that have to be checked by the responsible authority.

As first criterion the safety profile of the medicinal product should be positive. This criterion includes the direct and indirect safety profile. Direct safety means that the medicinal product should be safe if used correctly. It should also have low risk of serious adverse events as well as no relevant reproductive, genotoxic or carcinogenetic properties. There should be no interaction with other common drugs that may produce serious adverse events. The product should have an acceptable risk even if the product is not used as indicated, in the wrong dose or for a longer period than recommended.

The Indirect safety is affected by the patient's ability to diagnose his condition sufficiently. A non-prescription product should only be used to treat conditions that are easily self-assessable. It also should not hide symptoms of a more severe condition that needs definitive medical treatment. Otherwise the underlying condition might stay unrecognized and necessary treatment is delayed. For drugs that are used for short-term treatment, this danger can be addressed with warnings in the patient's leaflet that limit the duration of the self-treatment and recommend the patient to ask for advice of a healthcare professional.

Another type of indirect danger is that the pathogen might develop a resistance to the product due to exaggerated use. This leads to an impaired usefulness of the medicinal product. Especially antibiotics are affected, but also antiviral and antifungal drugs.

The second criterion to be considered is the danger of misuse. If the product is often used in a wrong way or for other causes than listed in the indications, the drug safety might be reduced and a non-prescription status is not advisable.

As third criterion the marketing experience of the medicinal product has to be checked. The non-prescription status is not recommended for new drugs with limited marketing experience or unknown side effects. Therefore new chemical entities can hardly get a non-prescription status within their first five years on the market. Also new strength, new routes of administration or new indications usually should not be introduced as OTC directly.

The fourth criterion is the route of administration of the product. Parenteral administered products should always be subject to prescription due to their complex administration route.

Some additional risk that arise from reduced supervision during the use of non-prescription drugs can be mitigated with an appropriate patient's information as substitute for the healthcare professional's advice (Article 54g of Directive 2001/83/EC). The leaflet of non-prescription drugs therefore is likely to include more warnings and explanations to prevent misuse. Risks can also be mitigated by a reduced strength, limited dose, optimized pharmaceutical form or reduced packaging size, thereby making a non-prescription status justifiable (Article 71 (4) of Directive 2001/83/EC). Especially the limited pack size can help to prevent severe overdosing and prevent a delay in seeking medical support.

2. MRP/DCP Registrations

"The classification status of medicines authorized in Europe remains a competency of the member states." [20]

Mutual Recognition Procedures (MRP) and Decentralized Procedures (DCP) provide the opportunity to register medicinal products in multiple EEA countries at once. During these procedures a Reference Member State (RMS) together with one or more Concerned Member States (CMS) decide on the registration status based on the Directive 2001/83/EC and the

“Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use”. However, as MRP and DCP procedures are based upon multinational agreement, these registration procedures lead to situations, in which approvals for different prescription statuses within one registration procedure are not obtainable.

During the MRP/DCP procedure, the applicant has to request a prescription status for his product in the initial application form. [21] This request is reviewed and evaluated by the RMS and the CMS. During the evaluation period, any member state will complain if they do not agree to the proposed prescription status and see a “potential serious risk to public health“. [22] Especially the wording of the harmonized common-texts (SmPC and PIL) differs significantly between prescription and non-prescription products and leads to disagreements if participating countries cannot agree on a common legal status.

If RMS and CMS cannot come to an agreement, a very time-consuming escalation process is triggered. At first instance, the application will be referred to the Coordination Group for Mutual Recognition Procedures and Decentralized Procedures (CMD), a committee with members of all EEA countries. If this committee does not come to an equivocal agreement, there is a second referral to the CHMP. They may then decide by majority vote.

Instead of delaying the registration procedure until the conclusion of the CHMP referral – which may take multiple years – it is advisable for pharmaceutical companies to remove deviating CMS from the registration procedure and finish the registration within an acceptable timeframe. Registrations in deviating CMS can be achieved with separate registrations instead. Especially for the registration of generics and well-known substances, national authorities usually refer to the statuses of comparable products in their market and will try to keep the status of new registered products identical to the existing ones.

3. Centralized Procedure

In the EEA, pharmaceuticals can also be registered with the Centralized Procedure (CP) as set out in the Regulation 726/2004/EC. Although the CP is only compulsory for some kinds of new active substances (Article 3 of Regulation 726/2004/EC), most new chemical entities are registered under this procedure [23] due to its major advantage: The CP leads to a registration in all EEA member states at once.

For the CP, the applicant should propose a legal status classification in their "notification of intent to submit an application" several months prior to the actual submission of the application. [24] The actual CP submission is submitted to the EMA. The application will then be evaluated by the CHMP, a committee that consists of delegates of all member states of the EEA (Article 61 of Regulation 726/2004/EC). However, not all member states have to contribute to the scientific evaluation which is done only by a chosen rapporteur and co-rapporteur. The CHMP also decides on the details and circumstances under which the medicinal product is made available to the patients (Article 9(4)(b) of Regulation 726/2004/EC). The opinion to accept a marketing authorization is made by simple majority. Based on this CHMP opinion, a decision is reached by the European Commission (Article 10 of Regulation 726/2004/EC) which is binding to all EU member states and immediately applicable (Article 288 TFEU), therefore leading to a common prescription status in all EU countries.

In contrast to the MRP/DCP, decisions in the CP never have to be unanimous. Therefore, registration status in all EEA member states will be identical and countries with divergent views are overruled by a simple majority decision. Due to this, countries can be forced to use a prescription status that they never would have authorized voluntarily (cf. Germany's divergent position in [95]). Applicants could make use of this in order to obtain a prescription status that would hardly be possible to acquire by other registration procedures. However, if the applicant wants to register a new chemical entity, the prescription-only status is almost inevitable due to missing market experience. [13] Thus, the advantages of a centralized procedure regarding the legal status are more evident for the registration of generics and in case of status changes according to Article 74 of Directive 2001/83/EC. While the sub-categories special and restricted prescription are sufficiently harmonized and set in the binding commission decision, [13] the sub-category renewable prescription and the discrimination between free sale and pharmacy-only still have to be set nationally.

4. Prescription Status in Germany

National registrations open up the opportunity to acquire a prescription status independently from other countries and their influence on a multinational registration procedure. However, pharmaceutical companies tend to register their products in multiple countries of the EEA which

makes a CP or MRP/DCP mandatory (Article 28 (1) of Directive 2001/83/EC). Therefore, most new submitted registrations in Germany are MRP/DCP registrations. [23]

The prescription status in Germany is regulated in § 48 AMG which is widely in accordance with the EU directive's content. Prescription-only is the default legal status of a product and necessary for all substances that are either "not commonly known" (§ 48 (1) AMG), i.e. without sufficient post-marketing safety data or can be dangerous even if they are used as intended or are often not used as intended and thereby posing a risk to health (§ 48 (2) AMG).

The legal status may only be changed to non-prescription after the medicinal product is marketed for at least three years and none of the abovementioned reasons for prescription-only status is valid anymore (§ 48 (3) AMG).

The restricted prescription and prescription of narcotics is mentioned only very briefly in §48 (8) AMG. While restricted prescription is hardly defined further, extensive additional regulations in the narcotics laws apply to narcotics.

Free sale drugs are described in § 44 AMG and further defined in § 1 et seq. AMVerkRV. In Germany, this category is limited and contains some well-established chemical drugs as well as many herbal products, most of them used for traditional medicine. Instead of a universal definition, the German legislator mostly refers to the ten extensive annexes of the AMVerkRV that include and exclude different pharmaceutical products. Additionally, the proposed indication of a drug is relevant for the assignment of free sale status. Only products for the treatment of minor ailments may be registered as free sale drug (§ 6 AMVerkRV).

For the sale of free sale drugs in a drugstore or supermarket, a competent person within the meaning of § 50 AMG has to be available in the store. The necessary certificate of competence can be acquired through examination at the Chamber of Industry and Commerce ("IHK") after a short preparation time of a few days. [25] Thus, the necessary qualification is significantly lower than the academic degree for acquiring the competency as pharmacist.

Decisions about switching a prescription status between prescription-only and pharmacy-only are made by the Expert Committee for Prescription Requirements ("Sachverständigenausschuss für Apothekenpflicht"), resulting in updates of the annexes of the AMVV. [26] Instead of regulating

individual products, the annexes are valid for all products with the mentioned API, strength and pharmaceutical form.

5. Prescription Status in the UK

The UK national legislation implemented Directive 2001/83/EC into their Human Medicines Regulations 2012, thereby achieving a partial harmonization within the EU. One of the most striking features of this law is the classification of medicinal products into three categories according to Section 62 (1): POM (Prescription-only medicine), P (Pharmacy-only drugs) and GSL (General Sales List, meaning free sale drugs).

The British law emphasizes the strong sector of free-sale medicinal products. The division between prescription and non-prescription products is in line with the EU directive 2001/83/EC. Prescription is necessary for products that:

- can be dangerous even if they are used as intended according to Section 62 (3) (a);
- are often used not as intended, thereby posing a risk to health according to Section 62 (3) (b);
- contain substances that require further investigation according to Section 62 (3) (c) or
- are for parenteral administration only according to Section 62 (3) (d).

These criteria are further explained in *The Guidance on How to Change the Legal Classification of a Medicine in the UK*. [27] Prescription-only products may also be prescribed by special nurses or pharmacists as independent prescribers (Human Medicines Regulations 2012, s214). Narcotics and restricted prescription drugs are described in Section 62 (4), while the restrictions for narcotics are further defined in other laws, especially the Misuse of Drugs Act 1971.

The requirements in order to obtain a freely-available status are much less challenging compared to the situation in Germany. In the UK, this status is available for all pharmaceutical products that can be sold “with reasonable safety” without the supervision of a pharmacist (Human Medicines Regulations 2012, s62(5)). In the eye of the MHRA, these are products that are taken for common ailments that are easily recognized and which usually last around 2–3 days. The products are only allowed to cause few troublesome side effects in normal use. [9] Typical products of this category are common painkillers or anti-allergics. The strength, packing size and indications are usually more limited than for prescription drugs with the same API. In the UK, no special

training is required for the sale of GSL products. GSL products can be sold at all places that can be “closed to exclude the public”(Human Medicines Regulation 2012 s221(2)), which even include petrol stations.

6. Narcotics Law in the EU and Germany

Although the classification criteria for narcotics are generally described in Article 71 (2) of Directive 2001/83/EC, the assignment of individual substances to the category of narcotics differs widely in the EU. General agreement was reached in banning substances listed in 1961 United Nations Single Convention on Narcotic Drugs [15] and 1971 United Nations Convention on Psychotropic Substances. [16] New narcotic and psychotropic substances can be defined by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the Council can order EU member states to regulate these new substances within a year according to their national laws (Article 9(1) of Decision 2005/387/JHA). Trade with drug precursors is also restricted according to Regulation No 273/2004, which applies to trade within the EU, as well as Regulation No 111/2005, covering the trade of precursors between the EU and third countries.

However, all harmonization efforts cannot obscure that the national laws on narcotics in the EU are quite different and only partially harmonized. [28] Reasons are mainly historic and lie in a different cultural attitude towards the use of narcotics.

In Germany, the prescription of narcotics requires a special prescription form (§ 9 BtMVV). These forms have unique serial numbers, multiple security features similar to bank notes and they have to be sourced directly from the BfArM (§ 13 BtMVV).

The handling of narcotics is very complex for doctors and requires much more effort compared to other medicinal products as the dispensing and continuance of narcotics has to be protocolled completely(§ 1 (3) BtMVV). The storage has to be done securely (§ 15 BtMG), containing rigorous requirements for secure storage space. [29] Due to extensive legal documentation requirements during trade (§ 1 BtMBinHV) and dispensing (§ 14 BTMVV), the handling of narcotics leads to an increased administrative burden for prescribers and pharmacies as well. [30]

Manufacturing and trade of narcotics is also impeded. For manufacturing, trading and distribution permission is necessary (§ 3 BTMG). This permission is limited by strict definition of allowed

substances and their amounts (§ 9 (1) BtMG). The stock of narcotics has to be checked regularly and all changes have to be reported to the authority (§ 18 BtMG). National trading requires an acknowledgement of receipt and delivery note for every change of ownership, both on official forms (§ 1et seq. BtMBinHV). International trade of narcotics requires an import license (§ 1 BtMAHV) and export license (§ 7 BtMAHV) for every cross-border trade.

Substances used for the production of narcotics are often classified as precursors. Due to the direct implementation of EU regulation 273/2004, their availability is reduced and much bureaucracy is needed to obtain and handle them.

7. Strategies & Case Studies: Choosing the Optimal Registration Procedure

Choosing the optimal registration procedure may influence the prescription status – or at least the time until a prescription status is granted. A CP is suitable to circumvent national obstacles and force member states to a certain prescription status. Only a single majority in the commission decision is necessary to obtain a prescription status that is immediately binding in all member states.

For example, Takeda obtained a new registration for Pantoprazole via CP in 2009. [31] The product was first approved in Germany in 1994, [32] and the market exclusivity expired long time ago. So at the time of Takeda's registration submission, there were over thirty generic competitors in the market. Due to the commission decision at the end of the CP, Takeda's Pantoprazole was the only Pantoprazole with OTC status, thereby building a monopoly in the OTC market. Although the data exclusivity for the new prescription status according to Article 74a of Directive 2001/83/EC was not granted, the competitors needed a lot of time to get the same prescription status. [33] The commission decision overruled Germany's national law, but was only valid for Takeda's product. Thus, all competitors in Germany had to wait for an amendment to the AMVV annex 1. [34] In other EEA countries, this approach provided a similar advantage for Takeda. Therefore the CP was a very clever way to quickly obtain an EEA-wide non-prescription status before competitors.

In other situations purely national registrations or separate MRP/DCP registrations with only a few participating countries can be advantageous. Especially if the applicant assumes that only a minority of the EU countries will agree to the proposed legal status. A good example for this

approach would be the registration of antibiotics as OTC. The *Guideline on changing the classification for the supply of a medicinal product for human use* lists *"if wider use of a medicinal product would increase the risk of resistance to the product"* (criterion 1.2.b) as obstacle to granting an OTC status. Therefore in most European countries antibiotics are prescription-only to restrict and control the drug use. Due to different mentalities and traditions there are still some EU countries like Belgium and Hungary where multiple antibiotics are available without prescription. [35] If a pharmaceutical company would register generic versions of these products, national and MRP/DCP registrations in these countries with fewer restrictions would most likely lead to the same OTC status. A centralized procedure would probably lead to a prescription-only status even in those countries that support OTC status, reducing the total sales opportunities of the product.

IV. Pharmaceutical Advertisement

1. Pharmaceutical Advertisement Law in the EU

The legal status of a medicinal product also impacts the possibilities for pharmaceutical advertisement. To quickly sum up European advertisement law, advertisement for non-prescription drugs is allowed publicly while advertisement for prescription drugs is only allowed towards healthcare professionals. The intention of the following section should not be to reproduce the pharmaceutical advertisement law completely; but only to explain the relevant differences and implications arising from prescription status.

The advertisement law in the EU has been harmonized with Articles 86 et seq. of Directive 2001/83/EC. National implementations are mainly in line with the Directive, especially advertisement laws in Germany and UK show only small differences to EU law.

Advertising to the public is not allowed for prescription-only medicine, for products that contain psychotropic or narcotic substances and for products that are reimbursed by the statutory health insurance (Article 88(3) of Directive 2001/83/EC).

For non-prescription drugs, advertisement to the public is allowed (Article 88 (2) of Directive 2001/83/EC), but only under the observance of strict restrictions. It must not contain misleading

information (cf. Article 90k), recommendations by healthcare professionals (90f), comparative advertisement (90b) or claims of guaranteed effectiveness (90b). Therefore, advertisement towards laypersons has to be much less aggressive than towards healthcare professionals. Advertisement directed at the general public has to contain at least product name, API and the invitation to read the package leaflet (Article 89 of Directive 2001/83/EC). It is not allowed to provide free product samples to the general public (Article 96 (1) of Directive 2001/83/EC).

Advertisement towards healthcare professionals is less restricted and thus offers much more possibilities for marketing strategies. The aforementioned prohibitions of recommendations, comparative or suggestive advertisement do not apply as long as the provided information is accurate, complete, verifiable, and up-to-date (Article 92 (2) of Directive 2001/83/EC). Instead of the invitation to read the package leaflet, advertisement for healthcare professionals always has to include "essential information compatible with the SmPC" (Article 91(1) od Directive 2001/83/EC). Free samples may be provided to healthcare professionals in limited amounts, limited packing sizes and only on written request of the professional.

2. National Implementation of Advertisement Law in Germany and the UK

Germany as well as the UK implemented the regulations on advertisement laid out in Directive 2001/83/EC into national law with only marginal deviations. In fact, UK adopted parts of the EU Directive literally.

UK pharmaceutical advertisement law is regulated in detail in the Human Medicines Regulations 2012, Articles 279 et seq. Further explanatory details are given in the so-called "Blue Guide" [36] which serves as a reference guideline. Advertisement for non-prescription drugs (GSL as well as pharmacy-only) to the general public is allowed, but forbidden for prescription drugs (Human Medicines Regulations 2012, s284). In comparison to the EU Directive's list of drugs under advertising restrictions, UK law explicitly added products for abortions as to be not allowed for promotion to the general public (Human Medicines Regulations 2012, s283).

In Germany, the advertisement for pharmaceutical products is regulated in the Pharmaceutical Advertisement Law (HWG). Advertisement for prescription drugs is restricted to healthcare professionals according to § 10 (1) HWG. Comparable to the UK national implementation, Germany has added certain product indications into its national law beyond the EU Directive's

restrictions for which advertisement to the general public shall not be allowed, namely drugs against insomnia, mental disorders and emergency contraception (§ 10 (2) HWG).

3. Addressing Different Target Groups

The non-prescription status enables pharmaceutical companies to target new customer groups in fast growing markets with high sales potential. Customers of OTC drugs tend to be health-oriented, educated and well-informed. [37] They are mostly young and wealthy people. [38] The price of a product is only a minor criterion when choosing a remedy. [39] Users of prescription drugs are usually older and less educated; consumption of prescription drugs increases steadily by age. [37] Products are consumed by these patients because prescribed by a healthcare professional whom they trust. They are less likely to buy a product on their own initiative. As they cannot to be influenced by advertisement, they are not likely to accept a premium price over the common prescription charge. [40]

However, it has to be taken into consideration that prescription and non-prescription products are preferred in different situations: Non-prescription drugs are faster to obtain and promise quicker relief, [9] which is crucial especially in situations where a fast administration secures good efficacy (e.g. emergency contraceptives, triptans). For the convenience of the consumer, visits to a general practitioner can be avoided and anybody can procure the remedy, as the ill person does not need to appear in person. This is an important criterion for conditions that render time-consuming visits to healthcare professionals to an unbearable burden, e.g. diarrhea, nausea, or migraine. Non-prescription drugs also allow patients to save consultation fees or prescription charges that, in some countries, can be higher than the costs of the medicinal product.

Prescription drugs are helpful in order to increase the patients' perceived and real safety, being especially important for multimorbid and older patients. The consultation of a doctor ensures that the complete health status of the patient is examined, including identification and treatment of underlying conditions, if required, and reduces the risk of drug interactions and incorrect use. [19] In addition, the reimbursement that is common for prescription drugs is advantageous for poor customers or in case of expensive products.

The co-existence of one or multiple prescription-only and OTC versions allows pharmaceutical companies to address different customers with (almost) the same product. During a switch to

OTC it is usually possible for the marketing authorization holder to maintain a prescription-only version of the product with different strength, pharmaceutical form or pack size. Generally speaking, most profit can be generated if all target groups or as many as possible are serviced and if the respective maximum price levels are charged. Further potential for profit can be leveraged by additionally differentiating non-prescription products in a powerful brand and a no-name discount product to address additional customer groups with a difference willingness to pay.

4. Strategies & Case Studies: Advertisement through the Product's Lifecycle

Advertisement strategies differ significantly between prescription and non-prescription products – especially due to the different target audience of the advertisement.

Any completely new drug requires advertisement for its market entry to raise awareness and gain market share. However, prescription drugs may only be advertised towards healthcare professionals: They will prescribe these products only if convinced that the product is superior to alternative substances or formulations. During patent coverage and protection period, the price of these new products stays on a reasonable high level due to absence of competition. During this phase in the product lifecycle, the product is usually reimbursed and its price is negotiated with HTA authorities that are unlikely to be influenced by advertisement.

Once the protection period expires, generic competitors will join the market and sell the product for a cheaper price. In this phase, the originator will lose market share. Especially in Germany, healthcare professionals have limited influence on the brand of the products they are prescribing because pharmacists will provide the patient with the product for which a discount agreement with his health insurance is in place (§ 129 (1) SGB V). At this stage, a valuable brand and good advertisement have less impact than good negotiations with health insurances, so advertisement for prescription medicines with generic competitors is often not profitable and will be reduced by most manufacturers. [41] If the advantages of a popular brand shall be further made use of, a switch to non-prescription status may be helpful: Being thereby allowed to also target customers, e.g. former patients treated under prescription, advertisement strategies may build upon the brand loyalty acquired during the Rx-phase of the product. [41]

Direct advertisement to customers bears the potential to build a powerful and well-known brand. However, originator products have a huge head start because they are already known by patients

as well as pharmacists and prescribers: Only 10.6 % of all purchase decisions for non-prescription drugs in pharmacies are made because of advertisement. Recommendations by physicians (14.6 %) and pharmacists (18 %) are much more important for the customer. [39] Customer satisfaction (51.9 %) is the most important reason for buying an OTC product, therefore customers do not tend to buy an alternative once they have been satisfied with a certain product, showing a high brand loyalty. Trusted and recognized brands help customers to develop the confidence for self-medication. [18] Continued advertisement is necessary even for originators and market leaders to retain brand awareness and trust.

A good example for the power of marketing and advertisement is the brand Voltaren®, name of the originator product diclofenac that was first introduced in 1973 [42] by Ciba-Geigy (now Novartis). The switch to OTC status for Voltaren® Schmerzgel in Germany was approved in 1999. [43] To be eligible for the non-prescription status, the registration holder Novartis only deleted an indication from the secondary marketing authorization without jeopardizing the business with the primary prescription-only registration. [44]

At the time of the switch, the market for topical OTC painkillers was already occupied by competitors like Ibutop® (Ibuprofen) and Mobilat® (Flufenamic acid) that got their OTC switches in 1989 (Ibuprofen) [45] and 1995 (Flufenamic acid) [46] respectively. For market penetration, Novartis made a huge study to assess competitors' advertisements as well as customers' demands. As a result, Novartis reached differentiation from its competitors by introducing the unique claim that the product is not only a strong pain relief but would also quicken the healing. [47]

Due to the switch to non-prescription, Novartis was able to address healthcare professionals as well as customers with their advertising. Prior to product launch, extensive lectures, trainings and promotional material was offered to pharmacists via sales representatives so that they would recommend the product to the customers. At the time of launch, a large scale advertising campaign based on adverts and a TV campaign was addressed to customers and healthcare professionals as well. [47]

Due to Voltaren®'s previous share in the prescription market, 29 % of laypersons knew the brand even before the advertising started. [48] With this excellent base, Voltaren® rose from its launch in July 1999 to market leadership for topical OTC painkillers in March 2000. [48] Today, the

brand Voltaren® has a value of over £ 2,8 billion and is the most valuable brand of its new owner GSK. [49] The OTC switch of Voltaren® – allowing successful use of the brand long time after the patent expiry – is today regarded as one of the most successful OTC switch of all times. Under prescription status, the longtime success of this brand would not have been possible. The turnover of the prescription product Voltaren® Emulgel® with the same API and strength as the non-prescription Voltaren® Schmerzgel decreased steadily due to reimbursement issues and is neglectable nowadays.

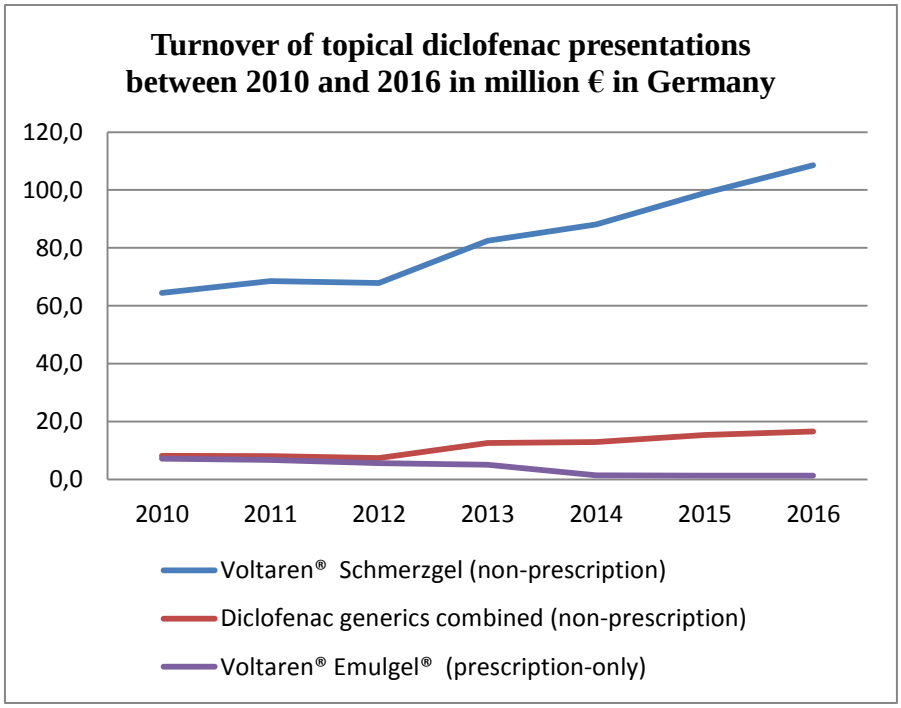

Figure 2: Comparison of turnover of topical analgesics based on diclofenac between 2010 and 2016. The originator Voltaren® (prescription and non-prescription) is compared with the remaining market of all other topical non-prescription diclofenac analgesics. The figure shows that the brand is highly appreciated by customers compared to its non-branded competitors' products and that the brand preference rises even more. Such a development would be impossible for a decades old prescription product with multiple generic competitors.
Source: Own design based on IMS Health DPM (see Appendix 2).

V. Reimbursement

1. Reimbursement in the EU

The prescription status of a drug has a high impact on the reimbursement by national healthcare systems in many countries. Without considering other factors, customers prefer products that are reimbursed in order to save themselves the expenses of their treatment. [40] Yet reimbursement is either limited in all European countries, comes with the disadvantage of price regulations or both. Typical mechanisms of price regulation are setting a price related to reference prices in other countries or using a cost-benefit evaluation to find a fair price for a pharmaceutical product.

Due to the divergence of national health systems, there is no harmonization on reimbursement in the EU. Still, the European Network for Health Technology Assessment (EUnetHTA) was established in 2008 to facilitate the collaboration of the European HTA agencies [50]. This network provides exchange of information but did not implement a joint assessment of medicines' benefits yet.

Generally speaking, prescription drugs are reimbursed and non-prescription products are not, although there are some exemptions according to respective national healthcare regulations. [51] Most countries adhere to the recommendation of the EU commission to forego price regulation on non-reimbursed products and accept price formation by market competition. [52]

Reimbursement is a quite extensive topic; therefore there will only be provided a short overview on the legal situation in the following, limiting the discussion to the points related to prescription status. Reimbursements in Germany and UK as two of the biggest pharmaceutical markets in Europe will serve as examples.

2. Reimbursement in Germany

86 % [53] of all Germans are members in the statutory health insurance. Their reimbursement is limited to products and services that are sufficient, appropriate and economical for the treatment of the patient's condition (§ 12 SGB V). Decisions on pricing and reimbursement of individual products are reached by the "Gemeinsamer Bundesausschuss" (G-BA, § 92 SGB V). Prescription drugs are usually covered by the health insurance (§ 31 (1) SGB V). Exempted are drugs that are

lifestyle medicine (§ 34 (1) SGB V, e.g. Viagra®), indicated for treatment of various minor ailments (§ 34 (1) SGB V, e.g. common cold), without sufficiently shown efficacy (§ 34 (3) SGB V), or drugs that are not economical or not actually necessary (§ 92 (1) SGB V).

For reimbursed products, patients only have to pay a small prescription fee between 5 and 10 Euros (§ 61 SGB V). There are exceptions for children (§ 31 (3) SGB V) hardship cases and patients with chronic diseases (§ 62 SGB V).

Non-prescription drugs are usually exempted from reimbursement by the statutory health insurance (§ 34 (1) SGB V). They can only be reimbursed if they are intended to treat a serious disease (AM-RL Annex 1) or for young patients (§ 34 (1) SGB V). However, some health insurances reimburse certain non-prescription products on a voluntary basis. [54]

German reimbursement law allows that the maximum price of new pharmaceutical prescription-only products can be set freely within the first year on the market. After that period, prices are negotiated between the MAH and the Central Federal Association of Health Insurance Funds (”GKV-Spitzenverband”, § 130b SGB V) based on the additional value compared to the standard therapy as shown in the benefit assessment (§ 35a SGB V) by the IQWIG. If there is no additional value, only costs of the standard therapy will be reimbursed.

In addition, pricing is limited by the German regulation on fixed charges for pharmaceutical products (“Festbetragsregelung”, § 35 SGB V). Price limits establish a common maximum price for certain substances or drug classes, so that even if a pharmaceutical product is available for reimbursement, there is a maximum price the statutory health insurance will cover. Eventually, patients have to pay the gap between the fixed maximum price and the price charged by the MAH. [55]

Generics can be bought by health insurances with discount agreements based on tenders (§ 130a (8) SGB V). Doctors can only prescribe API and pharmaceutical form; the specific product handed out by the pharmacy is based on the patient’s health insurance company and its respective discount agreement with the manufacturer (§ 129 (1) SGB V).

Private health insurances grant more freedom to their patients, based on the insurance contracts. They may reimburse additional products or agree on high deductibles. Generally, patients with a

private health insurance enjoy better medical care because the insurance reimburses all treatments that are “medically necessary”, not only those that are also sufficient and economical [56].

3. Reimbursement in the UK

In the UK most patients are insured with the National Health Service (NHS) as public healthcare provider. Healthcare is free, the costs of the system are covered by tax (98,8 %) and only 1.2 % are covered by patient charges. [57] Private healthcare insurances only play a minor role in UK.

Prescription-only products are usually reimbursed, as long as they are not blacklisted or greylisted. Blacklisted products are borderline products that:

- offer no true medicinal value,
- products for 17 different therapeutic categories such as contraceptives,
- products which are too costly to be justified or which provide no clinical advantage over cheaper products, or
- pharmacy-only and GSL-products. [58]

Greylisted products are products in use when a medical treatment is not inevitably necessary (e.g. Viagra®) and can only be reimbursed under very limited circumstances. [59]

Products eligible for reimbursement are covered with their full price, so that patients only have to pay a small prescription fee. However, certain groups of people are exempted from the obligation to pay the prescription fee, such as persons under the age of 16 or over the age of 60 years, students, pregnant women and new mothers, people with low income and patients suffering from chronic illnesses; these groups approximately account for half of the UK population. [60] However, pharmacy-only and GSL-products have to be paid by any patient on his own expense regardless of his status or circumstances.

Cost effectiveness is controlled by the National Institute for Health and Care Excellence (NICE). Pharmaceutical companies are theoretically free in their pricing (PPRS 7.14), but the chosen price will be considered in the cost-benefit evaluation by NICE. Products without a sufficient cost-benefit ratio are not recommended by NICE and thus do not have to be reimbursed by the NHS.

[61] An upper limit for pricing set by NICE is £ 20,000 to £ 30,000 cost per quality adjusted life year (QALY). [62] [63] More expensive drugs can only be reimbursed if they are part of a patient access scheme [64] – a freely negotiated price between the MAH and the Department of Health that can be regarded as special discount agreement.

In addition, there are price limitation systems to limit the total healthcare spending. One is the Pharmaceutical Price Regulation Scheme (PPRS). It applies to branded (PPRS 3.14) prescription-only medicine. The scheme was introduced in 2014 and is negotiated between the Department of Health and the Association of the British Pharmaceutical Industry (ABPI). The members of the PPRS scheme have agreed to hold the annual growth of expenditure on pharmaceutical products of the NHS between 0 % and 2 % (PPRS 6.11). A higher increase of expenses leads to automatic discounts (PPRS 6.2). Moreover, manufacturers subject to the PPRS are unable to exceed profitability limits set on the performance benchmarks of return on capital and return on sales. About 90 % of all pharmaceutical companies participate voluntarily in the PPRS. [65] If a company does not participate, it is covered by the statutory pricing scheme described in "Health Service Branded Medicines (Control of Prices and Supply of Information) (No 2) Regulations 2008." Most striking feature of this scheme is a price cut of 15 % based on the 2013 NHS list price of medicine (The Health Service Medicines (Control of Prices and Supply of Information) (Amendment) Regulations 2013, s3 (4)).

Healthcare professionals are free to decide specifically which product brand to prescribe; there is no automatic substitution of generic products. [60] However, generic POM products are only reimbursed up to the reimbursement price published in the Drug Tariff Part VIIIA. These prices are set by the Secretary of State. Prices of OTC and GSL products are not controlled and can be set at discretion by pharmaceutical companies. [66]

4. Strategies & Case Studies: Effect of Reimbursement on Pricing

Reimbursed and non-reimbursed products address different target groups: Customers of non-reimbursed non-prescription products have to take self-responsibility for their product choices and are willing to pay premium prices for products to which they attribute a high quality. [39] Customers of prescription products demand that the healthcare system will reimburse a medicinal product that is suitable for their therapy and do not accept products that are not reimbursed or are

above the fixed price according to § 35 SGB V. [67] [68] Practitioners even have to point this out to the patient before prescribing such a product (§ 73 (5) SGB V) so that they are less consumed [40] and have a low market share. Although 16.8 % of all German medicinal products covered by the fixed price regulation require an extra payment by the patient in addition to the usual prescription charge, their prescription rate is only 8.2 %. [69]

However, provided a product is completely reimbursed (except for the prescription charge), customers do not care much about the price and have a low price elasticity. Thus for reimbursed products, pharmaceutical companies only have to negotiate prices with the HTA bodies as agents of the public healthcare system. As long as the pharmaceutical product is still protected by patents or other protective rights, the product's additional benefit is most relevant for the pricing and pharmaceutical companies are often able to negotiate prices that would exceed the customer's individual willingness to pay. This benefit can easily turn into a disadvantage as soon as generic alternatives enter the market, as HTA bodies only aim for the product with the lowest price and cannot be influenced by marketing or a strong brand. With generic competitors, HTA bodies can easily introduce fixed reimbursement prices and, in Germany, healthcare insurances can even enter into discount contracts with pharmaceutical companies. With these in place, prescribed medicines can be exchanged for the concessional bioequivalent product by the dispensing pharmacist. Both tools of fixed price regulation and discount contracts force competitive pricing on the prescription market so that a switch to non-prescription might be worthwhile.

A good example to show the influence of the prescription status on reimbursement and pricing is the drug naratriptan in Germany. This migraine medication got the non-prescription status for boxes with no more than two tablets in 2006. [70] Larger pack sizes remained prescription-only (Annex I AMVV) to reduce the risk of intentional overdosing, which is quite common for painkillers. Especially for naratriptan, the switch opened access to multiple parallel target groups. Given the indication, it would be quite painful for patients with acute migraine attacks to stay in the waiting room to consult a general practitioner and get a prescription, and the possibility to obtain the drug in any pharmacy or even send someone else to run the errand is a great relief to the sufferer. Then again, the remarkable high price per tablet as well as the inconveniently small pack size for the non-prescription product justifies the need for prescription for chronic patients.

While the boxes with up to two tablets are not reimbursed at all and completely free in pricing, the pack sizes of four or more tablets are covered by a fixed price according to § 35 SGB V, which is € 18.11 for boxes with four tablets. [71] On the German market, there are five pharmaceutical products available with that pack size and four of them have a pricing that is identical to the maximum reimbursed fixed price. Only one product has a higher price, so that customers would have to pay an additional premium charge.

For the non-prescription naratriptan 2,5mg in boxes of not more than two tablets, the recommended retail price in Germany lies between € 6.72 and € 10.61 (see Table 1) with an average price of € 7.48. Thus, the price per tablet for the non-prescription product is significantly lower than for the prescription product – even if it is not taken into account that customers may additionally get discounts on the recommended retail price. The observation that non-prescription products are cheaper than prescription products holds true in general. [72] The lower margin in sales prices can be compensated by higher revenue.

Another interesting finding is that the price variance of the non-prescription naratriptan is significantly higher than for the prescription naratriptan. This high price range allows pharmaceutical companies to fully exploit the customer's maximum willingness to pay. The cheapest non-prescription product is a no-name generic (Naratriptan-Hormosan), while the most expensive product is the originator's well-advertised branded product (Formigran®). Some companies even use different brands for price differentiation. Hexal and 1 A Pharma are both subsidiaries of Sandosz [73] and it is not unlikely that both products have no differences in product quality. Nevertheless, the product sold under the well-known brand Hexal is much more expensive than the product sold under the discount brand 1 A Pharma. The prescription versions of these products are sold without price differentiation because customers are willing to pay premium charges for non-prescription products, but not for prescription products.

This analysis led to two important findings: Firstly, pharmaceutical companies avoid prices over the fixed reimbursement price for prescription drugs to prevent additional fees for customers; secondly, non-prescription products are generally cheaper, but their higher price range allows better price differentiation.

Name	Manufacturer	PZN[a] (2tab)	UVP[b] (2tab)	PZN 4(4tab)	AVP[c] (4tab)
FORMIGRAN® 2,5 mg Filmtabletten	GlaxoSmithKline Consumer Healthcare GmbH & Co. KG OTC Medicines	02195485	€ 10.61	n/a	n/a
NaraDex 2,5 mg Filmtabletten	DEXCEL Pharma GmbH	02195485	€ 6.75	n/a	n/a
Naramig® 2,5mg 4 Filmtabletten N1	UCB Innere Medizin GmbH & Co. KG	n/a	n/a	01719911	€ 21.53
Naratriptan – 1 A Pharma® 2,5 mg Filmtabletten	1 A Pharma GmbH	09322478	€ 6.90	09322490	€ 18.11
Naratriptan AL akut 2,5 mg Filmtabletten	ALIUD PHARMA® GmbH	09312936	€ 6.90	n/a	n/a
Naratriptan Hennig® bei Migräne 2,5 mg Filmtabletten	HENNIG ARZNEIMITTEL GmbH & Co KG	03212062	€ 6.87	n/a	n/a
Naratriptan Heumann bei Migräne 2,5 mg Filmtabletten	Heumann Pharma GmbH & Co. Generica KG	09542263	€ 8.29	n/a	n/a
Naratriptan HEXAL® 2,5 mg Filmtabletten	Hexal AG	09334719	€ 7.88	09334688	€ 18.11
Naratriptan-Hormosan bei Migräne 2,5 mg Filmtabletten	Hormosan Pharma GmbH	09487222	€ 6.72	n/a	n/a
Naratriptan Migräne STADA® 2,5 mg Filmtabletten	STADApharm GmbH	09391930	€ 6.90	n/a	n/a
Naratriptan-neuraxpharm 2,5 mg Filmtabletten	neuraxpharm Arzneimittel GmbH	09536452	€ 6.97	09536469	€ 18.11
Naratriptan-ratiopharm® 2,5 mg Filmtabletten	ratiopharm GmbH	09321616	€ 7.49	09318548	€ 18.11

[a] The PZN is the pharmaceutical registration number, a unique product identifier
[b] Price of non-prescription products stated in Euro as recommended sales price (UVP)
[c] Price of prescription products stated in Euro as pharmacy retail price (AVP)

Table 1: Sales price of naratriptan depending on reimbursement. Listed are all products for naratriptan 2.5mg that are currently available in Germany in boxes with two or four tablets. All boxes with two tablets are non-prescription products while boxes with four tablets are prescription-only. The table shows that four out of five prescription products do not surpass the fixed reimbursement price of € 18.11 to avoid additional charges for the customers. Prices for non-prescription products vary more widely to enable price discrimination. The originator product Formigran® by GSK uses a brand name to improve recognition as well as premium pricing.
Data Source: Query at Gelbe Liste, available at https://www.gelbe-liste.de/profi-suche on 8 August 2017.

VI. Changing the Prescription Status

1. How to Influence the Prescription Status in the EU

As the legal status of a medicinal product influences target groups, advertisement strategies and extent of reimbursement, a company might consider changing the status of a product due to commercial and economical reasons. Even though the prescription status of a drug is generally set by the regulatory authority in the course of the initial registration – under consideration of the applicant's request –, the registration holder may apply for a change of the assigned legal status later-on (Article 74 of Directive 2001/83/EC). New chemical entities usually start as prescription-only medicine as they lack sufficient post-marketing safety data, i.e. the product requires "further investigation" (Article 71 (1) of Directive 2001/83/EC). Before a switch to non-prescription status can be initiated, a widespread use for at least five years [19] should be provable.

Article 74 of the Directive 2001/83/EC defines the legal basis for changing the status of a medicinal product: According to this, regulatory authorities can change the legal classification of a product either upon application of the registration holder or in their own discretion whenever "new facts are brought to their attention." Classification changes can be made between all legal statuses and in any direction. However, pharmaceutical companies usually apply for conversion to a less restricted prescription status.

The switch between the main categories of prescription and non-prescription status is widely harmonized within the EU, being based on Directive 2001/83/EC and the "Guideline on changing the classification for the supply of a medicinal product for human use" [19]. Nevertheless, national authorities do not always come to the same conclusion about the correct legal status of a product, leading to divergent statuses in the member states.

Switches between sub-categories like "pharmacy-only" and "free sale" or the classification as narcotic are hardly harmonized at all and still rely solely on national considerations.

2. Changing the Legal Status from Prescription to Non-Prescription

Manufacturers are likely to apply for a switch to the non-prescription status before the patent expires so that they can gain a foothold in an expanding over the counter market ahead of generic competition. [74] This status change of a medicinal product from prescription-only to non-prescription is also referenced as “Rx-OTC switch”. It is covered by the “Guideline on changing the classification for the supply of a medicinal product for human use”. In order to apply for a change in the legal status of a product, a variation according to Regulation EC/1234/2008 has to be submitted. This special variation is classified as C.1.5.a or C.1.5.b according to the variation classification guideline [75] and counts as Type II (for initial re-classification) or Type IB variation (for subsequent generics and biosimilars), with effect on timeframe and complexity of assessment processing as well as level of charges.

Changing the legal status of a product that was registered nationally or via MRP/DCP is a purely national decision. [75] Only classification changes of products registered via CP are handled centrally.

Generally, a switch is only possible if the applicant can successfully argue that the patient’s benefit of a less restricted access outweighs the additional risks that may arise. Evidence may be provided by comprehensive data on the safety of the product, especially from the post-marketing period, including data on adverse reactions as well as post-marketing safety studies, if available. Moreover, data on the toxic potential, the possible interaction with commonly used drugs and consequences of misuse are necessary.

Strategies to minimize the product’s risks and misuse potential include reducing the number of indications, the recommended duration of the treatment, the product’s strength or pack size, or any combination thereof. Therefore, status changes usually imply significant changes to the labeling, SmPC and PIL of the product. It is quite common that the applicant keeps prescription-only registrations of the product without restrictions to indication, treatment duration, strength or pack size.

If the change of the prescription status is substantiated with significant clinical or non-clinical studies, the applicant may gain a one year of data exclusivity before competitors may apply for the same change of prescription status (Article 74a of Directive 2001/83/EC). These studies are

deemed significant if they are related to a new strength, new pharmaceutical form or route of administration, or a new indication. Also if new safety or efficacy data was generated for the non-prescription environment, this data would also be protected, given the underlying studies count as relevant and necessary. If the data exclusivity expires or is not granted at all, generic or biosimilar products' legal status can be easily changed with reference to the decision for the reference product (C.1.5.a variation type IB).

3. Changing the Legal Status from Narcotic to Prescription-Only

Medicinal products that are legally classified as controlled drugs incur additional costs and workload for prescribing, handling and distribution. Therefore it is in the interest of pharmaceutical companies to avoid an assignment of this status to any of its products, if possible.

While there are harmonized processes to classify a substance as controlled substance in the EEA, there are no harmonized processes or official applications to remove these restrictions from certain products. Therefore, only Article 71 (2) of Directive 2001/83/EC can serve as a guiding instruction for pharmaceutical companies that strive for an elimination of the unwanted narcotic status for one of their products. Generally speaking, a pharmaceutical company has to ensure that the product is not likely to "present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes" (Article 71 (2) of Directive 2001/83/EC). This means that the pharmaceutical company has to prove that the reasons, for which the product has been classified as narcotic in the first place, are no longer existent or decisive. The decision about a switch from narcotic to prescription-only status is reached nationally. In Germany, this decision is made by the Expert Committee on Narcotic drugs ("Sachverständigenausschuss für Betäubungsmittel", § 1 (2) BtMG).

Drug abusers try to consume drugs in a way to exploit their strongest effect, i.e. by reaching the maximum drug concentration in the brain within the shortest possible time. This type of consumption reinforces rewarding behavior and results in further misuse. [76] Usually, drug abusers achieve their goal by deliberately consuming increased amounts of the substance or changing the administration route to nasal or parenteral consumption. Pharmaceutical companies may now try to avoid the classification as narcotic for some less dangerous substances by sufficiently reducing the strength and pack size of a product, thereby limiting its potential for

abuse and addiction (c.f. exemption for low-dose diazepam in Annex III BtMG). More dangerous substances need additional effort to optimize a formulation to prevent tampering by consumers: Pharmaceutical companies therefore try to use abuse deterrent formulations that shall prevent unwanted ways of consumption. This could be the use of retard formulations (in order to distribute the absorption of the API over a longer timeframe) or use tablets with increased crushing resistance (in order to prevent nasal use). However, as the development of these additional pharmaceutical forms is quite cumbersome, pharmaceutical companies now tend to take these factors into account during the initial development of potential narcotics. [77]

A more classical approach is the combination of the opioid antagonist naloxone with certain opioids like oxycodone, tilidine or buprenorphine. Naloxone has the potential to cancel the effects of its combination partners if used parenterally. Due to the low oral bioavailability, these combination products are still effective if used orally. [78] Thanks to this, the combination prevents the abuse of the opioid substances by injecting, a route of administration that leads to a faster effect and higher concentration in the blood, thereby increasing the potential for addiction. Against this background, some of the naloxone-opioid combination products have been exempted from the narcotics status in Germany (Annex III BtMG).

4. Changing the Legal Status from Pharmacy-Only to Free Sale

Switches from pharmacy-only to free sale status are not regulated on an EU-wide basis; national regulations have to be observed. In Germany, the conditions for the switch are very strict: Switches are only possible for non-prescription drugs that do not show any direct or indirect danger for health, even if used incorrectly (§ 45 (1) AMG). Thus, switches to free sale drugs only occur for substances that are extremely harmless and well-known for decades or even centuries. The decisions about these switches are made by the Expert Committee for Prescription Requirements (“Sachverständigenausschuss für Apothekenpflicht”). In the last eleven years they held four meetings [26] and granted switches to free sale status for nine products, eight of them of herbal origin. Furthermore, four of the granted switches concerned only minor extensions to already existing permissions.

The condition that the switched substance may not show any danger is taken seriously. All requested switches for “only” reasonably safe drugs such as low dose Ibuprofen or

Acetylcysteine were rejected and even birch leaves took eight years of discussions until they got the concession. Against this background, pharmaceutical companies need many years of lobbying to obtain free sale status for one of their products; and none of the switched products had a contemporary originator or well-known market leader. With this in mind, such a switch is rarely an advisable option.

In the UK, restrictions for a switch to non-prescription status are significantly lower. Switches to free sale (called GSL) are possible for all drugs that can be sold "with reasonable safety" without the supervision of a pharmacist (Human Medicines Regulation 2012, s62(5)). This has been further defined by the MHRA as "where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser." [27]

Since 2006, there have been twelve switches to free sale status in the UK. The number alone does not show the difference to Germany: While in Germany the dangers of birch leaves were discussed from 2009 to 2017, UK released mass-market drugs like Diclofenac, Esomeprazole or Hydrocortisone to the retail stores. [79]

In the UK, the reclassification is made for single products and not for substances, thereby providing an additional incentive for the switch to the applicant. The necessary effort is comparable to the change from prescription to non-prescription status described in the EU Guideline. However, other products can subsequently be easier reclassified if they have the same API, strength and administration route. [9]

5. Strategies & Case Studies: Changing the Legal Status

Changes of the prescription status from prescription to non-prescription are possible within the boundaries of the well-defined legal frame discussed above. Actually, this type of change is nothing out of the ordinary: Since 1990, 43 switches have been granted in Germany, surpassed by the UK with 58 switches. [80] "Switches are motivated mainly by three factors: pharmaceutical firms' desire to extend the viability of brand names; attempts by healthcare funders to contain costs; and the self-care movement." [74] In contrast to these Rx-OTC switches, authorities have initiated re-switches in order to make a prescription mandatory again for some products. Since 2000, there have been 21 re-switches from non-prescription to prescription in Germany due to

safety reasons. [81] However, most of these re-switches did not affect the whole substance but only certain indications or pack sizes.

With an Rx-OTC switch, the healthcare system does not only save costs for drugs that are no longer reimbursed; the availability of medicinal products for self-medication also reduces the number of consultations of healthcare professionals, resulting in further cost savings. An example for this is Simvastatin which became available as OTC in the UK in 2004. According to the EU Guideline on changing the classification, this status should only be given to medicinal products that treat conditions with easy self-diagnosis and where delayed consultation of a healthcare professional does not significantly increase the patients' health risk. As these criteria do not match with statins, there were some speculations that this switch was tacitly approved to reduce the NHS healthcare expenditures. [82] The total prescriptions of statins declined by 36% within one year after the switch, [83] leading to significant savings for the healthcare system. Although only the 10mg strength of simvastatin was released from prescription, the switch also reduced the prescription rate of higher strengths and other statins.

However, the switch was initiated by the MAH Merck (now Merck Sharp & Dohme) [84], so it is not unlikely that revenue optimization and focus on a new target group (i.e. patients with low to moderate risk of coronary disease) were the key drivers for the switch application.

VII. Financial Econometrics

1. Facts and Figures

Pharmaceutical companies are profit-oriented enterprises that employ significant financial resources to pursue their activities. The impact of the legal status on market share, sales and profit is crucial for them.

Switching the registration status can be quite expensive and time-consuming for pharmaceutical companies. Is the difference in sales significant enough to make it worthwhile? Is there an optimal legal status from the viewpoint of a pharmaceutical company? There are few sources on the financial impact of the prescription status. In the following, available data with respect to the German market, [85] collected from different sources (mainly IMS Health), shall be combined

and analyzed to assess this question. The following findings are based on own calculations; the underlying numbers can be found in the Appendices.

Whether the legal status has an impact on the sales of a pharmaceutical product can be answered best by looking at a list of the pharmaceuticals with the highest revenue (see Figure 3). Ten out of ten blockbusters on this list are prescription-only originator products and it is known that prescription medicine constitute on average 80 % of the turnover of originator companies. [86]

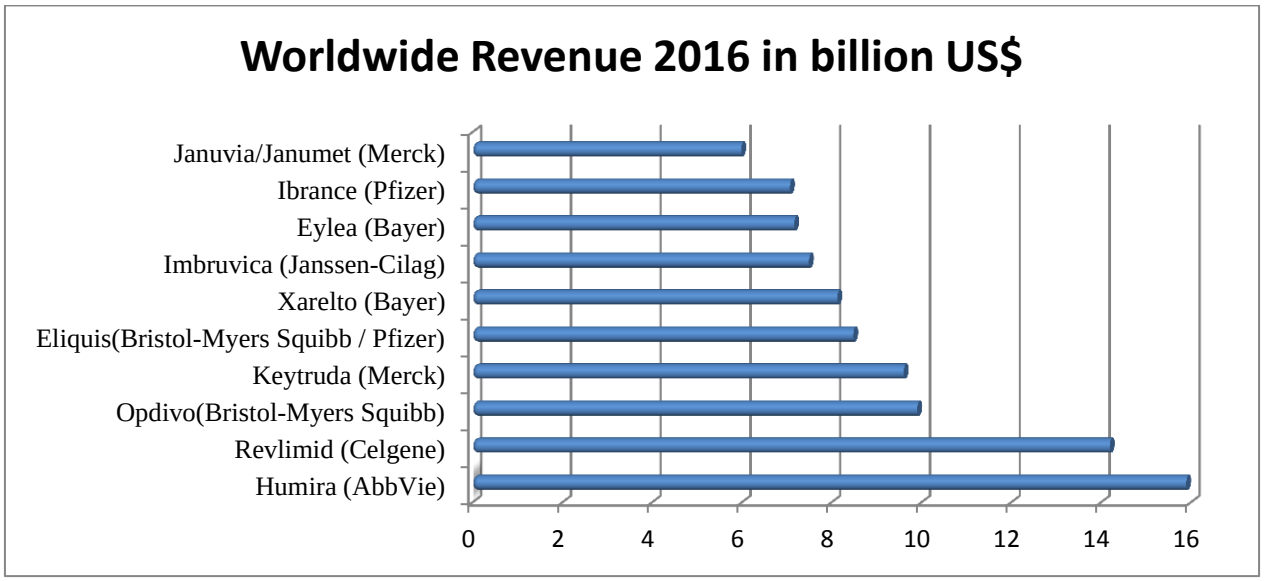

Figure 3: Pharmaceutical products with the highest revenue worldwide in 2016 (in billion US$). Source: Own design based on IMS Health® Data (Appendix 2).

Based on the figure above, it could be assumed that prescription-only is the financially most rewarding legal status a medicinal product might have. However, such a conclusion would be biased as all of these blockbusters are still within their protection period (i.e. without generic competitors) and their revenue is still burdened with the amortization of their research and development expenditure. Only a small fraction of medicinal products in the pharmaceutical market are at this early stage of their lifecycle, so the whole pharmaceutical market has to be analyzed in order to get a more conclusive overview.

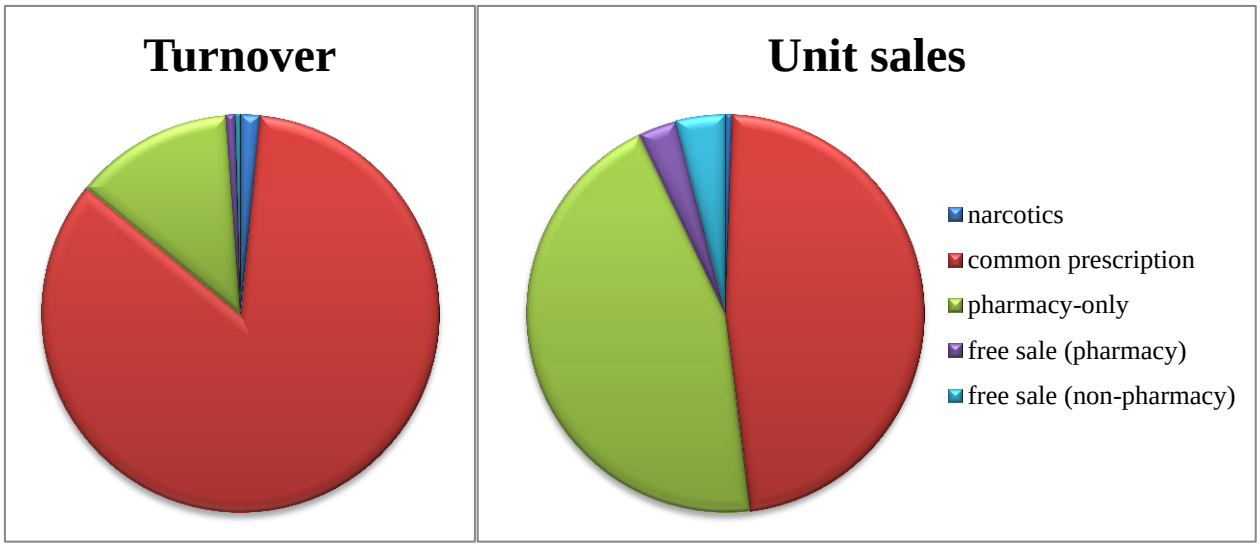

Figure 4: Turnover and unit sales by legal status and distribution channels in Germany in 2016. Source: Own design based on IMS Health ® Data (Appendix 4).

As shown in Figure 4, about 86 % of the complete turnover in 2016 for medicinal products was made by prescription drugs. However, the sales volume – measured in packaging units – of prescription and non-prescription drugs was nearly equal. This means that prescription drugs had 6.1 times more revenue than non-prescription drugs, i.e. non-prescription drugs were much cheaper on average than prescription drugs. An average unit of a prescription drug costs € 60.83 while one unit of a non-prescription drug only costs € 9.17; this is 85 % less.

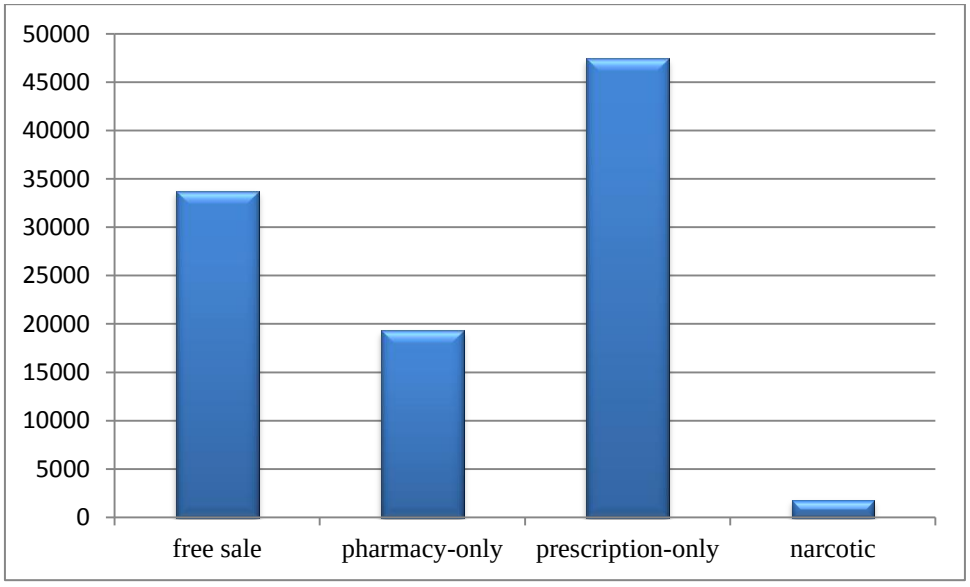

Figure 5: Number of medicinal product registrations in Germany (July 2017) by legal status. Source: Own design based on BfArM 2017 (Appendix 1).

If prescription drugs and non-prescription drugs are consumed with approximately equal frequency, it could be assumed that the number of product registrations is also similar. In fact this is actually almost true (Figure 5): 48 % of all registered pharmaceutical products are prescription-only and 52 % are non-prescription products. However, an unexpected 33 % of all registered pharmaceutical products are free sale drugs although this category only has a minor 1 % contribution to the total turnover. This is emphasized the number of sold packaging units per registration: Free sale drugs only sell 3,256 boxes per registration, pharmacy-only drugs sell 35,854 units per registration and prescription-only drugs sell 15,616 units per registration per annum.

2. Differences between Prescription and Pharmacy-Only

The figures above raise questions: Why are prescription drugs more expensive? Why are there fewer registrations for pharmacy-only products?

And why are pharmacy-only products consumed more than twice as much as prescription products (per registration)? All these facts can be explained with four special characteristics of the registration statuses:

1. Patent protection: Prescription drugs are more expensive on average than non-prescription drugs because they comprise most of the expensive patent protected drugs that raise the average price. New medicinal products entering the market with the prescription-only status need at least five years of market experience before they may switch to non-prescription status, usually even more. After the switch becomes a viable option, patents and the eight year data protection period (Article 10 (1) of Directive 2001/83/EC) are almost expired, triggering generic competitors to enter the market. This leads to a higher price competition and thus, on average, a comparatively lower price for non-prescription drugs.

2. Product value: The fair value of a product is aligned to the medicinal benefit it can offer. As OTC products are used without the supervision of a healthcare professional, they are usually intended to treat less severe conditions. [19] Treatment of minor illnesses has a lesser benefit than the treatment of serious diseases. Therefore, public healthcare systems with their HTAs as well as self-paying customers have a lower willingness to pay for OTC products.

3. Quantity of users and unit sales: Non-prescription drugs are used by a larger customer base than prescription drugs. To enable the OTC-switch, an API needs lots of market experience to estimate the adverse effects and safety of the drug. The necessary market experience can be obtained easier with a large base of patients, facilitating the switch for heavily used medicinal products. In addition, OTC products are intended to treat minor disorders that – fortunately – tend to be more abundant than serious or even deadly diseases. Therefore, pharmacy-only products are sold in more units per registration and have a better economy of scale, leading to lower marginal costs per product unit compared to prescription drugs.

4. Bias: Exemptions from prescription status are often restricted to small strength and pack sizes. Thus, packs with high strength and larger quantities that obviously come with a higher price per package, remain under prescription status. However, this bias has only a small effect in relation to the 6.1 times higher price of prescription drugs.

3. Non-Prescription Drugs and their Sub-Categories

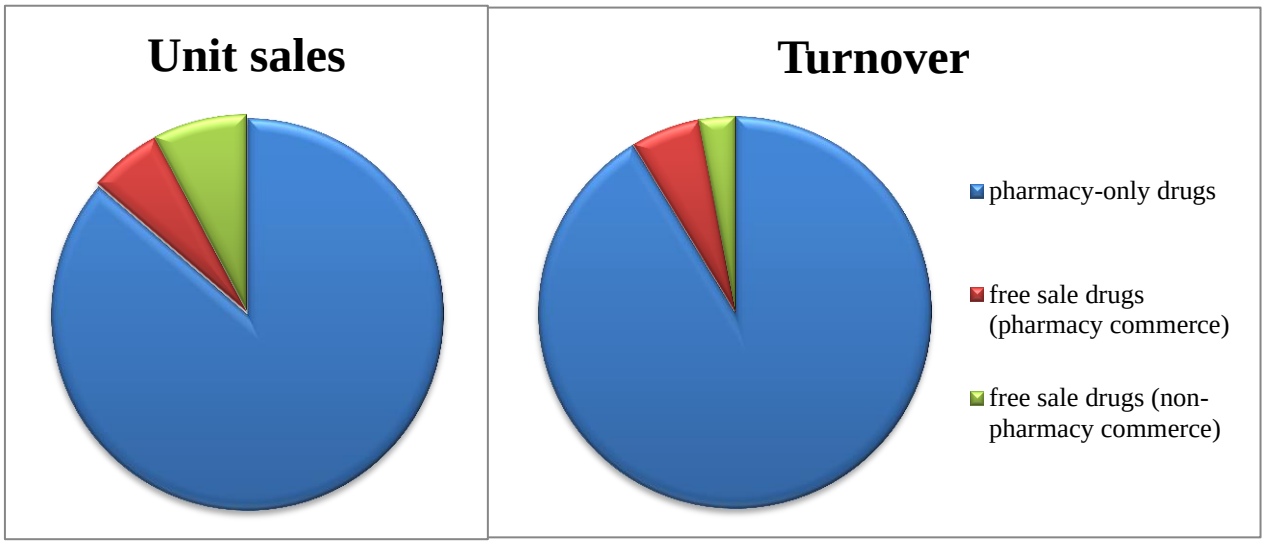

Figure 6: Comparison of sold units and turnover of non-prescription drugs 2016 in Germany. The figure shows the dominance of pharmacy-only drugs. Even 44 % of free sale drugs are sold in pharmacies.
Source: Own design based BAH, 2017, *Der Arzneimittelmarkt in Deutschland 2016: Zahlen und Fakten*, available at https://www.bah-bonn.de/bah/?type=565&file=redakteur_filesystem%2Fpublic%2FBAH_Zahlenbroschuere_2016_web.pdf, last accessed on 8 August 2017.

Only 8 % of turnover for non-prescription drugs are made with free sale drugs. So free sale drugs only play a minor role in the German overall sales distribution. This is in contrast to the fact that they account for 64 % of all non-prescription product registrations. The registration of a freely-available drug only generates a turnover of approx. € 17,500. Can these earnings even cover the administrative costs? The discrepancy between number of registrations and turnover can be explained by the special approach of the German standardized marketing authorization ("Standardzulassung", § 67 (5) AMG) that allows product registration for certain plain products with a simple notification only. About 41 % of all German registrations are standardized marketing authorizations and most of them are for free sale drugs. [87] These standardized marketing authorizations are not only used by pharmaceutical companies, but also many individual pharmacies use these form of authorization for their self-prepared pharmaceutical products (e.g. blended herbal teas).

Due to the low sales income, one could come to the conclusion that freely-available drugs are a neglectable subcategory of non-prescription drugs. The fact that 92 % of all non-prescription medicinal products are sold in pharmacies strengthens this [88] – and even 33 % of free sale drugs that could be sold elsewhere. Patients show a high trust in their pharmacies and regard them as first point of contact to buy medicinal products. However, free sale drugs are important because of the sales opportunities they provide.

Compared to pharmacy-only products, free sale drugs can be sold in any shop with specially trained sales staff and this additional distribution channel is expected to open new sales opportunities. As 33 % of free sale products are sold in pharmacies (including online pharmacies), the remaining 66 % are sold over other distribution channels. A comparison of turnover and unit sales shows remarkable price discrimination: The average price in pharmacies is € 8.10, outside of pharmacies it is € 3.23. Thus, the different distribution channels allow pharmaceutical companies and other sellers of medicinal products to target different customer groups and to skim their maximum willingness to pay.

In drugstores, there is a predatory competition between food, dietary supplements and free sale drugs. Customers need to be convinced to pay the additional charge for a drug like premium medicinal tea with health claim instead of buying the cheaper adjacent herbal tea that is classified as foodstuff. With this price competition, free sale drugs cannot be sold with a significant

surcharge in drugstores as it is possible in pharmacies; there, free sale drugs are more likely compared with OTC drugs by the customers, and their average price of € 8.93 raises the benchmark for the free sale drugs sold in the pharmacies.

In addition, pharmacies can be regarded as premium shops compared to drugstores. With their superior service, guidance by excellently qualified sales personnel, and exceeding image of quality they can rightly charge premium prices.

These price discrimination features are used by companies to place their product in an appropriate market niche. A good example is the free sale product Heparstad® (API: artichoke leaves, see Annex 1a AMVerkRV) that is only sold in pharmacies due to marketing reasons: The selection of pharmacies as exclusive distribution channel justifies the premium pricing of 644 % over the price for a comparable discounter product.[1] As companies are well aware of price discrimination options, it is very uncommon that a branded product is sold concurrently in pharmacies and drugstores.

4. Narcotics in Comparison with Common Prescription Drugs

The handling of pharmaceutical products under special prescription is quite complicated and time-consuming for all involved parties. In the following, it is therefore evaluated whether pharmaceutical companies tend to refrain from registering narcotics.

In the German BtMG Annex III, there are 86 narcotic substances that can be legally prescribed compared to 1795 registrations for narcotic products in Germany. [89] Thus, there are on average 21 product registrations per narcotic substance. In contrast, there are 2,165 prescription-only substances in Annex I AMVV compared to 47,450 prescription-only registrations in Germany. This results in a ratio of 22 product registrations on average per prescription-only substance. The ratio for narcotic substances is not significantly less than that for common prescription drugs. It can be concluded that even if the handling of narcotics is more complex, there are still many pharmaceutical companies willing to register narcotics, securing their supply to the customer.

[1] € 8.78 (AVP for box with 20 capsules) according to „Gelbe Liste“ retrived on 25.07.2017 https://www.gelbe-liste.de/produkte/heparstad-400-mg-hartkapseln_361634 compared to “Galle- und Verdauungskapsel 400 mg mit Artischocke” by dm-drogerie markt GmbH + Co. KG, priced at € 3.55 per 60 capsules, https://www.dm.de/das-gesunde-plus-galle-und-verdauungskapsel-400-mg-mit-artischocke-p4010355164322.html, both capsules have equal content and are registered as medicinal products.

However, when narcotic substances are registered with almost equal abundance although their handling is more expensive and cumbersome, are pharmaceutical companies registering narcotics only out of charity? Or it is worthwhile to occupy this niche? The sales volume of narcotics in Germany was € 812 million and 8.55 million units (Appendix 4). That is a price of € 95.04 per unit for narcotics compared to € 60.83 for prescription drugs in general; hence, pharmaceutical companies are certainly paid for their additional effort.

Do doctors refrain from prescribing narcotics due to the increased bureaucracy? In 2016, 99,350 units were sold on average for every narcotic substance that is available for legal prescription. For every common prescription substance, 338,529 units were sold, 3.4 times as much. Even though these figures may not answer the initial question, they underline that the prescription of narcotics is indeed a "special prescription" and not done injudiciously. The majority of narcotics are used for a well-defined frame of conditions only: As sedative for surgeries or strong analgesic for heavily suffering patients. It may be rightly argued that narcotics are not needed as often as common prescription drugs with their high variety of indications; but according to the numbers, it is quite unlikely that doctors prescribe them carelessly in situations where narcotics are helpful but not really necessary (e.g. moderate pain).

To sum up, narcotics play an important part in the German healthcare system. They are highly regulated and less often prescribed that common prescription drugs. However, they are registered with comparable frequency and yield a higher price. As their prescriptions as well as import and export licenses increases steadily, [23] it is expected that their significance will rise even further.

5. Economic Impact on Healthcare Systems

Self-medication with non-prescription products is a huge cost-saver for healthcare systems. These savings emerge from the shift in payment from the public healthcare system to the patient due to the common lack of reimbursement for non-prescription drugs. Additional savings derive from the decreased consultation of healthcare professionals. In addition, switching drugs from prescription to non-prescription status often leads to lower drug prices. [72]

Estimations about possible cost savings for the healthcare systems vary, but are always impressive. In Germany, the current use of non-prescription drugs leads to an estimated saving of € 4.5 billion annually; [90] in addition, increased self-medication could save more than € 11.5

billion annually in the EU. [91] Therefore, status switches from prescription to non-prescription products are not only in the interest of pharmaceutical companies, they are also actively supported by healthcare authorities like the MHRA. [51]

However, these estimations tend to look only on the bright side of non-prescription drugs and do not take into account the increased risks and potential cost of using medicinal products without consultation of a doctor. Only about 25 % of all patients read the whole patient information leaflet prior to use [2] and advice by pharmacists is not always to the fullest extent, especially in online pharmacies. Hence, non-prescription drugs bear an increased probability of incorrect use and misuse; consumers of these are more likely to delay professional treatment of serious diseases. The potency of non-prescription drugs is generally underrated by laypeople, so that they are more likely to be used outside of their indication or allowed dose, or that contraindications are ignored [92]. If release from prescription status to non-prescription status is handled too liberal, any follow-on treatment due to incorrect consumption of non-prescription drugs may cause a negative effect on public health and incremental costs for the healthcare system.

6. Strategies & Case Studies: The Status Change and its Effect on the Market

The sales volume of a pharmaceutical product can be raised with an OTC-switch due to increased advertisement opportunities and access to new target groups. An average boost of drug utilization on class level by 30 % can be expected. [93]

The nature of these additional customers may vary, depending on the indication of the product. The best result for pharmaceutical companies would be the mobilization of completely new target groups that have let their condition untreated prior to the switch. However, these groups are limited for most indications as most new target groups exchange a present treatment with the new OTC product. In the worst case scenario, the sales of the new OTC product rise while cannibalizing its prescription-only version.

This cannibalization effect due to a switch from prescription-only to OTC status could be observed 1993 in the UK for the switch of Zovirax® (aciclovir), a drug used for the treatment of lip herpes. At that time, aciclovir was the only effective treatment of herpes simplex on the market and thus without alternatives. While the sales of the non-prescription variant rose after the switch, the prescriptions of the co-existent prescription drug fell rapidly and stayed low. [92] A

contrasting example can be found 1994 in the switch of H2-antagonists (ranitidine, cimetidine, famotidine). The switch significantly reduced the market share of old antacids like sodium bicarbonate that had previously been available as self-treatment of acute heartburn in the non-prescription market. At the same time, sales volume of the prescription drug kept steady [92] as the products were still prescribed for the long-term therapy of gastroesophageal reflux and peptic ulcers.

A very remarkable effect on sales could be observed during the switch of the prescription status for EllaOne® (ulipristal) by the originator HRA-Pharma, one of the most discussed Rx-OTC-switches within the last decade. This emergency contraceptive was authorized in the EEA in 2009 and got a positive CHMP recommendation for the status change from prescription-only to OTC at the end of 2014. [94] In Germany, emergency contraceptives based on levonorgestrel were still prescription-only although they had a comparable safety profile and a much longer market experience and establishment. Although Germany opposed the OTC switch for EllaOne®, [95] the commission decision from January 7, 2015, was legally binding for all EU member states including Germany. However, due to a special provision about contraceptives in Article 4 of Directive 2001/83/EC there were some legal uncertainties [96] so that the product was not sold without prescription before the change of the AMVV on March 14, 2015. [97] With the same change of the AMVV, emergency contraceptives based on levonorgestrel were also exempted from prescription, but products with updated PIL and secondary packaging eligible for non-prescription sale were not available before mid of April 2015. [98] This led to the situation that EllaOne® was the only approved OTC emergency contraceptive in Germany for about one month.

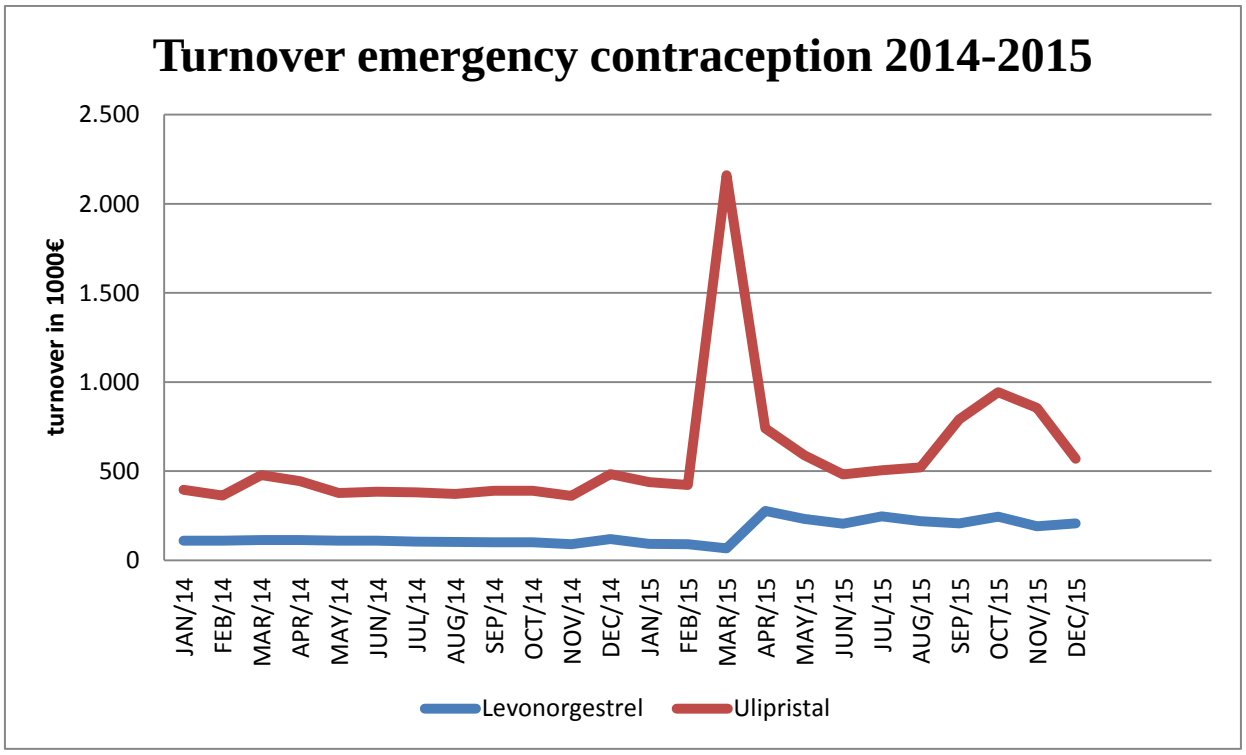

Figure 7: Turnover of emergency contraception between 2014 and 2015 in Germany. The figure compares sales for products with levonorgestrel 1.5mg in the indication emergency contraception with ulipristal (EllaOne®). As soon EllaOne® is available as non-prescription product, a huge peak in sales can be observed. One month later, levonorgestrel is also available as non-prescription and also shows rising sales. The available data only displays only the sale-in, i.e. purchases of the pharmacies from wholesalers or directly from the manufacturers. Hence, this data is not necessarily identical to the sales to customers.
Source: Own design based on IMS Health® DPM (see Appendix 4).

Figure 7 shows that the sales of ulipristal rose dramatically as soon as the non-prescription product was available in March 2015. It is expected that not all of the sold tablets were immediately used as emergency contraception but that pharmacies as well as customers built a stock of the product. At the same time, sales of levonorgestrel dropped slightly as the new non-prescription treatment was obviously preferred by many customers. When these products were also available as non-prescription drugs on month later, their sales rose again and stayed on the elevated level. Concurrently, sales of ulipristal normalized but stayed on a higher volume than prior to the switch. This indicates that the demand for emergency contraception in general has increased, regardless of the specific API. It can be assumed that due to the removal of the prescription requirements, hurdles were lowered for women to seek remedy: On the one hand, emergency contraception requires a timely prescription that may not always have been obtainable with reasonable effort for the women (e.g. on weekends or out of business hours); and on the

other hand is the new distribution channel suitable to secure women's anonymity which had formerly not been possible.

Usually the switch of all relevant strength and pack sizes of a product has a negative impact on customers that prefer reimbursed products. However, in Germany emergency prescription products are one of the few pharmaceuticals that can be conditionally reimbursed even if the product does not require a prescription (§ 24a (2) SGB V). So the switch still increased the possible target groups.

VIII. Conclusion

1. Summary

The legal status of a pharmaceutical product is intended to restrict its access and avoid dangers to patients. The two main categories "prescription drugs" and "non-prescription drugs" can be further divided in sub-categories for an even more precise adjustment of accessibility.

The non-prescription-status is eligible for drugs that meet four conditions: a good direct and indirect safety profile, low abuse and misuse potential, sufficient marketing experience and no parenteral administration. The subcategories of non-prescription drugs are free sale drugs and pharmacy-only drugs. While free sale drugs are safe enough to be sold in drugstores without the supervision of a healthcare professional, pharmacy-only drugs have to be dispensed by a pharmacist.

Prescription-only is the default legal status for all drugs that are new on the market or cannot meet the criteria to obtain non-prescription status. These drugs have to be prescribed by a doctor before they can be dispensed. Further sub-classifications are special prescriptions and restricted prescriptions. Special prescription drugs are narcotics with a high abuse potential. They are highly restricted and come with extensive and costly documentation obligations for transport, handling prescription and dispensing. Restricted prescription drugs are products for conditions that can only be treated in specialized institutions. They are often intended for serious diseases and may have severe adverse reactions, requiring close supervision.

The legal status of a product can be influenced by the registration procedure. The CP can force local authorities to implement a special legal status via commission decision by simple majority vote of all member states. The MRP and DCP are suitable for registering a product in multiple countries as long as all participating states agree on the correct legal status of the product. Otherwise the registration procedure will take an uneconomically long time. Separate MRP, DCP or national registrations are therefore advised for member states with dissenting opinions. For national registrations, it is in the respective member states' discretion to assign the legal status. For CP registrations, the status can only be changed centrally by the commission; for MRP/DCP and national registrations, these are purely national decisions.

Advertisement towards the general public is restricted to non-prescription drugs. Promotion towards healthcare professionals is generally less restricted and also possible for prescription drugs. Advertisement for non-prescription drugs can be used to enhance brand popularity, increase market share or charge premium prices in relation to competitor's products. Products with different legal statuses attract different target groups, thus having multiple statuses can increase the sales volume.

Reimbursement is not harmonized within the EU but based on common fundamental principles. In general, prescription drugs are usually (at least partly) reimbursed while non-prescription drugs are usually not reimbursed. Due to this, the pricing of non-prescription drugs is more flexible than the pricing and reimbursement of prescription drugs which is limited by various national mechanisms.

Under certain conditions, the legal status of a drug may be changed. Especially the switch of prescription drugs to non-prescription drugs is well documented and harmonized in the EU. The switch is possible for drugs that meet the strict safety criteria for non-prescription drugs once they have sufficient market experience. Changes of the legal statuses' sub-categories are less regulated and differ in accordance with national mentalities.

A product's legal status also influences its sales. Non-prescription products are usually cheaper and consumed in larger quantities than prescription products. Prescription drugs generate more turnover as they are generally more expensive. However, this is influenced by a few patent protected prescription-only blockbusters whereas a large bulk of non-prescription drugs consists of low price generics.

2. Outlook on Further Harmonization

Future efforts regarding the legal status of pharmaceutical products are expected to target at further harmonization within the EEA. These efforts are on the agenda of the EMA since Directive 2001/83/EC started the harmonization within the member states by setting, together with the related guidelines, common standards for all member states. Also, the EDQM and their "Committee of Experts on the classification of medicines as regards their supply (CD-P-PH/PHO)" support the harmonization actively. They even issued a list of recommended legal status for medicines depending on their API. [99]

However, despite all these efforts, the future of a harmonized registration status does not look very bright. While the growing importance of multinational registrations lead to great advances in the harmonization of the general classification for newly registered products, the harmonization of existing registrations is hampered by different mentalities, traditions and health policies. Also the sub-categories of the registration status cannot be easily harmonized. For free sale products, different distribution channels have evolved in the member states, and the narcotics status of a product is greatly dependent on the moral code of a country. Only the relevant UN conventions as well as the recommendations of the EMCDDA are accepted as a common base.

Still, the increasing importance of the non-prescription status can be seen as a recurring pattern in the member states as it is promoted by all relevant parties. Advocated by the self-care movement as well as the pharmaceutical industry, there is a big lobby for advancements regarding quick access to autonomous self-treatment. [100] Even the EDQM recommends the access to medicines without prescription whenever appropriate, [101] and the Working Group on Promoting Good Governance of Non-Prescription Drugs in Europe regards non-prescription drugs as an empowerment of patients to take responsibility for their own healthcare. [18]

Common rules for the reimbursement of prescription and non-prescription drugs are not expectable. The evaluation criteria for the cost-benefit assessment will be harmonized by EUnetHTA, but reimbursement in general as well as drug pricing cannot be harmonized by central authorities as long as there are huge obstacles such as the divergent healthcare systems as well prosperity gap within the EU member states.

3. Insights and Recommendations for Pharmaceutical Companies

There is no legal status fitting all. In order to determine the optimal legal status, the indication, market environment, price, reimbursement conditions and patent status of a pharmaceutical product have to be taken into account. Nevertheless, with the right tactics it should be possible to figure out which registration status fits best, and to make the most of it.

In Germany, free saledrugs are products with almost no risk potential. Although their number of registrations is high, the individual product generates only little turnover. It is mostly not worthwhile to initiate a switch to this status as the timelines until decision is reached may take several years, and blockbuster products are generally not eligible for this status. Nevertheless, for the right substances, a registration as free sale opens up a good range of opportunities: Registration without costs for research, development or dossier maintenance due to standardized registrations; distribution channels via low-budget drugstores on the one hand or as premium product in pharmacies on the other hand. In the UK, the switch to free sale is more rewarding than in Germany because the switch is allowed for blockbuster products as well and at the same time only valid for the applicant's product. In addition, switches to POM are possible sufficiently early in the product's lifecycle so that an originator can still benefit from the products high popularity.

New registrations as non-prescription drug are – with very few exemptions – only possible for generics and well-established products. In many drug classes, originators were able to occupy the premium segment completely, so that a competitor bears the risk of a low market share despite a huge marketing budget when placing a branded generic into the premium segment. Thus, market placements as affordable plain generics are less risky; but then their profit margin is comparatively lower. However, there are some examples of branded generics that got successfully established in the premium segment thanks to sufficient marketing (e.g. Grippostad® Hot Drink with its API paracetamol). A switch to non-prescription is generally recommended for originators whenever the necessary requirements can be fulfilled: Superior popularity as well as a possible one year data protection period after the switch allows a head start on the non-prescription market. Anyhow, only small pack sizes or low strength should be switched to retain the prescription market and address multiple target groups.

Whenever originators register new prescription drugs, they have to cover the usually extensive costs for research and development and thus need to sell their product for a high but reasonable price. Necessary agreements on reimbursement with the HTAs may set limits to what can be charged for the product. Towards the end of the protection period, a switch to non-prescription should be tried if promising. Otherwise the market share will decrease rapidly as soon as generic competitors join the market. Generic competitors are advised to outcompete their rivals with low prices as advertisement in order to influence the doctors' prescriptions is rarely cost-effective and sales volume is significantly dependent on successful negotiations with health insurances and HTAs who will prefer the delivery and reimbursement of products favorably priced.

Narcotics have a lower prescription rate compared to common prescription drugs; hence, new potential narcotics should be developed with abuse deterrent formulations to avoid restrictions in advance or at least to retain the possibility that they will be removed after a gain in market experience. Manufacturers of generic narcotics who want to participate in the high-priced segment of narcotics should consider registering multiple narcotic products as their profitability is highly subject to economy of scale due to the necessary administrative expense and infrastructure for handling.

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Appendices

Appendix 1: Number of medicinal product registrations in Germany (July 2017) by registration type and legal status.

Type of registration	**No. of registrations**
Approval according to §21 or §25 AMG	30550
Registration according to §38 or §39 AMG	1351
EU-Registration	20359
Standardized marketing authorization	42481
Subsequent approval according to §105 AMG	5019
Subsequent registration according to §39 or §105 AMG	2605
Total	102365
Legal Status	**No. of registrations**
Free sale	33778
Pharmacy-only	19328
Prescription-only	47450
Controlled drug	1795

Source: BfArM 18.07.2017, *Verkehrsfähige Arzneimittel im Zuständigkeitsbereich des BfArM*, available at http://www.bfarm.de/DE/Service/Statistik/AM_statistik/statistik-verkf-am-zust BfArM.html, last accessed on 8 August 2017.

Appendix 2: Turnover of topical diclofenac presentations in Germany between 2010 and 2016 in million Euros. The originator Voltaren® (prescription and non-prescription) is compared with the remaining market of all other topical non-prescription diclofenac analgesics.

Product	2010	2011	2012	2013	2014	2015	2016
Voltaren® Schmerzgel (non-prescription)	64,5	68,5	67,9	82,4	88,1	98,9	108,5
Diclofenac generics combined (non-prescription)	8,2	8,1	7,4	12,6	13,0	15,4	16,6
Voltaren® Emulgel® (prescription-only)	7,2	6,7	5,6	5,1	1,4	1,4	1,4

Source: IMS Health® DPM (not publicly available).

Appendix 3: List of pharmaceutical products with the highest revenue worldwide in 2016 in billion US$.

Originator	**Name**	**Worldwide Revenue 2016 in million US$**
AbbVie	Humira	15901
Celgene	Revlimid	14197
Bristol-Myers Squibb	Opdivo	9912
Merck	Keytruda	9609
Bristol-Myers Squibb / Pfizer	Eliquis	8486
Bayer	Xarelto	8131
Janssen-Cilag	Imbruvica	7499
Bayer	Eylea	7171
Pfizer	Ibrance	7074
Merck	Januvia/Janumet	5989

Source: IMS Health®, 2016, cited after Statista GmbH, 2017, *Top 50 Arzneimittel weltweit nach Umsatz im Jahr 2016 und Prognose für das Jahr 2022 (in Millionen US-Dollar)*, available at https://de.statista.com/statistik/daten/studie/312865/umfrage/arzneimittel-top-praeparate-weltweit-nach-umsatz/, last accessed on 8 August 2017.

Appendix 4: Turnover and unit sales by legal status in Germany in 2016.

Legal Status	**Turnover in million €**	**Unit sales in million packaging units**
Narcotics	812	8.55
Common prescription	44264	732
Pharmacy-only	6782	693
Free sale (pharmacy)	389	48
Free sale (non-pharmacy)	200	62

Source: IMS Health® OTC report, cited after BAH, 2017, *Der Arzneimittelmarkt in Deutschland 2016: Zahlen und Fakten*, available at https://www.bah-bonn.de/bah/?type=565&file=redakteur_filesystem%2Fpublic %2FBAH_Zahlenbroschuere_2016_web.pdf, last accessed on 8 August 2017. Data for narcotics is from IMS Health® DPM (not publicly available). Prices are retail prices (AVP /EVP).

Appendix 5: Turnover of emergency contraception in Germany 2014-2015 in € 1000.

Month	Levonorgestrel 1.5mg	EllaOne®
JAN/14	110,5	395,6
FEB/14	109,0	363,1
MAR/14	113,1	477,5
APR/14	113,1	443,4
MAY/14	108,9	376,9
JUN/14	109,2	384,2
JUL/14	105,0	381,4
AUG/14	102,8	371,4
SEP/14	100,2	388,8
OCT/14	101,3	389,4
NOV/14	89,3	360,2
DEC/14	118,4	483,2
JAN/15	92,2	437,9
FEB/15	90,5	421,4
MAR/15	66,2	2.159,0
APR/15	275,8	739,7
MAY/15	232,4	589,2
JUN/15	204,8	481,5
JUL/15	246,1	504,5
AUG/15	218,5	520,8
SEP/15	207,3	790,6
OCT/15	244,1	943,4
NOV/15	190,3	855,0
DEC/15	206,2	568,8

Source: IMS Health® DPM (not publicly available).

Eidesstattliche Erklärung

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

Bad Nauheim, den 14.08.2017
Datum, Ort Unterschrift