

**Rx-to-OTC switch and the provision of
data exclusivity in Europe - specification and
elaboration of eligibility criteria based on a
status quo analysis**

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“Curiosity is the essence of the scientific mind.”
(Watterson 1993)

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Abbreviations

Abbreviation	Explanation
ADR	adverse drug reaction
AE	adverse event
AESGP	Association of the European Self-Medication Industry
AMA	American Medical Association
AMG	Arzneimittelgesetz (German Medicines Law)
ASHP	American Society of Health System Pharmacists
ATE	average treatment effect
AUS	actual use study
AUT	actual use trial
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMI	body mass index
BPH	benign prostate hyperplasia
BTC	behind-the-counter
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHD	coronary heart disease
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CHPA	Consumer Healthcare Products Association
CP	centralized procedure
CRF	case report form
CTD	Common Technical Document
CUSTOM	Consumer Use Study of Over-The-Counter Lovastatin
CYP P450	cytochrome P450
DAE	Deutsche Arbeitsgemeinschaft Epidemiologie
DCP	decentralized procedure
DE	data exclusivity
DGEpi	Deutsche Gesellschaft für Epidemiologie
EBM	evidence-based medicine
EC	European Community
EEA	European Economic Area
EEC	European Economic Community
EHC	emergency hormonal contraception
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FD&C	Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration

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Abbreviation	Explanation
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GERD	gastroesophageal reflux disease
GMDS	Deutsche Gesellschaft für Medizinische Informatik Biometrie und Epidemiologie e.V.
GMP	Good Manufacturing Practice
GP	general practitioner
GSL	general sales list
H ₂	histamine 2
HCP	healthcare professional
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HMO	health maintenance organization
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEA	International Epidemiology Association
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
ISPE	International Society for Pharmacoepidemiology
LCS	label comprehension study
LDL	low density lipoprotein
LUTS	lower urinary tract symptoms
MAH	marketing authorization holder
MCA	Medicines Control Agency
MCO	managed care organization
MD	Medical Doctor
MHRA	Medicines and Healthcare products Regulatory Agency
MISG	Ministerial Industry Strategy Group
MOTC-SMS	Mevacor Over-the-Counter Self-Management System
MRP	mutual recognition procedure
N/A	not applicable
NAFTA	North Atlantic Free Trade Agreement
NCE	new chemical entity
NDA	new drug application
NDAC	Nonprescription Drugs Advisory Committee
NRT	nicotine replacement therapy
NSAID	non-steroidal inflammatory drug
NTA	Notice to Applicants
OCLC	Online Computer Library Center
OECD	Organization for Economic Co-operation and Development

Continued on next page

Abbreviation	Explanation
OTC	over-the-counter
P	pharmacy-only medicine
PAES	post-authorization efficacy study
PASS	post-authorization safety study
PEI	Paul-Ehrlich-Institut
PGD	patient group direction
Pharm. Eur.	European Pharmacopoeia
PIL	patient information leaflet
POM	prescription-only medicine
PPI	proton pump inhibitor
PR	public relations
PSUR	Periodic Safety Update Report
QALYs	quality adjusted life years
QoL	quality of life
RCT	randomized controlled trial
Ref.	reference
RMP	risk management plan
RMS	risk management system
Rx	only available on prescription (Lat. “Recipe”)
sNDA	supplemental new drug application
SPC	Summary of Product Characteristics
SSS	self-selection study
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUTVA	Stable Unit Treatment Value Assumption
t.i.d.	ter in die (Lat. “three times a day”)
TRIPS	Trade related Aspects of Intellectual Property Rights
TV	television
U.S.C.	United States Code (Code of Laws of the United States of America)
UK	United Kingdom
US	United States
VfA	Verband forschender Arzneimittelhersteller
WHO	World Health Organization
WMA	World Medical Association
WSMI	World Self-Medication Industry
WTO	World Trade Organization

Zusammenfassung

Insbesondere seit den 80er Jahren des letzten Jahrhunderts finden Entlassungen von Arzneimitteln und/oder der zugehörigen Indikation aus der Verschreibungspflicht (Rx) in den Bereich Selbstmedikation (OTC), so genannte „Rx-to-OTC Switches“, nicht nur in den USA, sondern zunehmend auch in Europa Verbreitung. Patienten profitieren dabei von einem direkteren und schnelleren Zugang zu einem breiteren Arzneimittelspektrum, dem andererseits die Risiken einer fehlenden ärztlichen Kontrollinstanz gegenüberstehen. Nichtsdestotrotz hat sich heute, ausgehend von der anfänglichen Entlassung von Medikamenten zur Behandlung akuter, leichter und selbstlimitierender Krankheitsbilder, eine Tendenz hin zur Entlassung zunehmend komplexerer Arzneimitteltherapien zur Behandlung und Prävention (semi-)chronischer Erkrankungen etabliert. Der Wert dieser Entwicklung für das Gesundheitswesen ergibt sich dabei nicht nur aus dem wachsenden Bewusstsein der Bevölkerung für Krankheitsrisiken und –folgen sowie entsprechende eigenverantwortlicher Therapiemaßnahmen, sondern auch aus einer damit verbundenen langfristigen Entlastung der Gesundheitssysteme. Wachsende Anforderungen an Arzneimittelinformation sowie eigenständiges Therapiemanagement und vor allem Therapiesicherheit als notwendige Begleitelemente gehen damit zwangsläufig einher. Innovative Entwicklungen im Bereich Selbstmedikation durch den Rx-to-OTC Switch geeigneter Therapieoptionen zeichnen sich demnach zwar durchaus ab, sind jedoch grundsätzlich von Komplexität und hoher Ressourcenbindung geprägt, was eine angemessene Unterstützung durch das gesetzliche und regulatorische Umfeld erforderlich macht. Der europäische Gesetzgeber hat daher mit Einführung von Artikel 74a, Richtlinie 2004/27/EC, die Möglichkeit der Vergabe einer einjährigen Exklusivitätsperiode etabliert, sofern der Switch auf Basis „signifikanter“ präklinischer oder klinischer Daten beschieden wurde. Das Instrument „Datenexklusivität“ gehört zu den geistigen Eigentumsrechten und untersagt in diesem Fall den Arzneimittel-Zulassungsbehörden, sich im Rahmen der Prüfung generischer Zulassungsanträge auf originäre Switchdaten zu beziehen, was die Bearbeitung und gegebenenfalls Zulassung letzterer faktisch erst nach Ablauf eines Jahres möglich macht.

Zielstellung: Ziel der vorliegenden Arbeit war es, die folgenden Hypothesen bezüglich der Möglichkeit der Vergabe von Datenexklusivität für Rx-to-OTC Switches in Europa zu überprüfen bzw. zu substantiieren:

Hypothese 1: Anhand der angegebenen Kriterien und Datenkategorien ist es unter den aktuellen gesetzlichen Rahmenbedingungen in Europa praktisch nicht möglich, Datenexklusivität für Rx-to-OTC Switches zu erhalten.

Hypothese 2: Vorhandene Kriterien und Datenkategorien müssen präzisiert und neue definiert werden, um die Vergabe und den Erhalt von Datenexklusivität bei Rx-to-OTC Switchen möglich zu machen.

Methodik: Eine umfangreiche Literaturrecherche zu den Themen „Rx-to-OTC Switch“ und „Datenexklusivität“ bildete die Grundlage der Status-quo-Analyse und der Hypothesengenerierung. Der Hypothesenüberprüfung diente eine retrospektive Analyse des Rx-to-OTC Switches von Clotrimazol zur Behandlung von Vaginalmykosen

(am Beispiel des Originatorpräparates Canesten® GYN von Bayer) unter den gegenwärtigen Prämissen zur Vergabe von Datenexklusivität. Darüber hinaus wurden ausgewählte nationale und internationale Experten mithilfe eines qualitativen Fragebogens zur Einschätzung der aktuellen gesetzlichen Rahmenbedingungen und zu Vorschlägen bezüglich deren Präzisierung bzw. Novellierung unter den Aspekten OTC-Relevanz, Qualität und Machbarkeit interviewt. Auf Basis einer weiteren Literaturrecherche wurde der Einsatz sogenannter „Propensity Scores“ bei der statistischen Auswertung von Beobachtungsstudien zur Erhöhung der Datenvalidität als mögliches Qualitätskriterium für eine Exklusivitätsvergabe diskutiert. Eignung und Praktikabilität dieses Ansatzes wurden nachfolgend anhand eines existenten Datensatzes überprüft.

Ergebnisse: Beide Hypothesen konnten durch die Forschungsergebnisse bestätigt werden. Die retrospektive Analyse des Clotrimazol-Switches zeigt, dass sich für einen im Lebenszyklus weit fortgeschrittenen Switch-Kandidaten in Anbetracht umfangreicher präklinischer und klinischer Daten vor und für die Rx-Zulassung kaum eine Möglichkeit für die Generierung neuer potentiell „signifikanter“ Daten bietet. Vor allem die Sinnhaftigkeit präklinischer Daten wurde in diesem Zusammenhang von einem Großteil der Experten hinterfragt. Die „Signifikanz“ neuer Daten wurde vielmehr im Sinne einer Relevanz für die mit der Statusänderung angestrebte Selbstmedikation gesehen. Vor diesem Hintergrund sind die aktuell in den Gesetzestexten verwendeten Terminologien und Datenkategorien nicht nur unspezifisch, sondern auch praktisch kaum anwendbar, sofern in rein konservativem Sinne interpretiert. In der zugehörigen Switchguideline aufgeführte Kriterien sind ebenso wenig ausreichend konkret. Für eine erfolgreiche Vergabe von Datenexklusivität im Rahmen zukünftiger Rx-to-OTC Switches ist folglich eine Präzisierung vorhandener bzw. die Definition neuer Kriterien und Datenkategorien unter Berücksichtigung der Besonderheiten der Selbstmedikation nötig. Dies wurde von den Befragten auch mit Blick auf die steigenden Anforderungen im Rahmen der Entlassung zunehmend komplexerer Therapieoptionen im Grundsatz mehrheitlich befürwortet.

Von besonderer Bedeutung ist dabei in erster Linie eine Erweiterung der Definition klinischer Daten über die klassischen Phase I-III bzw. IV Daten hinaus. In Anbetracht der fehlenden ärztlichen Überwachung im angestrebten Status der Selbstmedikation sollte diese explizit auch Daten zu Selbstdiagnose, Patientenverhalten und Arzneimittelutilisation aus nicht-interventionellen Beobachtungsstudien (NIS) einbeziehen, um Wirksamkeit und Sicherheit auch unter OTC-Bedingungen antizipieren zu können. Unter Einhaltung wissenschaftlich anerkannter Qualitätsstandards liefern letztere wichtige Erkenntnisse bezüglich Therapiepraxis, -erfolg und -sicherheit unter Alltagsbedingungen. Durch den nicht-experimentellen Studiencharakter kann es jedoch unter Umständen zu Verzerrungen der Studienergebnisse kommen. Mithilfe bestimmter statistischer Verfahren wie der sogenannten Propensity-Score-Analyse können diese minimiert und damit die Validität der Ergebnisse erhöht werden. Als wesentliches Qualitätskriterium für NIS Daten sollte diesem Ansatz daher bei deren Bewertung für die Vergabe von Datenexklusivität Rechnung getragen werden.

Im Bereich „Prälinik“ lassen sich dagegen nur wenige Szenarien wie z.B. die Ermittlung von Interaktionspotentialen als potentiell OTC- und damit exklusivitätsrelevant definieren.

Die Re-analyse bereits existenter präklinischer und klinischer Studienergebnisse unter OTC-Aspekten wird als exklusivitätsunterstützend, jedoch nicht ausreichend erachtet. Durch die Aufnahme einer zusätzlichen „nicht-klinischen“ Datenkategorie in den relevanten Gesetzestext sollten darüber hinaus auch Erkenntnissen aus epidemiologischen oder Marktforschungsuntersuchungen sowie Umfrage-Ergebnissen entsprechende Berücksichtigung finden. Nicht selten liefern diese für eine Switchentscheidung essentielle Informationen zu Compliance, Patientenzufriedenheit, Lebensqualität etc. Konzepte zur Risikominimierung im Falle der Entlassung komplexerer Therapieoptionen inklusive umfangreicher Informations- und Edukationsprogramme für Patienten wie Fachpersonal, Abgabemodelle oder auch Therapiemanagement/-monitoring Instrumente für Patienten würden ebenfalls hierunter fallen, sofern nicht in die klinische Datengenerierung z.B. im Rahmen einer NIS eingebunden.

Schlussfolgerung: Um ihre Funktion hinsichtlich der Initiative innovativer, komplexer Rx-to-OTC Switches zukünftig faktisch erfüllen zu können, müssen die gegenwärtigen gesetzlichen Rahmenbedingungen für die Vergabe von Datenexklusivität spezifiziert bzw. modifiziert werden. In der vorliegenden Arbeit wurden Vorschläge für Kriterien und Datenkategorien für die Qualifikation von Daten für die Vergabe von Datenexklusivität bei Rx-to-OTC Switches erarbeitet. Unter dem Aspekt der damit verbundenen Anforderungen und Anstrengungen auf Seiten des pharmazeutischen Unternehmers, vor allem aber mit Blick auf die für eine erfolgreiche Einführung und Etablierung eines Switches nötige Transparenz und Konsistenz hinsichtlich essentieller Begleitmaßnahmen wie z.B. Information und Edukation, wird zudem eine Verlängerung der derzeitigen einjährigen Exklusivitätsperiode empfohlen.

In jedem Fall ist es vor dem Hintergrund der in dieser Arbeit diskutierten Thematik wünschenswert, im Rahmen von oftmals unterschiedlichen Interessen oder Meinungen unterliegenden Rx-to-OTC Switchentscheidungen eine fundierte wissenschaftliche Bewertung als zentralen Bestandteil eines solchen Prozesses zu etablieren, die der angestrebten Statusänderung angemessen und entsprechend transparent ist.

1 Introduction

1.1 Background

Patients' increasing empowerment in managing their own health and their demand for wider and convenient access to self-medication with over-the-counter (OTC) drugs based on enhanced knowledge about their disease status are major factors that have contributed to a constantly growing OTC-business worldwide. Moreover, the increasing economic burden of national health care systems has to be accounted for. In consequence, a rising number of Rx-to-OTC switches is currently seen both in the United States (US) and in the European Union (EU), with the United Kingdom (UK) as the cutting-edge, as well as in Asian Pacific countries which are increasingly following suit. Having started in the 2nd half of the 20th century, the Rx-to-OTC movement now seems to have reached a new "era": there is a trend in self-medication from treating acute, easily recognizable, and self-limiting conditions in the past towards the prevention or treatment of (semi-)chronic risk factors and conditions today. This evolution is obviously associated with major challenges, such as a clear definition of a successful disease management process, of conditions concerned, and the active role of the stakeholders involved. In this respect the temporal and costly investment usually undertaken by the pharmaceutical company initiating and enforcing the switch of a certain drug substance or product points out the importance of the provision of adequate incentives to envisage accordant Rx-to-OTC switches eventually resulting in benefits not only for patients, but for national health care system and its various actors as well. In its Directive 2001/83/EC, as amended by Directive 2004/27/EC, the European Commission, therefore, implemented Article 74a which addresses the possibility of the provision of one year of data exclusivity in case of eligibility of the data submitted with the respective Rx-to-OTC switch application.

1.2 Aim

The European Directive 2001/83/EC, as amended by Directive 2004/27/EC, provides the legal framework for the reward of data exclusivity as one form of incentive to be granted to pharmaceutical companies as part of the Rx-to-OTC switch of a certain drug substance or medicinal product. The wording of the respective Article 74a, however, is rather unspecific and lacks precise information about what data in particular is required to be eligible for data exclusivity. To date, the only attempt to interpret this legislation is given in the "Guideline on changing the classification for the supply of a medicinal product for human use" (European Commission 2006a). Yet, as this kind of guideline is also relatively unspecific in this regard, there is an obvious need for a more definite expression of criteria and data

categories justifying eligibility for data exclusivity against the background of the transfer of drugs with a long record of safety and efficacy from a highly regulated and monitored Rx status to an OTC status which is much more dependent on reliable self-control and self-guidance. Importantly, the setup of such criteria and requirements should be based on a common understanding of relevant preconditions for treatment with the respective medicinal products in a self-medication environment by all stakeholders involved in the Rx-to-OTC switch process and be adapted to its future development.

The present work therefore discusses and sets up an outline of definite, eventually revised and additional criteria as well as data categories justifying data exclusivity for Rx-to-OTC switch products with respect to their usage under the particular circumstances of self-medication. Based on these considerations, the existing one-year period of data exclusivity provided by the EU legislation will be equally reconsidered with the objective of – if applicable - proposals for optimization.

Finally, identified items and requirements could provide the basis to eventually derive a business model which could then at best be used for guidance regarding the fulfillment of relevant criteria (e.g., in terms of strategy, timing, etc.).

1.3 Methodology

The preparation of the present doctoral thesis was based on several different strategic approaches and methods including desktop research, case study analyses, and qualitative expert interviews.

Secondary research in terms of a comprehensive and systematic review of relevant literature with respect to the topics “Rx-to-OTC switch”, “data exclusivity”, and “propensity score” (for databases used see Section A.1 in the appendix) as well as the identification, analysis and discussion of relevant up-to-date case studies publicly accessible via internet initially contributed to the formulation of the two main research hypotheses (see Section 4.6 and Subsection 4.6.2).

A case-study analysis based on published and unpublished proprietary data relating to the original Rx registration of Bayer’s Canesten® GYN and its subsequent Rx-to-OTC switch was used for the purpose of practical exemplification of research results. Data was identified, retrieved (e.g., dossiers, study reports, publications, etc.), screened, and analyzed from the retrospective (see Chapter 5).

In addition, a written questionnaire composed of 24 questions related to the issue of data exclusivity within the context of the legal framework was developed as primary research instrument in order to discuss the assumed hypotheses. Both multiple choice and open format questions were used for evaluation. The questionnaire was designed in German language and later on translated into English, in order to be able to collect data from international experts alike (see Section A.2 in the appendix). Experts selected account for the main stakeholder groups involved in Rx-to-OTC switches: pharmacists, physicians, industry, regulatory/political authorities, third party payers (health insurance companies), and patients/consumers. Subsequent analysis of questionnaire data was based on descriptive statistics. A detailed description of the qualitative survey results is given in Chapter 6.

Within the context of literature review, so-called “propensity score methodology” was identified and discussed as a possible statistical tool aiming at the reduction of bias effects and thus increasing the validity of observational study results. Furthermore, in order to demonstrate practical applicability underlying its potential role in the issue of data eligibility for the grant of exclusivity, propensity score technique was applied to the analysis of existent, non-interventional, (i.e., observational) study data (see Subsection 7.2.3).

2 The Rx-to-OTC switch movement: background, implications and trends

"The transfer of drugs from prescription to OTC status is a logical and systematic development of today's healthcare environment" (Gossel 1991).

2.1 Evolution of self-care with OTC medications

Today, self-medication with OTC drugs is often called "OTCness" meaning "the widespread availability of safe and effective nonprescription medicines for responsible consumer self-care, in accordance with the applicable laws, regulations and voluntary industry codes affecting manufacturing, packaging, and labeling of quality products and the advertising of those products in all media" (Soller 1998). Self-medication with OTC drugs is nowadays of great importance for the management of a wide range of common diseases. According to the American Pharmaceutical Association, the treatment of 60 - 90 % of illnesses is initiated by some form of self-care (Marwick 1997), making up around 60 % of the whole medical care in the US, yet at the same time accounting for less than 2 % of US healthcare spending (Gossel 1991; Marwick 1997). "This makes it likely that, as a low-cost alternative, OTC drug use will continue to grow" (Marwick 1997).

In fact, self-medication with drugs existed long before any regulation by legislation came up and users without prescription simply purchased any drugs needed (Gossel 1991). The definition of "OTC" in the modern sense has evolved slowly over the past years with the OTC Review process in the US at the core of scientifically based regulatory legislation describing safety, effectiveness (Hodgson et al. 2007)¹ and labeling as the most essential quality criteria of OTC medication in the sense of a benefit-risk evaluation (Soller 2002). Accordingly, an OTC drug, if used correctly, should be associated with a low incidence of serious side effects or adverse events (AEs) as well as a low potential of harm in case of abuse, under conditions of widespread availability. In terms of effectiveness, the pharmacological effect should result in clinically significant relief of symptoms as claimed. Labeling should be clear and correct, providing adequate directions for use and warnings likely to be understood by the ordinary individual (Soller 1998).

The US OTC Review process started in 1972 and is still ongoing. It is based on the Durham-Humphrey Amendment from 1951 and amends the Federal Food, Drug, and Cosmetic Act (FD&C) which was passed in 1938. The FD&C required manufacturers, for the first time, to

¹ In general linguistic usage "effectiveness" refers to a treatment effect which is observed under "real-world" conditions of regular practice. It has to be differentiated from "efficacy" which in contrast relates to a treatment effect that is demonstrated under strictly defined conditions within clinical randomized controlled trials (Black 1996; D'Agostino 2007; Hlatky et al. 1984; Hodgson et al. 2007).

establish drug safety and allocate adequate drug labels directed towards healthcare professionals (HCPs) (Palumbo 1991) and is thus to be considered as the starting point of modern OTC history (Juhl 1998). The Durham-Humphrey Amendment was to overcome deficiencies of the FD&C and provides the statutory base for the categorization of drugs in two specific classes, namely, prescription and self-medication (Gossel 1991). It assumes OTC as the default status for drugs unless they cannot be used and marketed safely without medical supervision and thus should be available prescription only. Specifically, this refers to drugs with habit forming properties, an inherent unfavorable safety profile, or an approval as the result of a new drug application for use under professional supervision (Soller 2002). As consequence of the thalidomide tragedy (q.v. Section 5.1), the adoption of the Kefauver-Harris Drug Amendments in 1962 marks the “pivotal event that triggered the current drug reclassification process” (Gossel 1991; Rosenau 1994). Its overriding aim was to tighten control - manufacturers now had to prove not only safety, but also effectiveness, for the product’s intended use (WSMI 2009).

Likewise, a respective philosophy underlies the classification rules of the European Community. All medicines should be available without prescription unless they meet one of the criteria included in Article 71 of the European Community Code (i.e., Article 71 of Directive 2001/83/EC) rendering their supply necessary to medical prescription (Stitching AESGP Foundation 2002).

“Medicinal products shall be subjected to medical prescription where they

1. are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or
2. are frequently and to a very wide extent used incorrectly, and as a result are likely to present a danger to human health, or
3. contain substances or preparations thereof the activity and/or side effects of which require further investigation, or are normally prescribed by a doctor to be administered parenterally.”

The statutory premise that drugs are prescription by exception (Soller 2002) is hence at the core of both EU and US legislative approaches.

2.1.1 The Rx-to-OTC switch movement

The early reclassification movement dates back to the 1950s when paracetamol was switched from prescription to nonprescription status, resulting in a long record of safety with respect to usage in self-medication today (WSMI 2009). The modern era of switch was set off in 1984 with the switch of ibuprofen in the US, challenging aspirin as the hitherto predominant non-steroidal anti-inflammatory drug (NSAID) available OTC. This was succeeded by a number of reclassifications of substances or drugs suited for the treatment of easily recognizable, self-limiting and self-manageable acute conditions traditionally being part of the self-medication arena. In the following, the upcoming global “megatrend” of a heightened health, wellness and beauty consciousness is commonly seen as catalyst (CHPA 2000; Stitching AESGP

Foundation 2002). At the same time, benefits associated with the upcoming reclassification movement, such as the empowerment of the individual with wider and convenient access to novel self-care therapeutics, the possibility of the pharmaceutical industry to enhance profitability, and - what is of major importance - substantial cost savings to healthcare systems, fostered the further development of the Rx-to-OTC switch process (Soller 1998). As a result of growing confidence of the public and opinion leaders in health and health management, medicines already available OTC for distinct conditions (e.g., hydrocortisone for contact dermatitis) were proposed for deregulation, further indications (such as eczema), and longer term use (Bond 2008). On the other hand, more effective therapeutic options established in prescription setting were suggested to be released to nonprescription status for the treatment of traditional, well-established OTC indications (e.g., H₂-blockers or PPIs for the treatment of heartburn). Today, these two “streams” of switch movement have consequently resulted in the switch of both former Rx drugs as well as indications which tend to be more and more complex and (semi-)chronic in nature (Stitching AESGP Foundation 2002; WSMI 2009) (cf. also Figure 1 and Section 2.4).

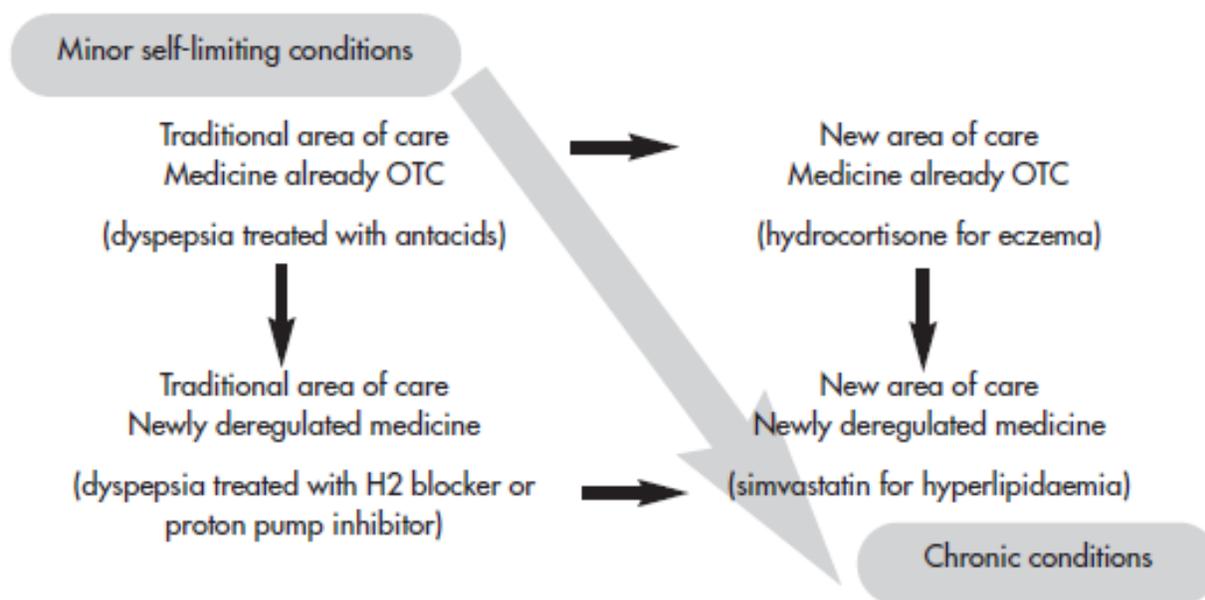


Figure 1: Development of the Rx-to-OTC movement: widening of the traditional self-medication arena from minor, self-limiting conditions towards the prevention and self-management of chronic conditions by increasing the number of Rx-to-OTC switches of both drugs and indications (from Bond 2008)

In Europe the scope of conditions deemed suitable for self-treatment without medical direction, including “mild to moderate pain”, “cough and cold”, “constipation”, and minor skin problems, was quite limited until 1980. However, similar to the US, cultural and political changes based on patients’ shift in their attitude towards health management resulted in

a growing desire to take responsibility for their own health since then seem to have brought about a “new OTC paradigm” (Shiffman 2008).

Of note, according to Rosenau who dealt with the evolution of self-care as a whole, “the switch movement has resulted in a substantial, but as yet unrecognized, modification of the implicit definition of prescription drugs. The Rx designation no longer signifies that a drug is inherently unsafe, potentially toxic, or harmful except when used under [medical] supervision [...]. Increasingly, it indicates a preliminary trial status, necessary until experience accumulates and an estimate of benefit-to-risk can be established, at which point the drug can be switched OTC” (Rosenau 1994). Moreover, the continued efforts to identify the informational needs of the general public and HCPs alike, as well as to detect and examine potential new areas for self-treatment to expand the range of self-manageable conditions clearly account for the globally growing importance of the Rx-to-OTC switch movement today.

2.1.2 Definition of “Rx-to-OTC switch”

As can be deduced from the aforementioned, the term “Rx-to-OTC switch” relates to the process of transferring proven prescription drugs (Rx) to nonprescription, so-called over-the-counter (OTC) status. Mahecha describes the US Food and Drug Administration’s (FDA) definition of an Rx-to-OTC switch as “over-the-counter (OTC) marketing of a drug product that was once a prescription (Rx) drug for the same indication, with the same strength, dose, duration of use, dosage form, population, and route of administration” (Mahecha 2006). In most cases, however, due to the absence of control by a physician, the OTC indication, population, as well as duration of use, etc. are of a narrower and more restrictive scope as compared to Rx.

2.2 The rationale for Rx-to-OTC switches

In light of the complex nature of the prescription to nonprescription reclassification process and the fact that there are many stakeholders involved, there is certainly no single “one-size-fits-all” rationale for Rx-to-OTC switches. The driving forces behind switches are rather diverse and multifactorial as well as depending on potential benefits implied by a specific switch for the various advocacy groups affected.

Outside the pharmaceutical industry sector the most important intrinsic driving force behind the Rx-to-OTC switch movement is probably embedded in the ever prevailing need for the implementation of cost-containment measures and the wish to transfer drug distribution costs from the government to the individual consumer (Bond 2008). Multiple economic analyses of Rx-to-OTC switches demonstrated overall cost savings to the health care system by shifting parts of these costs “from the public purse to the private” (Aronson 2009; Soller 1998; Sullivan 2005). The economic impact on different players in this system, however, has been discussed controversially.

The trend towards deregulation of prescription medications through switch to nonprescription status has also been supported by a fair part of the pharmacy profession. Thus providing

the possibility for these professionals to prove their skills based on a larger range of effective treatments for patients as well as - depending on the individual situation - providing further economic opportunities (Bond 2008; Gossel 1991).

Historically, the predominant party initiating the switch of a certain ingredient or drug product from Rx to OTC classification has been placed in the ranks of the pharmaceutical industry. In her analysis of the characteristics of Rx-to-OTC switch processes Mahecha argues that the motivation of a pharmaceutical manufacturer is mainly based on strategic reasons regarding drug product sales in the context of life-cycle-management (cf. Figure 2), the defense of generic competition after Rx patent expiration or the enlargement and growth of an OTC drug portfolio in response to consumer needs and demands for innovative self-medication products (Gossel 1991; Mahecha 2006; Pawaskar 2007). In doing so, “fostering self-reliance and enhancing consumer choice without compromising the consumer’s safety and economic well-being [should] stand as the guiding values for the switch evaluation process” (Stitching AESGP Foundation 2002).

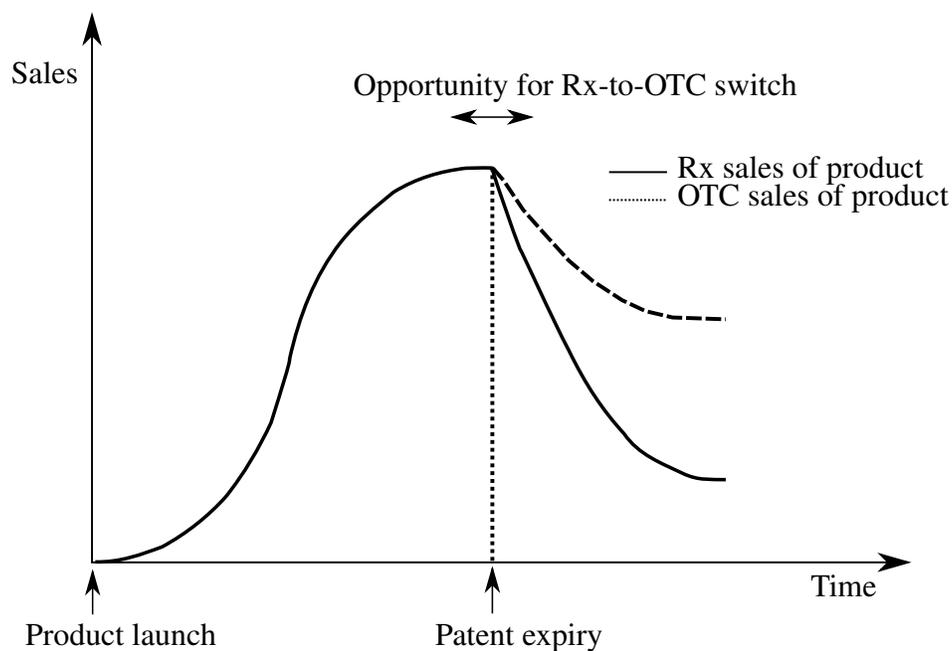


Figure 2: Life-cycle of a pharmaceutical product with and without reclassification from prescription to nonprescription (i.e., OTC) status (based on Bradley 1998)

Furthermore, Palumbo mentions the interesting fact that in countries with an accordant institutionalized health system, the option to reclassify drug products enables them to “virtually eliminate the specter of third party payer constraints” making certain restrictions disappear (Palumbo 1991), such as, for example, national price regulations, as well as rebate

contract, and/or reimbursement issues (if applicable) (Enns et al. 2011).

Based on the preceding arguments it is, thus, not astonishing that almost all of the top-selling OTC drugs once have been switched from prescription status (Burstein 1994; Soller 1998). In fact, in the US, for example, Rx-to-OTC switch products account for about 50 % of all OTC sales with some of them building up a completely new self-medication category previously not available to consumers (e.g., smoking cessation aids or treatments for hair re-growth) (Mahecha 2006). Likewise, in Europe eight of the top twenty brands are by now the result of product switches (Tisman 2010).

2.3 Implications of the Rx-to-OTC switch movement

The reclassification of a drug and/or its corresponding indication is associated with a multitude of benefits, but also risks affecting not only the general public as the major user of the switched products, but also other institutions involved, such as HCPs like pharmacists and doctors, health insurance companies, managed care organizations (MCOs), and last but not least the government represented by its accordant authorities.

The impact of the Rx-to-OTC switch movement on the various advocacy groups involved has been studied in a multiplicity of analyses. Deep insight into the way and extent to how different stakeholders are impacted by individual Rx-to-OTC switches is of major importance for the understanding of practical implications and potential resistance to certain reclassification proposals. However, as such an evaluation is not at the focus of the present work, the following chapters give a rather short overview of the benefits and risks generally associated with the Rx-to-OTC switch movement and briefly discuss its overall social, political and economic consequences without providing an in-depth analysis.

2.3.1 General benefits and risks

Above all, the evolution of the Rx-to-OTC switch movement has provided hundreds of millions of consumers all over the world with a wider and more convenient access to a steadily increasing range of appropriate treatment options in self-medication. The importance of this empowerment of individuals in managing their own health with new switch-derived self-care choices (Soller 1998; Soller 1999) will increase even more with the necessity of the prevention of an emerging “global epidemic of chronic non-communicable diseases” (WSMI 2009).

Furthermore, the OTC availability of a wide range of treatment options offers consumers the opportunity to save costs and time by allowing them to directly self-treat common and troublesome conditions with easily recognizable symptoms without having to wait for a doctor’s advice (AESGP 2004; CHPA 2000; Stitching AESGP Foundation 2002). A reduced time interval from onset of symptoms to treatment is particularly crucial for time-critical products like, for example, emergency hormonal contraception (EHC) which is most effective when taken without much delay (WSMI 2009).

Moreover, as mentioned before, overall benefits actually not only accrue to the individual, but to the society as a whole by considerably decreasing overall expenses of social security and national healthcare costs thus allowing better allocation of limited healthcare resources

and physician's time to relevant matters beyond the scope of self-care (AESGP 2004; CHPA 2000; Stitching AESGP Foundation 2002).

Finally, as it is stated in the World Health's Organization's (WHO) principal guidelines on nonprescription medicines, a wider availability of nonprescription medicines is considered an effective tool for the reduction of the widespread major problem of self-medication with prescription drugs (WHO 2000).

Apart from the benefits described above, a comprehensive analysis and evaluation of the Rx-to-OTC switch movement should also contain a critical examination of potential risks and disadvantages associated with the reclassification of drugs. Importantly, the usage of OTC drugs heavily depends and relies on consumers' ability to appropriately self-diagnose and self-treat (Pawaskar 2007; Stitching AESGP Foundation 2002). In general, greater accessibility to self-medication lacking medical supervision harbors dangers and risks of incorrect use, a delay of diagnosis, and/or masking underlying serious conditions and thus the potential for causing individual harm (Brass 2001; Ferner 2008; Pawaskar 2007). Appropriate strategies for tackling these potential risks should continuously be developed (Ferner 2008). This is of major importance especially in light of emerging evidence that the public no longer assigns the same amount of respect to the potency of an OTC drug as compared to an Rx drug (see also Subsection 3.5.3). In the UK, for example, potential risks or dangers of nonprescription medicines seem to be disregarded by consumers in favor of their benefits due to the "widely held belief that regulatory authorities would not allow 'dangerous' medicines to be available from the community pharmacy" (Gilbert et al. 2006). Consequently, there are legal provisions and means in place enabling an Rx-to-OTC switch decision to be eventually reversed (see Subsection 3.5.2).

Moreover, in terms of costs, contrary to what is mentioned above, some critics refer to studies showing that the costs of switches might outweigh the benefits – citing consumers' out-of-pocket costs for OTC drugs and costs which could derive from inappropriate use of self-medication (Pawaskar 2007). A detailed analysis of the economic impact of Rx-to-OTC switches is yet always to be put into perspective in terms of overall healthcare costs. This is not within the scope of the present thesis, but has repeatedly been addressed elsewhere (see for example Carlsten 1996; Cohen 2005a; Keeler 2002; Russell 1988; Ryan 1990).

2.3.2 Impact on different stakeholders

The impact of the Rx-to-OTC switch movement on various stakeholders affected in terms of assumed benefits and potential negative effects is briefly described below and summarized in Figure 3.

Regulatory Authorities In terms of switching from prescription to nonprescription status, the main challenge of regulatory authorities is, without doubt, to strike a balance between the benefits of an enlarged choice of medications for self-treatment and a potential harm to public health on account of unsupervised or inappropriate use (Ferner 2008; WSMI 2009). Risk aversion and public health guarantee are of utmost priority. Given the increasing number of complex switches, there is an obvious need to create new research tools for the

support of regulatory decision making - a mainly data-driven process - as well as to increase and ensure adequate know-how on the part of authorities in order to provide better ante-approval understanding of the anticipated OTC usage patterns.

Besides the potential gain in scope of action for the science of regulatory decision making, authorities may also benefit from the application of lessons learned on relevant aspects of switch products (e.g., labeling, etc.), in turn leading to a continued development of tools ensuring a consumer-friendly and safe intake of OTC drugs.

Finally, the necessity of multiple stakeholder involvement and close industry co-operation within the reclassification process is likely to contribute to a continual improvement of the drug approval process ideally complying with the industry's desire for maximal consistency and transparency (Soller 1998).

Against this background, it is of interest that contrary to the well-established traditional approach of manufacturers being the driving forces behind switch applications, the US Food and Drug Administration is about to explore its legal authority to initiate switches of drugs it assumes suitable for OTC, thereby relying on foreign data if these drugs are already available OTC outside the US (Cohen 2005a).

Consumers/Patients Overall, consumers/patients seem to be very satisfied with the evolution and nature of the OTC sector. According to a survey conducted for the Consumer Healthcare Products Association (CHPA) in the US in 1992, 92 % are satisfied with the medication they have used for self-care (CHPA 2000; Pawaskar 2007). In addition to improved and timely accessibility and positive convenience aspects mentioned before (see Subsection 2.3.1), a UK survey has identified four factors for patients favoring to buy OTC drugs: preference for OTC purchase, knowledge of OTC availability of products, prescription charge liability status, and no current use of other prescribed medicines (Gilbert et al. 2006). Nevertheless, potential hazards of ab-/misuse or masking of underlying diseases have to be taken into account as drug-associated consumer/patient risks that are largely inherent to the nature of self-medication.

Pharmacists Based on the national distinctions in the availability of nonprescription medicines (see also Section 3.1), the role of pharmacists significantly differs among the various healthcare systems throughout the world. In countries where many OTC drugs are available only from “behind-the-counter” (BTC) (as is the case, for example, in Germany, most of the other European countries, as well as in a few countries outside the EU), pharmacists generally provide assistance by consulting consumers on the proper choice and use of OTC drugs thereby functioning as “pharmacy class comfort-zone” (Hemwall 2010) in terms of medical advocates for self-care practices. On the contrary, this active counseling role seems to take a back seat in countries where the majority of OTC drugs are available from general stores such as the US, for instance. In that case appropriate pack sizes, as well as easy-to-understand drug labeling, among other factors display key elements of consumer and/or patient guidance (Palumbo 1991).

In any event, the continued switch of therapeutic options more and more complex in na-

ture will enhance the necessity of pharmacists in customer education (Palumbo 1991), an idea commonly well appreciated as it enables them to make better use of their professional skills and expand their competence in the field of healthcare (Bond 2008; Ferner 2008). Rx-to-OTC switches offering the opportunity to recommend effective and affordable OTC treatments for a wide range of common diseases may frequently be seen as a “vehicle for achieving recognition and compensation for associated increased responsibilities” (Rosenau 1994). Certainly, the expansion of pharmacists’ field of activity likewise supports an enhanced responsibility in their role as safeguards of public health (Juhl 1998). Appropriate materials such as disease specific protocols or questionnaires for counseling and educational support of patients in managing or preventing complex and chronic conditions might contribute to pharmacists’ future performance (Stitching AESGP Foundation 2002; Wechsler 2000) and are already used and tested in some progressive countries, such as the UK (CHP Canada 2010; Hemwall 2010; MISG 2010).

Interestingly, in his forecast of the prospective task of pharmacists against the background of an advancing Rx-to-OTC switch movement from 1985, Schondelmeyer already viewed the “pharmacists of the future” in a differentiated and more specialized role. Next to their traditional duty of counseling consumers as a primary source of information and advice, Schondelmeyer envisioned pharmacists as key contributors to pharmacovigilance as he considered the outcome of an individual drug therapy scheme rather than drug products being central to patients’ and pharmacists’ focus (Schondelmeyer 1985).

Rx-to-OTC switches, hence, offer pharmacists the chance to demonstrate their ability and the need to assist in the use of cost-effective OTC drug therapy. “Professional pharmacy bodies have played a key role in the deregulation process which [contributes] to the paradigm shift of community pharmacists from a technical, supply oriented role to a more clinical, cognitive [counseling] role” (Bond 2008). Their willingness to more fully utilize their profession in an integrated health care service has been demonstrated and recognized in UK Government policy papers, for example (Bond 2008). Yet, unless pharmacists take advantage of the opportunities provided, there is a certain risk that they will be “left completely out of the loop” (Palumbo 1991).

Physicians In her critical analysis of a switch’s impact on the medical profession, Byrns shed a light on physicians’ point of view from both the public health and individual patient perspectives (Byrns 1998). Physicians generally seem to support OTC drugs as a class, including those switched from Rx status, with a view towards wider availability and access to pharmaceuticals for appropriate self-treatment. The reduced number of patients with minor and trivial complaints will leave more time for the treatment of patients with serious medical conditions (Ferner 2008).

Nonetheless, concerns are raised by physicians especially with regards to potential risks associated with OTC usage in general and with usage by special populations, such as children or the elderly, in particular. Another crucial element omitted with self-medication is the close relationship between patients and their doctors who offer medical guidance and supervision on medications and their intake, which may also be required for OTC drugs.

Tracking of OTC drugs may become increasingly difficult, as these are not tracked by most pharmacy systems and patients often are not asked specifically about the use of such drugs when medical and drug histories are recorded (Brass 2001). Many caveats are addressed by the American Medical Association (AMA) which is, for instance, working on: clear labeling requirements for OTC drugs, disease management, and patient education programs encompassing OTC drug usage, and the need for special provisions of OTC drugs for medically indigent populations. Against this background, there has been discussion about the loss of control perceived by physicians as a result of change to their supervisory role. As patients rely consistently more on OTC products for initial therapy, they will present to physicians, if at all, only late in the course of their illness.

In conclusion, from the physicians' point of view adequate criteria for switch drugs would have to be established in an individualized approach, and based on the collaboration of the pharmaceutical industry, authorities, and HCPs. Pharmacists are considered as important advisors and gatekeepers in the selection of OTC medication in this approach (Byrns 1998).

Industry Overall, the increasing number of Rx-to-OTC switches has a mainly positive impact on the pharmaceutical industry. When an Rx drug product approaches patent expiration manufacturers often use switching as a kind of life-cycle instrument that, in theory, enables them to enlarge their targeted consumer groups and revenue by gaining a foothold in the market ahead of generic competition (Bond 2008; Cohen 2005b; Creyer 2001; Euromonitor International 2010; Harrington and Shepherd 2002; Pray 2008; Stitching AESGP Foundation 2002). Ideally, this in turn allows companies to intensify their research and development activities in specialist fields of medical research (e.g., diabetes, cancer, etc.).

In addition, by providing greater and easier access to their products, pharmaceutical entrepreneurs might strengthen their brand recognition and contribute to an increased awareness of widespread diseases by providing therapeutic and preventive, risk-lowering treatment options suitable for self-medication and self-management (Euromonitor International 2010). However, with more and more drugs being switched to nonprescription status and used without medical supervision, regulations for OTC drugs are about to get much stricter largely owing to safety reasons. In this regard, it is also estimated that the demand for improved safety and efficacy/effectiveness studies justifying a drug's usage in self-medication will augment (Euromonitor International 2010).

Healthcare system: third party payers Third party payers, represented mainly by health insurance companies and MCOs, such as health maintenance organizations (HMOs), benefit from savings on Rx drug reimbursements eventually replaced by mostly uncovered OTC drugs and, hence, from shifting costs to the private purse of patients (Rosenau 1994; Wechsler 2000). Additionally, the switch movement will ultimately reduce the volume of doctor visits due to easy access to a wider range of self-treatment options. This will certainly help cut costs by reducing the amount of reimbursement, at least in a short-term perspective (Pawaskar 2007; Rosenau 1994; Soller 1998). Within this context, the US Rx-to-OTC switch application of the antihistamine products Claritin[®] (active ingredient: loratadine), Allegra[®]

(fexofenadine), and Zyrtec[®] (cetirizine) in 1998, at a time when these were still under patent, was unprecedented and groundbreaking. It was the first switch petitioned and initiated by a 3rd party payer, namely WellPoint Health Systems (health insurer), aiming at a better control and potential reduction of their immense healthcare expenditures (Pawaskar 2007; Spencer 2002; Wechsler 2000). As first member of its class, loratadine has been approved by the FDA and made available OTC in 2002 after patent expiration (Cohen 2005a).

On the other hand, however, it has to be borne in mind, that these short-term cost savings might be offset over the long-term on the occasion of serious safety problems by reason of inappropriate use, severe adverse events or suboptimal therapy (Brass 2001). This might eventually result in an increase in doctor visits or even hospitalization associated with a dramatic rise in healthcare expenditures (Pawaskar 2007; Rosenau 1994). In fact, “payers are struggling to determine the best policy to address issues associated with the switched medications”.

The overall effect of moving prescription medications to nonprescription status on health plans and third party payers is as complex as the interactions of the various stakeholders who are a part of this process. Next to distinct characteristics of the various national health plans, specific conditions of a certain switch (i.e., dosage strength, formulation, etc.) as well as respective behaviors of physicians, pharmacists, and patients affected seem to be of great importance (Rosenau 1994).

2.4 Current trends in the Rx-to-OTC switch movement

There are several factors of influence that have to be highlighted in a larger societal context when it comes to current trends in the Rx-to-OTC switch movement.

First of all, as previously mentioned (see Subsection 2.1.1), the heightened health consciousness among the general population has become a global “megatrend” bringing forth an enhanced desire of individual responsibility for self-health management (CHPA 2000; Hoy 1994). The explosion of information access is another megatrend, with the internet as a growing source of health information (CHP Canada 2010; CHPA 2000) which has in large part contributed to the medical education of a certain proactive population segment. This segment is characterized by higher levels of education, income, and “consumer sophistication”, also termed “Do-IT-Yourself (DIY) Health Care Consumers” (Hoy 1994). Moreover, aging societies account for rising healthcare cost pressures. A globally increasing number of chronic diseases and disabilities as well as more retirees per workers provoke greater cost pressures not only on national health economies, but also on societies in general (CHP Canada 2010).

A shift in targeted OTC indications and corresponding medication from the acute treatment of easily recognizable, minor ailments towards focusing on the prevention and treatment of chronic, possibly asymptomatic illnesses is one approach in tackling the emerging public health threat of chronic diseases through empowering people to take better care and control of their own health. Switching appropriate medications to OTC within the context of comprehensive switch programs can help modify and control primary risk factors underlying major non-communicable chronic diseases (WSMI 2009).

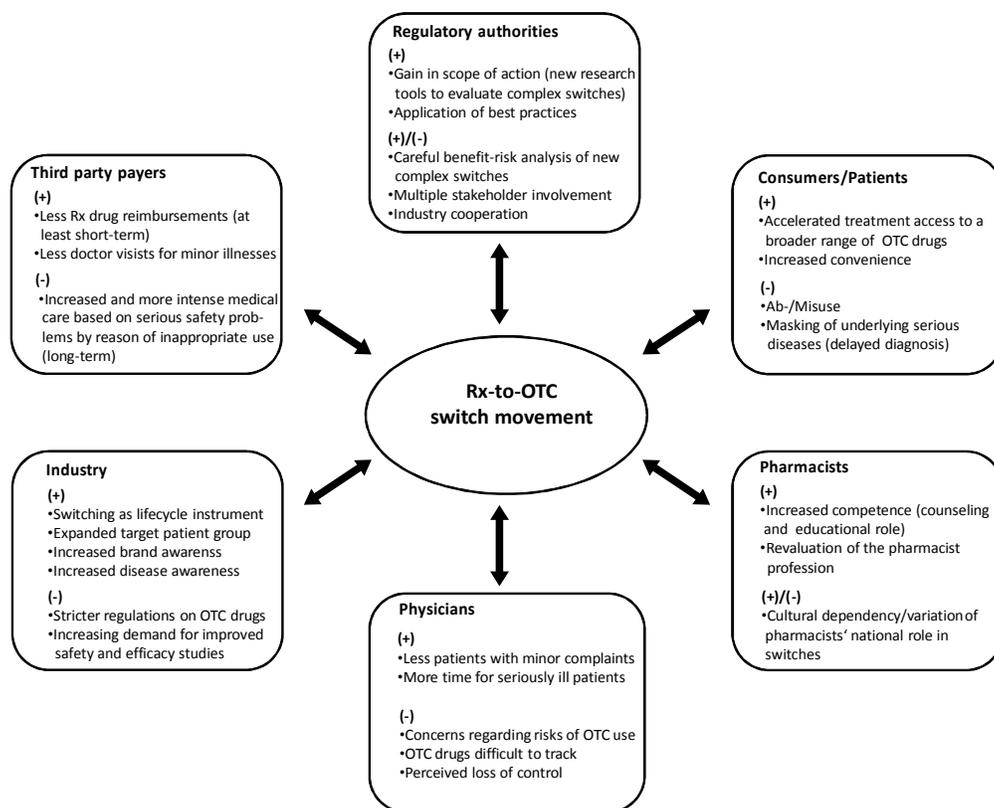


Figure 3: Implications of the Rx-to-OTC switch movement on various stakeholders

In order to identify new areas for switch that might fit into the above mentioned approach, in 2001 an AESGP task force developed a tool to review indications or conditions that might come into consideration for a possible expansion of self-medication in the future (Stitching AESGP Foundation 2002; WSMI 2009). One output was a chart mapping both the range of indications currently suitable for OTC and other indications under consideration according to two dimensions. One dimension encompasses various forms and stages of medical management ranging from self-diagnosis and self-management to doctor consultation, other HCP advice, and patient self-management with or without medical devices. The other dimension is to display the duration of drug usage and type of condition – that is, short-term/acute, recurrent/semi-chronic, and long-term/chronic (see Figure 4). The indications placed in the top half thereby represent indications of the traditional self-medication arena. The ones located in the bottom left emanate from the concept of a so-called “collaborative care setting” where a doctor initially establishes a medical diagnosis and recurrent symptoms are recognized by patients and treated with OTC drugs under pharmacists’ advice – an approach

realized in some cases in the UK, for example. New indications which were suitable but not yet available for self-treatment at that time² are mapped in the bottom right. They were considered as potential candidates for self-treatment, e.g., in a collaborative care setting, after clarification of additional questions regarding:

- type of illness (stable vs. life-threatening condition),
- disease management: self-monitoring and self-treatment of asymptomatic diseases, treatment regimen (simple vs. dose titration), patient compliance.

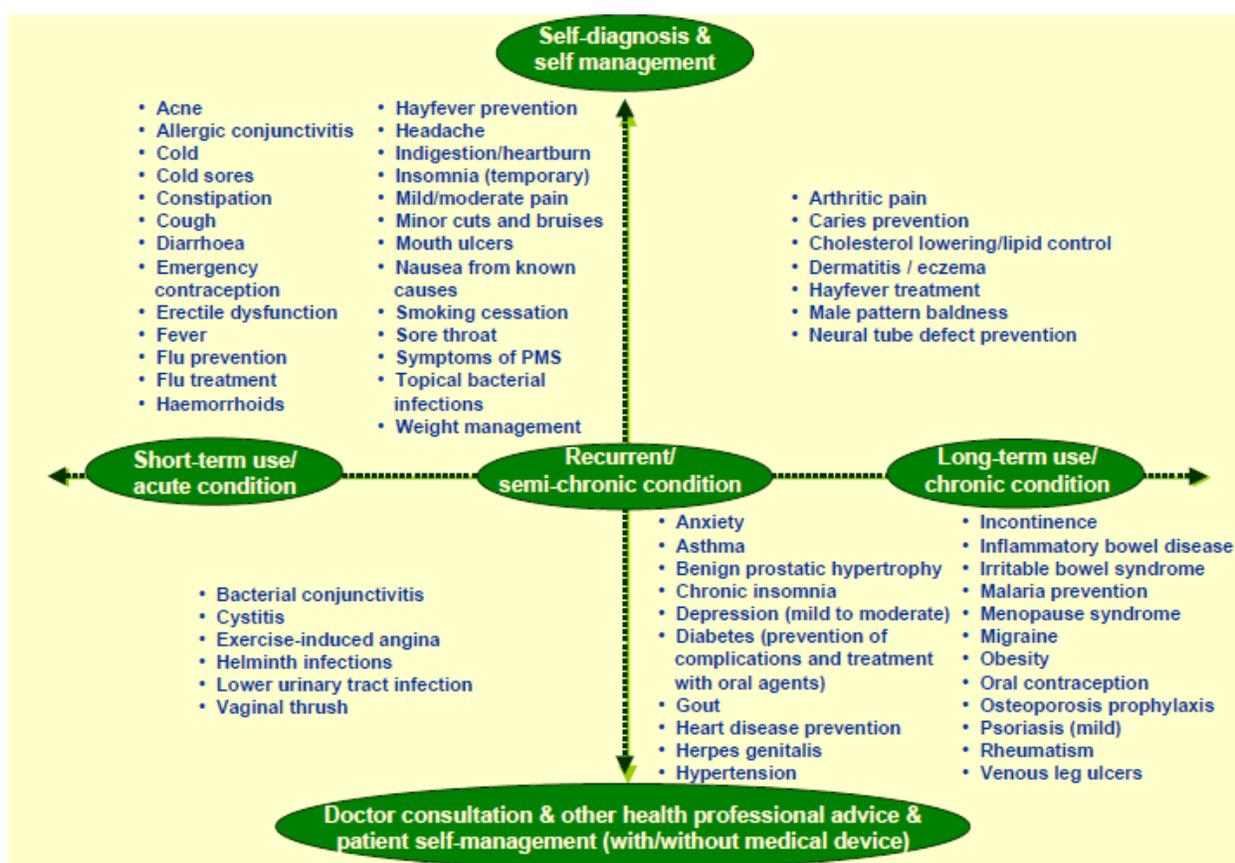


Figure 4: Map developed by a task force of the AESGP in 2001 for identification of potential new areas for self-medication (from *Stitching AESGP Foundation 2002*)

In summary, the intention to expand the traditional self-care arena in a consumer-/patient-centered approach should be regarded as a major outcome of this project. Self-medication, hence, leaves the path of mere symptomatic treatment of self-limiting conditions and is increasingly directed towards the prevention and treatment of more complex,

² Nowadays some of them are already available OTC in selected countries.

often asymptomatic chronic disease states. A major challenge in this arena of looser medical direction will surely be the development of a “one-size-fits-all” approach to achieve a population based benefit (Hemwall 2010). The working group agreed that a potential public benefit of better management of chronic and symptomless conditions will largely depend on the collaborative work of HCPs, patients and other stakeholders as well as the provision of comprehensive training material and high-quality information with respect to the conditions envisaged. Of course, it has to be recognized that each potential switch is accompanied by specific questions which will be addressed in miscellaneous ways by the various countries concerned as they all differ in terms of specific healthcare characteristics such as patient information and HCP support (Stitching AESGP Foundation 2002; WSMI 2009).

As depicted by Cohen, et al., a similar tendency to the one described above is to be found in the US. “For patients, the trend towards more switches will take self-care to a new level, focused increasingly on chronic prevention of serious illnesses”. This movement seems to be accompanied by important regulatory changes: the FDA consistently evaluates the potential of OTC status for certain drugs treating chronic conditions thus enlarging the range and number of medications available for self-treatment (Cohen 2005a).

2.4.1 Switch in support of better healthcare behaviors

First of all, effective and responsible treatment with nonprescription medicines not only enables citizens to control and manage their own health situation, but may also help raise awareness for certain conditions which formerly caused sufferers not to seek medical treatment due to embarrassment about their situation.

As an example, “urge incontinence” (also known as “overactive bladder”) fits in this category of conditions that people often are afraid of disclosing and hence present very late to the doctor. Several studies show that more than 70 % of those with current urinary incontinence do not tell any healthcare provider and health practitioners are asked about the condition spontaneously only in 18 % of visits (Hemwall 2010; Soller 2002). In men, the prevalence of urge incontinence is assumed to be quite high (73 %) and so is the impact on patients’ quality of life (QoL) (Stitching AESGP Foundation 2002). Experts agree that urge incontinence constitutes an OTC manageable condition and should be brought to the self-medication area as it could effectively contribute to the reduction of the large number of “silent sufferers”. Broad information campaigns could point out that there is something available that can help already at an early stage of the condition. Moreover, the condition has proven to be self-recognizable and citizens usually are able to clearly differentiate between “urge” and less common “stress” incontinence (urine leakage when laughing, coughing or sneezing). Besides, a potential delay in its diagnosis and treatment is far from life-threatening.

Furthermore, there is a growing need for prevention and treatment of (semi-)chronic diseases and associated risk factors which has also been addressed by the WHO: “Without action, an estimated 388 million people will die from chronic diseases in the next ten years. [...] Each of us has a choice: whether to continue with the status quo, or to take up the challenge and invest now in chronic disease prevention” (WHO 2005). As already mentioned above, the majority of these chronic diseases are associated with a set of common, modifiable risk

factors whose minimization or optimization, respectively, should be paramount to each of a society's individuals.

Tobacco use, obesity, or raised cholesterol levels are probably the most prominent examples of these risk factors. Easily accessible OTC medication targeting their modification can certainly help them be tackled by empowering, but at the same time pledging people to look after themselves. Tobacco use is one of the leading preventable causes of death throughout the world (Shiffman 2008) and so are obesity and raised cholesterol levels – all eventually bringing forward long-term disease states like hypertension, coronary heart disease (CHD), diabetes, and at worst premature death (WSMI 2009).

In some countries drugs aimed at the management of the aforementioned risk factors are already available OTC, yet there are still a number of countries where they are not, often due not only to safety concerns, but also political reasons. Nicotine replacement therapy (NRT), for example, has already been widely used in self-medication and has shown a considerable rate of success. In his ten-year evaluation of the US NRT switch to OTC Shiffman sets the associated increase of NRT users, i.e. potential former smokers, at a remarkable 152 % - a safe and at the same time cost-effective approach to reduce tobacco dependence (Shiffman 2008). Self-medication with orlistat as first licensed therapeutic option for weight loss is now also possible in many European countries as it was approved by the European Medicines Agency (EMA) in 2009 as the first ever centralized switch (q.v. Subsection 3.5.1). Despite controversial opinions, simvastatin was reclassified as the first member of the statin class to a “pharmacy-only” (P) drug in the UK in 2004. It is provided to people at moderate risk of getting a heart attack within the next ten years for the reduction of their cholesterol levels upon comprehensive counseling by a pharmacist (cf. also Subsection 3.5.1).

All in all, switching drugs with an adequately established safety and efficacy profile from prescription to nonprescription status might significantly contribute to the improvement of individual self-care behavior, benefiting not only individuals but also public health by raising awareness of certain conditions and the importance of early treatment and prevention.

2.5 Summary and conclusion

Historically, the Rx-to-OTC switch movement is to be seen as a result of cultural, social, and political influences and developments. The reclassification of a growing number of medications from prescription to nonprescription status has contributed to coping with patients' increasing demand for self-empowerment in the face of growing public health consciousness. In general, implications on various stakeholders are multifaceted, resulting in an overall benefit for public health provided that the respective switch candidate turns out to be appropriate for safe and effective self-medication.

However, the development of the Rx-to-OTC switch movement indicates that the time of more or less “simple” switch projects targeting acute, minor, and self-limiting diseases seems to have come to maturity, thus, giving rise to a trend towards increasingly complex switches involving the prevention or treatment of (semi-)chronic diseases or associated risk factors. According to the author, this trend should be seized as an opportunity to further raise people's disease awareness and their sense of proactive responsibility for their individual

health status both of which are indispensable preconditions in view of the increasingly burdened health systems' ability to persist in the long run. Against this background, the author believes that it will be important and valuable to further encourage and foster innovative Rx-to-OTC switches presupposing that benefits outweigh risks and the latter are to be managed accordingly.

3 The Rx-to-OTC switch process: legal basics, regulatory requirements, and prominent examples

The following chapter will give a short overview of legal and regulatory basic conditions and prerequisites related to the Rx-to-OTC reclassification process as well as point out to some noteworthy examples.

3.1 Legal classification of medicinal products

The availability of prescription and nonprescription products strongly differs all over the world depending on the various legal classification systems. Several influencing factors have been identified in this regard such as a nation's economic orientation, wealth, traditions and political system (Gilbert et al. 2006). In the US, for example, there are two major classes of drugs, namely prescription and nonprescription. Evidently, prescription drugs are only available with prescription from qualified prescribers such as doctors, dentists or supplementary prescribers. On the contrary, apart from few exemptions which are only available from behind the pharmacy counter, most OTC drugs can be purchased in any convenience or grocery store without HCP intervention. Other national healthcare systems (e.g., Australia, New Zealand, and the EU countries of Finland, Sweden, France, Germany, and the UK) have introduced nonprescription subcategories. A so-called "pharmacist-only" or "behind-the-counter" class requiring pharmacist assistance next to a "pharmacy-only" or "pharmacy self-selection" class, e.g., are available in Australia, New Zealand and Canada in addition to the "general sale" of OTC products through any retail outlet (where applicable) (Gilbert et al. 2006; Palumbo 1991; WSMI 2009). The UK, for example, allows for three legitimate means to obtain licensed medicines: prescription-only medicines (POM) from qualified prescribers, pharmacy-only (P) medicines without a prescription under supervision of a qualified pharmacist, and general sales list (GSL) medicines without a prescription available from, for instance, a pharmacy or a convenience/grocery store (Aronson 2009). Moreover, "new technology has allowed a new range of outlets including online sales and catalog ordering" (Elder 2013). In a wider context, the term "switch" refers to changing any status of classification, that is, next to the switch from prescription to nonprescription status it may also apply to the switch from P to GSL status provided that these categories exist in the respective countries. However, in the present work the term is exclusively used to refer to a switch from Rx to OTC classification.

3.2 Switch criteria

A brief overview of the criteria to be addressed and fulfilled in a sufficient way for successfully change a drug's legal status from Rx to OTC will be given below.

3.2.1 Evolution of regulatory criteria for switching a medicinal product from prescription to nonprescription status

Building the basis for the scientific/medical and regulatory decision making process that determines OTC status, common regulatory switch criteria still valid today have evolved during the OTC Review process from the fundamental definitions of safety, effectiveness, and labeling as well as the requirement for a risk-benefit analysis (Soller 2002). In particular, these definitions authorized safety and effectiveness in relative terms, meaning "a low incidence of side effects, a low potential for abuse and a reasonable expectation of effectiveness in the target population under conditions of intended use" (Soller 2002). Furthermore, the demonstration that the label is written for consumers/patients and ensures safe and effective product use (CHPA 2000) is viewed as a foundational statutory criterion for OTC availability. The label of an Rx-to-OTC switch candidate must provide "adequate directions for use" as it acts as direct intermediary between consumers/patients and the drug with the physician and the pharmacist (at least partly) left out of the loop (Juhl 1998).

Based on these regulatory principles, in 1989 US FDA's Center for Drug Evaluation and Research (CDER) issued, for the first time, a public industry guidance list of 13 criteria for switching drugs from prescription to nonprescription status, also known as "Peck's Principles" (see Table 1). However, in contrast to today's state-of-the-art criteria, these fundamentals primarily focus on the switch candidate itself and do not include current refinements additionally emphasizing the condition, consumer/patient understanding of product use, and conditions of actual use (Soller 2002).

Again in the US, with the approval of a number of switches and based on OTC post-marketing experience, the perspective of switch criteria has gradually changed entailing the publication of a renewed set of state-of-the-art principles by Dr. Robert DeLap ("DeLap's Principles", see Table 3) in 1998. In addition to the criteria referring to the switch candidate itself, these renewed principles reflect the emphasis on patients' correct self-diagnosis, label comprehension, and actual use (Soller 2002). On these grounds adequate OTC labeling designed for and tested by "average" consumers/patients is regarded as fundamental in responsible self-medication since the outer packaging allows consumers/patients to quickly and easily decide about the appropriateness of the medicine for their needs. In accordance with this view, studies indicate that 96 % of consumers read the label of an OTC drug before they first use it (Gossel 1991). Beyond that, the US OTC scientific/regulatory paradigm was enriched by the introduction of "use-effectiveness studies" (i.e., so-called "actual use studies" (AUS)), in a simulated OTC setting, as "techniques to characterize the potential safety and effectiveness of OTC ingredients" complementing more or less traditional effectiveness studies such as well-controlled clinical trials (Soller 1999).

Table 1: *Switch principles elaborated by CDER Director Carl Peck, MD, at the 1990 Annual CHPA Research and Scientific Development Conference (from Soller 2002)*

Peck's "Switch Principles"

1. Does the switch candidate have special toxicity in its class?
 2. Does the candidate have a large margin of safety?
 3. Does the candidate's frequency of dosing affect its safe use?
 4. Has the candidate's safety profile been defined at high dose?
 5. Has the candidate been used for a sufficiently long time on the prescription market to enable a full characterization of its safety profile?
 6. What is the worldwide marketing experience of the switch candidate?
 7. What foreign countries market the candidate OTC? What is its experience in those countries?
 8. What do the "use data" show?
 9. Has a vigorous risk analysis been performed?
 10. Has the efficacy literature been reviewed in a way to support the expected usage and labeling of the switch candidate?
 11. Is there a full understanding of the pharmacy-dynamics of the switch candidate?
 12. Is the minimally effective dose for the proposed OTC indication known?
 13. Have possible drug interactions for the switch candidate been characterized?
-

Within the EU, criteria for classifying a medicinal product as subject to a medical prescription or not, according to Articles 71 and 72 of the European Community Code, are itemized in the European switch guideline ("Guideline on changing the classification for the supply of a medicinal product for human use", see Section 3.3).

Yet, despite the above mentioned evolution of definite standard criteria for the eligibility of drugs to be available without prescription, OTC status is hard to define in an ultimate way. This allows evaluative regulatory agencies the most freedom of choice, but puts considerable pressure on the pharmaceutical industry when deciding whether to pursue an OTC switch or not (Burstein 1994).

3.2.2 Issues to be addressed to fulfill regulatory switch criteria

In order to fulfill the aforementioned switch criteria, both in the US and in Europe, basic principles of toxicology, clinical pharmacology, and epidemiology have to be applied when petitioning a switch of a certain substance or drug from prescription to nonprescription status. Specifically, pharmaceutical companies are well-equipped to address the sorts of potential issues that typically arise in the context of OTC availability. Issues to consider and address by pharmaceutical companies in their switch application are summarized in Table 3.

Overall, today's criteria for marketing a product classified as OTC are fairly rigorous on principle (Gossel 1991), representing a solid regulatory/scientific foundation for the further evolution of OTC drugs not only to prevent specific life-style conditions but also to treat

Table 2: *Switch principles elaborated by Robert DeLap, MD and Director of the Office of Drug Evaluation V, at the 1998 CHPA Research and Scientific Development Conference (from Soller 2002)*

DeLap’s “Switch Principles”

Fundamentals:

1. Can the condition be adequately self-diagnosed?
2. Can the condition be successfully self-treated?

Points to consider:

1. Is there a need for physician evaluation of the condition?
2. What is the nature and severity of adverse effects of consumer misdiagnosis and delay in correct diagnosis?
3. Regarding effective product use, what is the nature of consumer understanding of product use?
4. What is the consumer understanding of the expected benefit?
5. Does the consumer have the ability to assess treatment effect?

Safe product use:

1. What is the consumer understanding of product directions for safe use?
 2. What is the consumer understanding of what to do if the product isn’t working?
 3. What is the consumer ability to identify adverse effects and the consumer ability to determine when adverse events may require professional care?
 4. What is the consumer expectation of safety?
-

(semi-)chronic conditions and diseases. “The broader public health discussions on risk management of prescription pharmaceuticals will likely impact this process in a positive way, if the focus of OTC risk management places the consumer at the center of pre- and post-marketing assessments of drug safety and effectiveness, using a collaborative benefit/risk co-management approach to self-care” (Soller 2002). Hence, the potential for further self-care empowerment of consumers is based on a scientific paradigm which defines specific target populations with readily recognizable conditions, previously diagnosed conditions or self-diagnosable diseases, and determines which drugs, based on appropriate dosage and labeling, can provide a reasonable expectation of benefit with a low potential for toxicity.

3.3 Switch procedures

As opposed to the basic switch criteria which generally tend to be the same in every country (see also Subsection 3.2.1), switching procedures actually vary among different countries not least due to individual governmental systems and leadership. In general, a case-by-case assessment of a product or ingredient according to benefit/risk considerations, as depicted in Subsection 3.2.1, should be at the core of the switch assessment process with issues such as

Table 3: *Issues to consider and address by pharmaceutical entrepreneurs when filing an Rx-to-OTC switch application (based on CHPA 2000)*

Fulfillment of regulatory switch criteria: toxicology, clinical pharmacology and epidemiology

1. Potential safety issues:
 - toxicity:
 - carcinogenicity
 - reproductive toxicity
 - side effects
 - therapeutic hazards:
 - misdiagnosis (self-selection, self-diagnosis)
 - treatment failure (delayed professional treatment)
 - incorrect use (long-term self-monitoring, overdose, misuse)
 - drug interactions
 2. Potential effectiveness issues, based on nature/severity of condition:
 - choice of dose, dose interval, age restrictions, etc.
 3. Ability of label to convey core communication objectives
 4. Benefit/Risk assessment
-

reimbursement status or professional monopolies to be left out of a respective evaluation. On all accounts, a well-grounded, transparent and comprehensible switch procedure is essential for successful switch regulation (WSMI 2009).

In Europe, depending on the country concerned, different regulatory and/or legal parties as well as expert groups are involved in a drug's or ingredient's, respectively, application for reclassification.

In Germany, for example, the switch procedure is clearly determined in the German Medicines Law (AMG): an "Expert Committee for the Classification of Medicines" enunciates a recommendation while the final decision is incumbent on the legal Federal Ministry of Health. It is important to note that reclassification processes in Germany, as well as in some other European countries, usually are "class switches" meaning that they are ingredient-related thus applying to all eligible products containing the respective ingredient in the respective dosage for the respective indication. On the other hand, reclassification applications (e.g., in the UK) are evaluated by the national regulatory authority (Medicines and Healthcare products Regulatory Agency (MHRA)) with advice from a suitable expert committee, expert advisory groups or, if applicable, even public consultations. Legal status is changed based on a successful reclassification proposal. Yet, in contrast to the aforementioned German class switch, all other theoretically eligible products for reclassification with the same active substance have to apply separately for a so-called "product switch" (WSMI 2009). At this time the latter procedure seems to be preferred in Europe as in most member states reclassifications are grounded on a product basis (AESGP 2010).

On a European level, the European Medicines Agency deals with a growing number of pan-European switch applications for active ingredients or drugs aiming at a common legal and regulatory basis for the same legal status in every European country (q.v. Section 3.4). When assessing a reclassification request, the EMA is supported by the Committee for Medicinal Products for Human Use (CHMP) which is engaged with benefit/risk assessments.

The main principles and criteria as well as specific data requirements to be delivered by a marketing authorization holder (MAH) within Europe for an application to change the classification for the supply of a medicinal product from Rx to OTC are outlined in the EU “Guideline on changing the classification for the supply of a medicinal product for human use” (European Commission 2006a). It was adopted in 1998 by the European Commission for the sake of enhanced transparency and harmonization of switching conditions among European countries. As an example of a supranational legal framework and political support, the guideline came into effect on January 1st, 1999, and was last updated and amended in 2006 (WSMI 2009). In total, the guideline consists of five parts dealing with different aspects to be fulfilled and considered, respectively, when applying for a switch (e.g., switch criteria, data requirements, name of the medicinal product, etc.).

In particular, part three of the guideline addresses data exclusivity due to the fact that based on Article 74a, Directive 2004/27/EC, the MAH is awarded one year of data exclusivity provided that the switch application contains “significant pre-clinical tests or clinical trials”. However, in effect, information on interpretation and specification in terms of detailed requirements is somewhat imprecise. Against this background, the present thesis focuses on the substantiation, elaboration, and discussion of distinct criteria, data categories and requirements potentially eligible for the grant of data exclusivity with the intention to make current legal provisions more concrete and thus practically applicable (see Chapter 4 ff.).

3.4 Regulatory drug approval and switch strategies in Europe

From a strategic point of view, different scenarios for changing a drug’s and/or indication’s classification status are possible. For example, a completely new authorization may be applied for if no OTC version has been available in the European Union so far. Alternatively, the scope of an existing OTC product in a certain dosage and with a certain indication might be enlarged by switching other/additional dosages or indications to OTC via the variation of already existing authorizations. In any case, depending on the regulatory pre-conditions of existing Rx or potentially OTC authorizations, the regulatory process of Rx to OTC reclassification is often quite complex in nature.

In general, a medicinal product may only be placed on the market in the European Union³ when a marketing authorization has been issued by the competent authority of a member state for its own territory (a national authorization) or when an authorization has been granted for the entire Community (a Community authorization) in accordance with

³ more precisely, in the European Economic Area (EEA) including Norway, Iceland and Liechtenstein

effective legal requirements (i.e., Article 6, Directive 2001/83/EC, as amended⁴, and Article 3, Regulation (EC) No 726/2004).

With respect to the approval of a medicinal product⁵ in the EU, different routes may be followed depending on the envisaged scope of merchandising: if the focus lays on marketing and commercialization in one particular EU member state, the national application procedure (as exemplarily briefly described above for Germany and UK, see Section 3.3) is to be applied. It is reviewed and decided on by national authorities based on national requirements and guidelines. If a medicinal product is planned to be marketed under the same conditions in several, or even all, European countries and hence approval across several or all EU countries is necessary, three different ways of seeking approval have been established since the latest review of the pharmaceutical legislation: approval via mutual recognition procedure (MRP), decentralized procedure (DCP), or centralized procedure (CP) with the two former being alternatives to the latter if this is not mandatory.

More specifically, the so-called “mutual recognition procedure” is to be followed in case the medicinal product already possesses a marketing authorization in one EU member state. “Mutual recognition” implies that EU countries may approve the decision made about the approval of a medicinal product by another EU country. Hence, the procedure is based on mutual recognition of national marketing authorizations (Medicines Agencies 2010).

In contrast, the decentralized procedure should be used for products that have not previously been approved in any member state (i.e., have not yet received authorization in an EU country (Medicines Agencies 2010)).

An approval for a medicinal product intended for use in every EU member state simultaneously may be obtained by applying to the European Medicines Agency via centralized procedure (q.v. also Section 3.3). Within the EMA, a scientific committee for human medicinal products composed of one representative of each member state, the CHMP prepares an opinion preceding a formal approval by the Commission. The classification adopted by “Community decision” has to then be followed by the member states to avoid the co-existence of a central and national marketing authorization. As to eligibility for CP, so called “mandatory” and “optional” approval routes have to be differentiated. Article 3(1) and the Annex of Regulation (EC) No 726/2004 define the mandatory scope of the CP as obligatory for a selected group of medicinal products and new active substances, respectively (e.g., medicinal products developed by means of biotechnological processes, medicinal products for human use containing new substances for the treatment of certain diseases such as cancer, neurodegenerative, or auto-immune diseases or medicinal products designated as orphan drugs). In contrast, the optional scope of the CP may apply in the following situations: according to Article 3(2)(a) of Regulation (EC) No 726/2004 a medicinal product containing a new active substance that has not previously been authorized in the Community qualifies for the central procedure (i.e., will be “first in class”). Moreover, by virtue of Article 3(2)(b) of Regulation (EC) No 726/2004 the proof that the envisaged medicinal product is innovative

⁴ i.e. Directive 2004/27/EC

⁵ either based on a new chemical entity (Rx or OTC) or on a substance with well-established use in a new combination or with significant innovations providing therapeutic benefit (e.g., new classification, new indication, new pharmaceutical form, etc.)

in nature (i.e., significant therapeutic, scientific or technical innovation, for example, introducing a new administration route or combination) or “in the interest of patients health at Community level” is at the basis of this optional route. Finally, Recital 9 of Regulation (EC) No 726/2004 allows for optional access to the CP “in cases where use of a single procedure produces added value for the patient” thereby underpinning Article 3(2)(b).

As regards the choice of an appropriate Rx-to-OTC switch drug approval strategy, theoretically all of the above mentioned approval procedures are available depending on the envisaged target markets for a certain switch candidate. Up to this point national switch procedures have comprised the majority of OTC approvals in Europe (Senior 2010), although with the huge drawback of extended review times and thus a long time until the marketing authorization is finally issued (e.g., up to two years or even longer for Rx-to-OTC switch approvals).

In contrast, specific challenges are to be overcome in the case of multinational switches, regarding the many different cultural norms and especially the very diverse roles pharmacists play across Europe. Nevertheless, up to now a number of switches have also been applied on the basis of a supranational, central procedure with the successful reclassification of orlistat in 2009 as pioneering example. Within this context, CP comes into consideration automatically (i.e., mandatorily) for a specific Rx-to-OTC switch candidate, if the active substance of the Rx drug has originally been approved via the prescription drug centralized process (Senior 2010) as it was the case for orlistat (see also Subsection 4.4.4). Besides, it is the above mentioned “optional” route of the CP that paves the way for a central Rx-to-OTC switch application and its eventual approval.

In any event, independent of the route taken into consideration, a switch application primarily based on financial arguments is commonly viewed as “invalid” and therefore not accepted. In general, switches are scientifically rigorous, case-by-case, weight-of-evidence, data- and dialogue-driven processes (Pawaskar 2007; Soller 2002). Most of the switch candidates are more or less “old” substances with well-established use and sometimes even available OTC in some countries inside or outside the EU such that cumulative safety data can and should be an integral part of the regulatory assessment report.

3.5 Major switches and re-switches

The following chapters intend to briefly describe examples of fundamental switches and re-switches over recent years in order to deduce essential learnings and potential caveats for upcoming switch projects.

3.5.1 Examples of notable switches worldwide

There are a number of switches that are worth mentioning at this point, however, as the present thesis is limited in scope, only a selection of them will be described somewhat more in detail. An overview of important switches worldwide over the last twenty years is given in Table 4.

Vaginal mycosis/Bacterial candidiasis. *Candida* vulvovaginitis or vaginal candidiasis, a vaginal yeast infection, is the second most common diagnosis in women with vaginal symptoms (Gurwitz 1995). The condition can be effectively treated with the active imidazole substance “clotrimazole”. It was the first “azole” compound for the treatment of fungal infections in humans, introduced in 1973 by the Bayer company (Canesten®). In 1990 and 1992 topical clotrimazole was switched for the treatment of external mycosis on a national basis in the US and the UK, respectively, followed by many other countries (AESGP 2004; Lipsky 1999). Important for a successful outcome was the fact that vaginal yeast infections occur frequently and most women do not require medical intervention for a diagnosis. Warnings on the packaging state that medications are not intended for women with a first occurrence of symptoms, but for those with a medically supported pre-existing condition. In this setting, the pharmacist is a key guide and gatekeeper, referring patients not eligible for OTC treatment to the doctor. In general, compliance is high, side effects are rare, and most patients effectively respond to treatment. Since its availability for vaginal use in OTC, no adverse events due to misuse have been reported and concerns regarding an unnecessary increase in consumption have thus not been substantiated. Patient education includes advice on how to prevent future infections, and scientific brochures as well as public relations (PR) activities help to inform about self-medication. As a result of the OTC switch, patients benefit from quicker and convenient access to an effective treatment option without the need to consult their doctors for symptoms they are profoundly familiar with. Moreover, multiple study analyses confirm a reduction in the number of physician visits for vaginitis, leading to valuable cost savings to public social healthcare budgets (Gurwitz 1995; Lipsky 1999; Lipsky 2000).

Heartburn and acid indigestion. Treatment of heartburn and acid related disorders has changed radically over the last twenty years with the OTC switch of H₂-blockers (or H₂-receptor-antagonists) and proton pump inhibitors (PPIs), respectively. Prior to 1995 nothing but antacids or antirefluxants had been available to medically self-treat symptoms mild in nature. The market first changed when H₂-blockers (e.g., famotidine 10 mg (PepcidAC®, Johnson & Johnson/Merck)) based on a systemic mode of action were introduced in the early 1990s for treatment and prevention of more severe symptoms. With the introduction of the first PPI, omeprazole 20 mg (Prilosec OTC®, Procter & Gamble) in 2003, the OTC market changed again. It was then the only product approved for the treatment of frequent heartburn ($\geq 2x/week$), the cardinal symptom of the so-called gastroesophageal reflux disease (GERD) affecting around 30 % of patients. PPIs likewise act systemically providing lasting, although not immediate, relief from heartburn and are the current medical standard medication. Treatment algorithms have changed accordingly over time and PPIs have experienced an explosive growth over recent years, with other PPI substances gradually following the omeprazole switch. At a global level, PPIs’ retail sales rose dramatically from 2002 to 2004 - highly influenced by the switch in the US.

In June 2009 the EMA approved Nycomed’s OTC application for Pantoloc Control® (pantoprazole 20 mg) as the second centralized pan-European Rx-to-OTC switch in history. In the

absence of automatic eligibility for the central switch procedure (see Section 3.4), the switch request was based on a non-automatic approach “in the interest of patients health at Community level” according to Article 3(2)(b) of (EC) No 726/2004 and was approved following unanimous votes by 27 member states. On the other hand, the concurrent application for one year of data exclusivity according to Article 74a of Directive 2004/27/EC was rejected. A more detailed analysis of the denial will be given in Subsection 4.4.4. Pantoloc Control[®] has since gradually been launched in most EU member states. In contrast to the US, the switch of PPIs within Europe has not caused significant growth in retail value sales at a global level so far (Euromonitor International 2010). One possible explanation might be the pharmacy staff’s reserved position due to a fear of masking underlying serious diseases. Another factor influencing pharmacy recommendation might be the ongoing discussion of the possible interactions of PPIs with other medications and their potential clinical impact. This situation was probably even worsened in light of the flood of non-consistent informational and educational material provided by originators and generic manufacturers of OTC PPIs in respective European countries.

Obesity. Another milestone in the arena of self-medication was the addition of orlistat (tetrahydrolipstatin) for weight management and treatment of obesity. Its primary function is to prevent the absorption of fats from human alimentation, thereby reducing caloric intake. It is well known that being overweight or obese in the long run increases risk for severe chronic diseases such as hypertension, coronary heart disease, diabetes, and even premature death. In general, weight management just like smoking cessation is initially typically approached as a self-help endeavor without formal medical treatment and requiring radical behavioral changes (effort and discipline). Just like tobacco dependence obesity is a chronic, relapsing condition demanding long-term management and treatment.

The OTC switch of orlistat 60 mg (alli[®], GlaxoSmithKline) in a number of countries for use in combination with a modified diet has filled an important weight management gap. In January 2009 orlistat was approved as the first ever centralized switch in Europe by the EMA to help curtail the increasing prevalence of heart disease, making it the first licensed weight loss aid suddenly available without prescription throughout Europe. Orlistat 60 mg was automatically eligible for a switch via the centralized route, as its Rx counterparts have also been authorized by way of central application (cf. Section 3.4). One year of data exclusivity was equally requested in the application but refused by the evaluating committee (q.v. Subsection 4.4.4). The switch was accompanied by a heavy media campaign including TV advertising, as well as consumer and pharmacy support packages. A comprehensive network via the “myalli” website targeted at consumers committed to behavior change with user forums, chat rooms, and blogs delivers tailored behavioral support and helps to set up a special weight management plan (“not just a pill, but a program”). Pharmacies were profoundly equipped with educational and informational material even prior to the switch (DAZ 2010). Initial concerns about ab- or misuse were addressed by post-marketing surveillance measures closely monitoring in-market performance.

In the US, the switch of orlistat was very successful in 2007, yet in 2009 there was a decline

in use due to the lack of good weight-loss results and gastrointestinal side effects. In May, 2010, the US FDA decided that a warning about potential liver damage had to be added to the drug facts label⁶. Moreover, one criticism of OTC obesity drugs is that disease status is also largely related to psychological and behavioral factors not included in the clinical evaluations of weight-loss results and people might consequently only lose weight temporarily without necessarily rooting out the real cause. New dietary guidelines about to be completed in many countries place more emphasis on healthy diets instead of pills to achieve weight loss, and more and more competitors are on the rise in supplements and functional food (Euromonitor International 2010). Thus, whereas the reclassification of orlistat as the first approved European centralized switch was groundbreaking in terms of regulatory decision making, its successful establishment in the market is still to come.

Raised cholesterol levels. An illustrative example of tackling major health problems by helping people lower their individual risk factors for chronic diseases is the treatment of raised cholesterol levels with statins. This class of drugs is also termed “HMG-CoA reductase inhibitors” due to its ability to inhibit the so-called HMG-CoA reductase, an enzyme with a central role in hepatic cholesterol production. Increased cholesterol levels represent a major preliminary stage in the development of cardiovascular diseases such as coronary heart disease, a common cause of death, and statins are used in the prevention of these. The WHO estimates that more than 50 % of CHD in developed countries is due to high blood cholesterol levels (AESGP 2004). In a dosage of 10 mg, simvastatin was reclassified from POM to P status in 2003 in the UK for treatment of raised cholesterol levels (Zocor Heart-Pro[®], McNeil). OTC simvastatin is indicated for individuals at moderate risk (> 15 % (AESGP 2004)) of a heart attack in the next ten years. Product specific clinical study data have shown that the product is able to significantly reduce low density lipoprotein (LDL) cholesterol levels (by around 27 % after four weeks of treatment) thus clearly decreasing – depending on the starting level - the risk of major coronary events (e.g., death or myocardial infarction) after continuous treatment (WSMI 2009). Importantly, primary prevention of CHD through self-care requires a framework of collaborative care with the intervention of specially trained HCPs, like pharmacists, to assess individual risk factors, give advice, and continually monitor self-treatment (AESGP 2004). From a pharmacy training point of view, the switch of simvastatin 10 mg in the UK setting has been a model switch: based on a detailed protocol pharmacists are to guide and advise consumers about their appropriateness for treatment and to provide information on individual risk factors as well as adequate lifestyle provisions. As opposed to the recommendations of pharmacists associations such as, for example, the American Society of Health-System Pharmacists (ASHP) (American Society of Health-System Pharmacists 2005), cholesterol tests before starting OTC simvastatin treatment are not envisaged in the UK based on the view that the target group will benefit from reducing cholesterol level irrespective of the starting point. Independent of the unwillingness of certain pharmacists to sell the product without a full diagnosis by a physician, pharmacovigilance data collected from nonprescription use in the UK have not yet shown any significant prob-

⁶ cf. shortened URL: <http://goo.gl/Lx4JA> linking to www.fda.gov, last accessed 2012-12-29

lems associated with this switch (WSMI 2009).

However, this switch has been intensively discussed among experts and a similar switch application for lovastatin 20 mg (Mevacor[®], Merck & Co.) has been twice rejected in the US so far. Critics deem a daily dosage of 10 mg simvastatin, as it is recommended for OTC usage, as too low for a full beneficial effect (Aronson 2009) and state that beneficial effects have only been shown in high risk populations (Choudhry 2005). Unrestricted access may encourage unnecessary use by low-risk patients or OTC statins might just be taken as a substitute for indispensable behavioral changes (e.g., diet, exercise, smoking cessation). Moreover, as for the aforementioned NRT or orlistat treatment, medication itself is not sufficient to obtain the desired effects: needed are comprehensive consumer support programs going far beyond labeling by providing education about the condition treated as well as emphasizing behavioral modification which emphasize that lifestyle changes are required to achieve the full benefit of the drug. Such supportive programs are designed voluntarily by the sponsoring companies and the FDA so far has been reluctant to approve such non-traditional switch proposals in the absence of a clear legal authority for official assignment (Hemwall 2010). Others still hold the opinion that hypercholesterolemia is a chronic, unremitting, and asymptomatic condition requiring an accurate diagnosis based on clinical testing as well as practitioner-directed medical management (Soller 2002). Last but not least, the occurrence of drug-related adverse events, even though limited from a Rx perspective, gives rise to concerns. With widespread use, a small excess risk for toxic effects might easily translate into a large number of adverse events (Choudhry 2005). Muscle injury (myopathy, rhabdomyolysis) as a well-known example has already been associated with high-dose statin use. Post-marketing surveillance, epidemiological studies, and adverse drug reaction (ADR) reporting are important instruments for the detection of potential side effects related to drug therapy – after but maybe even more so before a potential Rx-to-OTC switch (American Society of Health-System Pharmacists 2005).

Central to the FDA's rejection of the lovastatin 20 mg switch application was the industry-funded CUSTOM study, a consumer/patient use study of OTC Mevacor. Based on a actual use study concept having been in practice in the US for several years (see also Subsection 3.2.1), it was designed to observe consumers' initial and continued statin use to lower LDL cholesterol in the setting of OTC statin availability in simulated retail pharmacies with participants recruited by mass-media advertising (Brass 2004; Choudhry 2005). The study evaluated more than 3,300 subjects' ability to self-manage high levels of LDL cholesterol by using a multifaceted cholesterol self-management program (Mevacor Over-the-Counter Self-Management System (MOTC-SMS)) (Melin 2004). The dataset also included follow-up information on purchasers for up to six months of self-managed therapy. Results showed that the majority of study participants appropriately self-selected OTC statin therapy and acceptably managed ongoing treatment (Melin 2004). However, only 10 % of users of OTC lovastatin met all of the label eligibility criteria and 10.3 % had a potential contraindication (Choudhry 2005). 62 % achieved the LDL target goal and interactions with physicians were common. The authors concluded that MOTC-SMS can effectively guide consumers to make appropriate decisions with respect to managing their elevated LDL cholesterol levels and in-

interact with HCPs if necessary (Melin 2004). Nevertheless, despite infrequent in CUSTOM, the use of OTC statins by consumers needing more intensive statin therapy or facing the risk of potential drug-drug interactions still holds reasons for concern (Brass 2004). One major shortcoming of the study was the fact that it was not designed to evaluate clinical outcomes and therefore not able to demonstrate efficacy/effectiveness (American Society of Health-System Pharmacists 2005).

Taken together, the benefits of statins in patients at moderate risk are well documented. Correct self-diagnosis and continued monitoring of treatment effects, however, certainly are challenges still to deal with (AESGP 2004).

Table 4: Examples of major Rx-to-OTC switches of certain indications and active ingredients/medicinal products, respectively, in the last twenty years

Indication	Active ingredient/Product (manufacturer)	Country/Region	Year
Heartburn	Famotidine 10 mg/Pepcid AC [®] (Johnson & Johnson/Merck), Cimetidine 100 mg/Tagament HB [®] (SmithKline Beecham)	US	1995
Smoking cessation	Nicotine replacement therapy devices (gums, patches): Nicorette [®] (GlaxoSmithKline), Nicotrol [®] (McNeil)	US	1996 ⁷
Emergency hormonal contraception	Levonorgestrel/NorLevo [®] (HRA Pharma)	France	1999
Allergic rhinitis	Loratadine 10 mg/Claritin [®] (Schering Plough)	US	2002
Frequent heartburn	Omeprazole 20 mg/PriLOSEC OTC [®] (Procter & Gamble)	US	2003
Raised cholesterol levels	Simvastatin 10 mg/Zocor Heart-Pro [®] (McNeil)	UK	2003
Bacterial conjunctivitis	Chloramphenicol 0.5 % eye drops/Optrex infected eyes [®] (Optrex)	UK	2005
Migraine	Naratriptan 2.5 mg/Formigran [®] (GlaxoSmithKline), Sumatriptan 50 mg/Imigran Recovery [®] (GlaxoSmithKline)	Germany, UK	2006
Chlamydia infection	Azithromycin 500 mg/Clamelle [®] (Pliva Pharma)	UK	2008
Obesity	Orlistat 60 mg/alli [®] (GlaxoSmithKline)	US EU	2007 2009
Reflux symptoms	Pantoprazole 20 mg/Pantoloc Control [®] (Nycomed)	EU	2009
Prostate health	Tamsulosin hydrochloride 400 mcg/Flomax Relief [®] (Boehringer Ingelheim)	EU	2009

⁷ In some European countries nicotine replacement therapy devices have been available over-the-counter even earlier – that is, from the beginning of the 1990s (e.g., UK: OTC-switch of nicotine gum in 1991).

3.5.2 Examples of major re-switches

Whenever a drug is used in an OTC setting, bearing in mind the risk of abuse is of great significance. Dramatic harm, public and media attention can result in changing legislation that reverses liberalized access to effective medication (Rosenau 1994). Although so far a very rare event due to long-term clinical use of drugs and careful regulatory evaluation (WSMI 2009), there are some examples of drugs switched back from OTC to Rx status (e.g., thalidomide as hypnotic drug in 1961 in some German federal states (Kirk and Friedrich 2001) before its withdrawal from the market (see also Section 5.1), the antihistamines terfenadine and astemizole in 1997 in the UK) or even fully withdrawn from the market (e.g., in the US antimicrobial hexachlorophene in 1977, antihistamine methapyrilene in 1979, and laxative danthron in 1987) (Bond 2008; CHPA 2010; WSMI 2009).

By way of example, the antihistamine terfenadine was re-switched both in Europe and in the US (Ward 1999; Wise 1997). In the UK, terfenadine was reclassified from POM to P status in 1997 (see above). The non-sedating antihistamine ranks among the most widely used treatments for hay fever in Britain (ca. 2.3 mio. Britons) and has a good safety record when used as recommended (up to 120 mg/d) (Wise 1997). After intake as a prodrug, it is converted into its active metabolite fexofenadine and usually completely metabolized in the liver. However, if liver-metabolization is impaired or overloaded it might reach circulation and cause serious or even fatal cardiac arrhythmias (“torsade de pointes” arrhythmias). This may be the case if co-administered with drugs like erythromycin or ketoconazole inhibiting the Cytochrome (CYP) P450 system in the liver, the main enzyme system in charge of hepatic metabolism, or if taken both by people with heart or liver disease and in overdose (Ward 1999; Wise 1997). The determining factor for re-switch considerations was the discovery of an interaction potential with grapefruit juice which would lead to an increase of terfenadine concentrations in the blood associated with an enhanced complexity of precautions needed for safe use.

Interestingly, response to these suddenly uncovered risks differed between individuals, that is, consumers/patients and institutions, such as the Medicines Control Agency (MCA) in the UK. Although patients experienced greater anxieties and awareness of risks, there was little evidence of disaffection or disuse of terfenadine. The MCA, however, promptly decided to reclassify terfenadine to prescription-only status again.

The example above demonstrates that certain - especially serious - adverse events may only become manifest after many patients have taken a drug and that residual uncertainty always remains (Ferner 2008). Current drug development programs are generally not large enough for reliable detection and recognition of very rare, serious AEs and reliable predictions still cannot be made (Friedman 1999). One major limitation is the fact that many clinical trials do not take place in a real-life setting and thus specific susceptible patient groups, such as the elderly or children, who have to be taken into account when it comes to considering the risks of e.g. non-compliant drug usage etc.

Ab- or misuse of a certain drug or reversed manufacturing of active ingredients is another driver for potential re-switches. Actual use of a certain medication is not always predictable based on protocol-driven clinical trials that are designed primarily to demonstrate a prod-

uct's effectiveness. The alkaloid and antitussive substance codeine, for example, was switched back from OTC to Rx status in many countries between 2006 and 2010 due to reasons of abuse. Similarly, alkaloid and methamphetamine precursor pseudoephedrine and antitussive dextromethorphan are used for the composition of illegal drugs and therefore included in drug control enforcement lists or even banned from OTC usage in certain countries.

When evaluating a new drug to become available without prescription, benefits must outweigh risks. In the case of drugs for self-medication minor risks may be acceptable, whereas more serious ones might only be acceptable if drugs are targeted at the treatment of life-threatening illnesses. However, given the regulatory authorities' fear of switching drugs in doses higher than the lowest effective dose, it has to be taken into consideration that the OTC dosage – if lower than the therapeutic standard dose - might not be optimally effective (Friedman 1999). Thus, post-marketing surveillance must by all means become an integral part of drug regulation including the involvement of multiple stakeholders, such as pharmacy personnel and other HCPs, the pharmaceutical entrepreneur, and not least the patients themselves.

3.5.3 Key lessons and implications for future Rx-to-OTC switches

As can be concluded from above, there have been a rising number of switches since the Rx-to-OTC switch movement was started about sixty years ago. Interestingly, it has to be noted that so far every single switch has been different in nature and there seems to be no “one-size-fits-all” approach to a successful switch application. Yet, the analysis and evaluation of relevant Rx-to-OTC switches, including the case studies depicted above, fosters further knowledge and enables determination of both key success factors as well as remaining challenges, which will shortly be discussed in the following.

From an overall perspective, switches have first of all proven successful if they had a beneficial impact on public health as demonstrated by the example of the Rx-to-OTC switch of NRT which has resulted in both an immense amount of former smokers thereby preventing premature death as well as in a huge net health economic benefit (Keeler 2002; Shiffman 1997; Shiffman 2008). In particular, with respect to the targeted beneficiaries of a switch (i.e., patients and also HCPs as their advisers) a distinct added value provided by a specific switch has to be apparent and visible, such as the rapid relief of acute symptoms or the prevention of severe, (semi-)chronic diseases by successful self-management of associated risk factors.

Secondly, a drug newly switched to and communicated as self-medication fulfilling a so far unmet medical need will probably direct patients to pharmacies in order to address complaints they might not or only insufficiently have treated before (“silent sufferers”). A prominent example was the aforementioned reclassification of the antimycotic agent clotrimazole to treat vaginal mycosis (cf. Subsection 3.5.1 and Chapter 5). Another candidate definitely falling within this category would be an effective treatment for urge incontinence, for instance.

Thirdly, the availability for self-treatment with emergency hormonal contraception (see Subsection 4.4.2) or triptans to treat migraine exemplarily shows the importance of complying with patients' demand for increased and timely access as an essential element of a successful

Rx-to-OTC switch. Direct medical access including, at best, profound pharmacy consultation enables them to effectively relieve their symptoms in due time and carry on with their daily-life activities.

In her analysis “Rx-to-OTC switches: trends and factors underlying success”, Mahecha has identified four specific categories whose variable factors are estimated to have large influence on the outcome of a switch (cf. Figure 5). These categories are the “product” and its characteristics in terms of: efficacy, safety, etc., as well as brand recognition; the “company” and its marketing expertise and strategies; the “market” in terms of consumer/patient need, entrance time, and price positioning; and last but not least, and maybe most important, the “regulatory field” including factors like the available (clinical) evidence to support approval and at best case the provision of data (and market) exclusivity (Mahecha 2006). The role of data (and market) exclusivity as a general key success factor in the launch of new products or new indications, etc. and its justification for Rx-to-OTC switches will be dealt with in Chapter 4 ff.

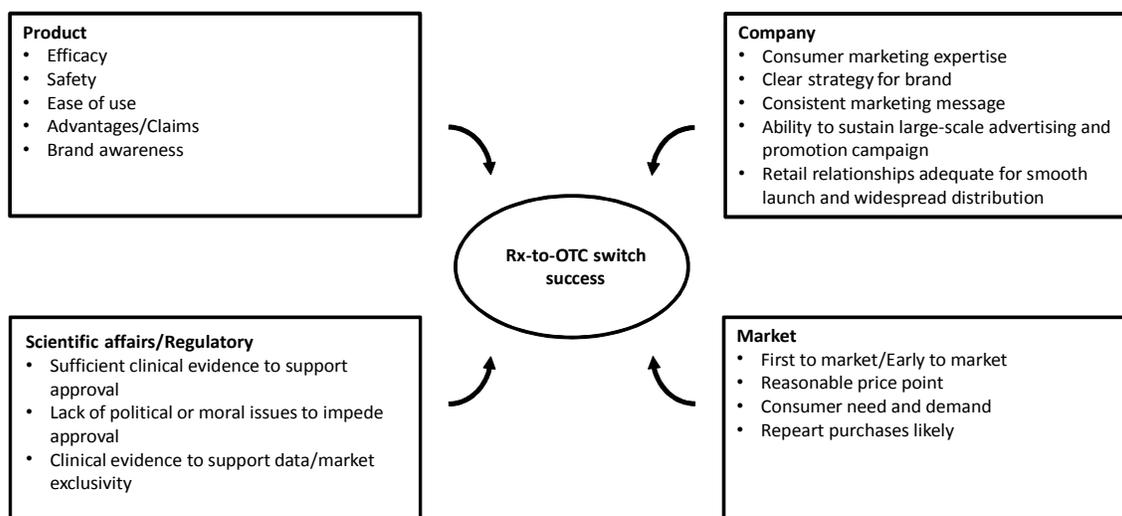


Figure 5: Factors contributing to successful and sustainable Rx-to-OTC switches (based on Mahecha 2006)

Referring to the “product” category, product differentiation certainly displays a critical determinant for a specific switch candidate to be sustainably established (Francesco International 2009). Other than the fundamental and naturally inherent pharmacological properties of a molecule that cannot easily be changed, there are various variables that might be added or modified to differentiate from competitors and provide meaningful benefits and features to consumers at the same time. Depending on the OTC competition including not only existing OTC products, but also other Rx products likely to be reclassified, meeting current category requirements must be standard. “Ideally, a switch should be better than the current OTC

product advantages with none of their disadvantages” (Francesco International 2009). In terms of medications, basically three main types of product benefits, namely efficacy, safety, and ease of use offer starting points for differentiation – OTC appropriateness and commercial feasibility provided.

Furthermore, crucial planning of a switch comprises the setup of adequate measures for monitoring and managing anticipated risks. Post-marketing surveillance of OTC products should encompass not only the implementation of a classical, robust, and easily accessible pharmacovigilance system facilitating (spontaneous) reporting of suspected AEs/ADRs, but also monitor for “upstream” behaviors that may put consumers at risk (e.g., use by inappropriate populations). This form of “behavioral surveillance” might be accomplished through accurately timed and intensive analyses of test market results, or consumer surveys, and might then be countered by educational advertising as well as appropriate risk minimization measures (e.g., restriction of age, pack size, etc.) (Shiffman 2008).

In addition, findings from further analyses allude to the central role of clear and comprehensive product information with regards to the various target groups and their individual risks. The labeling of OTC (switch) products has been ascribed an educational role and therefore is estimated to be critical for consumer/patient understanding as well as appropriate and compliant use in self-medication. In particular, a switch candidate’s safe, effective, convenient, and compliant use based on adequate labeling has to be imputed to regulatory affairs, on the one hand, and company activities, on the other (Juhl 1998). As depicted in Figure 6, these should be directed towards patients/consumers and mediated by HCPs including both doctors and pharmacy staff.

Information has to be presented in a way that patients/consumers can choose the appropriate medication on their own and use the medicine safely and effectively (WSMI 2009). “The hallmark of OTC drugs is not self-diagnosis, it’s self-treatment” (Peter Baron Hutt, expert on food and drug law) (White and Beall 2001). Labeling as the superordinate means of communication with the consumer should not only be legible and easily comprehensible. Accurate information on warnings and directions for use are imperative and self-evident (Stitching AESGP Foundation 2002). This means, appropriate specifications have to be worked out on the regulatory side and assiduously implemented by sponsoring companies. They might conduct so-called “label comprehension studies” (LCS) as well as observational actual use trials (AUTs) in order to continually improve labeling on the basis of insights in consumer understanding (Hemwall 2010; McCook 2007). The development of “test market” concepts as a general form of behavioral research has been suggested elsewhere to address case-specific (switch-related) questions as well as to affirm the identified target population and exclude potential risk populations, respectively (White and Beall 2001). In light of more complex switches being more often seen today, accompanying educational programs, most suitably personalized, have emerged as useful information and training tools. Prominent examples of recent switches using this kind of information kits are the aforesaid Prilosec OTC[®] and alli[®]. They provide assistance via mail, toll free phone lines, and/or internet. Apart from information and training on indication and medication use, such campaigns are designed

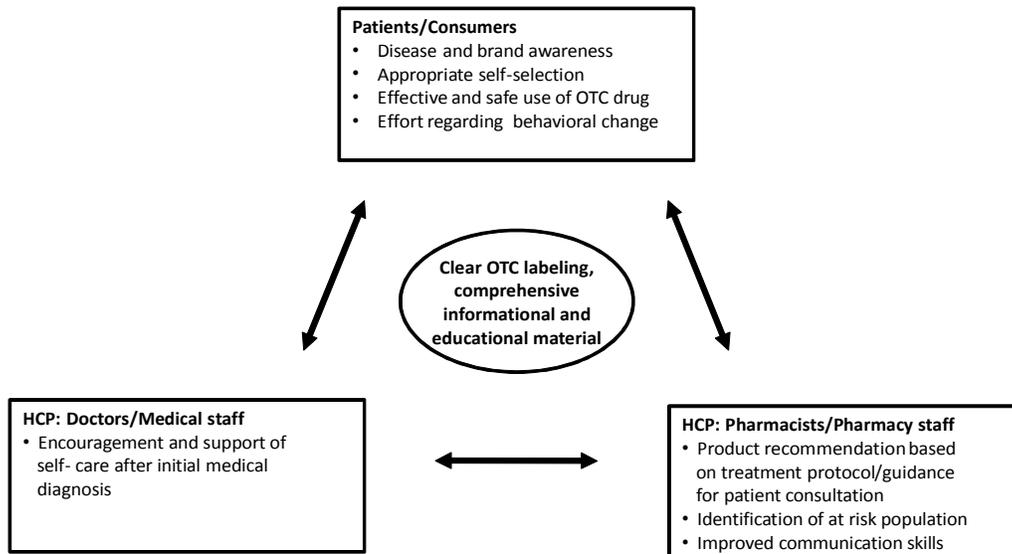


Figure 6: Central role of OTC label, product information, and communication to minimize individual patient risk

to create disease awareness, on the one hand, and consumers' action towards tackling their health problems, on the other. Advertising of NRT, for example, was explicitly targeted to “committed quitters” ready to quit and campaigns emphasized the importance of consumer efforts (e.g., Nicorette[®] Gum: “You can do it, Nicorette[®] can help”) (Shiffman 2008). Such programs are regarded to be a great educational opportunity with as much potential for a positive public health impact as the drugs themselves by not only informing but also driving consumers to consult a HCP, if applicable (Fuster and Mearns 2009).

Likewise, adequate information and support of HCPs is considered an essential Rx-to-OTC prerequisite. Imagining an increase of disease diagnoses initially made by a doctor, discussed with the patient, and treated by the latter on recurrence of symptoms, the important role of doctors in encouraging and supporting self-care activities becomes apparent. Stakeholder consensus about the targeted indication in self-medication has to be taken for granted to successfully implement such a collaborative care approach that might be necessary for specific indications switched from Rx to OTC. In the same way, this holds true for pharmacists as third key-player in this patient-doctor-pharmacist triangle. Pharmacists should not only receive comprehensive information and training on the product in advance and continuously during marketing phase, but should also acquire some practically relevant communication techniques (Stitching AESGP Foundation 2002). Recommendation and advisory procedures (e.g., of when to seek medical assistance) could be depicted in concrete treatment protocols or guidelines on how to conduct a consultative dialogue with patients. In this respect, the UK leads the way by its availability of pharmacy protocols for a number of indications. Moreover, these kinds of informational campaigns should be integrated into school curricula

and public education programs in the form of an intensive co-operation between academia, professional bodies, and manufacturers.

Last but not least, from a strategic point of view a possible reclassification of Rx products to self-medication should be an integral part of a product's life-cycle analysis and be initiated along with early stakeholder (regulatory, legal, HCP, etc.) buy in aiming at continued support and consensus regarding the targeted indication (MISG 2010; Stitching AESGP Foundation 2002). Within this context "short-term management thinking" is viewed as "enemy number one" (Francesco International 2009), as meaningful competitive advantages only result from well-timed and proactive planning and development of a switch project. Taking into account different developmental steps like competitive intelligence analysis, market research, and scientific/regulatory issues (dossier submission, review, and approval) as well as preparations regarding the switch product itself, the whole switch process is estimated to require 43-82 months from the managerial "go-decision" until the launch of the final product with an approved labeling⁸ (Francesco International 2009).

Regarding the other side of the coin (i.e., concerns and challenges to overcome in terms of Rx-to-OTC switching) drug safety is, of course, a major issue. Rare adverse events may only become manifest after many patients have taken the respective drug (MISG 2010). Specifically, in light of changing medication consumption patterns with a trend towards higher medication related to an ageing population, the problem of AEs including drug interactions might even get worse (Friedman 1999; Temin 1983). The potential risk of inaccurate self-diagnosis by patients possibly associated with a delay or even lack of needed therapy is another crucial element (Brass 2001; MISG 2010).

Additionally, compliance is a major issue referring to both potential mis-/abuse and inappropriate use by populations at risk (Shiffman 2008) eventually resulting in severe or even fatal outcomes and irregular use. Especially in the face of preventive treatments and mainly asymptomatic conditions, adherence to continuous therapy certainly is to be deemed an issue to tackle. Innovations in drug delivery systems as well as labeling, promotion, and pharmacy guidance can theoretically assist with that (Bond 2008; Choudhry 2005). Advances in technology, widespread availability, and acceptance of reliable, easy-to-use monitoring devices may equally contribute to a compliant, safe, and effective self-treatment of (semi-)chronic conditions (Brass 2001). One possible explanation for frequently observed non-compliance might be the fact that OTC drugs often are considered as ordinary commodity and less effective than prescription medicines (Bond 2008; White and Beall 2001). Creating and raising public awareness of the necessity to take OTC medicines with caution and respect is hence imperative (Bond 2008). Counseling and motivation by physicians has an important share in this context and should always be kept in the loop as there is justifiable concern that the loss of their role as prescriber might undermine physician engagement (Shiffman 2008). Increased resistance as a potential result of inappropriate medication use is another concern to be raised here, although even more on a public than an individual health level. OTC

⁸ This is, of course, also depending on the regulatory switch strategy/procedure chosen and the specific lead time needed by the regulatory body involved.

approval of acyclovir was denied partly due to this reason (Juhl 1998).

Furthermore, switching the appropriate dosage displays a main challenge. Trying to switch the lowest dosage possible for self-treatment due to safety reasons always bears the risk of being not effective, especially, if the switched dosage is below the standard therapeutic dosage (Euromonitor International 2010; MISG 2010). With people increasingly getting bigger in size, this issue has become a major concern for the industry, as dosing might not be as effective. Thus, the challenge of creating a “one-size-fits-all” approach to achieve a population-based benefit gets even greater, as future switches should rather tend towards customized dosing for appropriately addressing the effect of people’s different body sizes (Euromonitor International 2010; Hemwall 2010). Finally, in case of (central) European switches with the intention to launch the OTC product throughout entire Europe, there may be hurdles on a regulatory, political, and cultural level regarding the inevitably existing discrepancy among member states regarding approved indications and recommended OTC dosages as well as the different roles of pharmacists across Europe (MISG 2010; Stitching AESGP Foundation 2002).

3.6 Summary and conclusion

The reclassification of a drug and/or associated indication(s) from Rx to OTC status typically constitutes a scientific data-driven and highly regulated process. For a medicinal product to be granted OTC status, it must possess both a proven adequate safety margin and accordant effectiveness. Apart from that, easily understandable, consumer-friendly labeling is of utmost importance to ensure appropriate self-directed usage in the absence of medical guidance. Depending on the regulatory switch strategy chosen (i.e., national approval or approval in some or even all European countries) the process of Rx-to-OTC switch might take several months or even years.

As demonstrated by previous notable switches, a careful evaluation of the envisaged Rx-to-OTC switch based on scientific and economic conditions, the potential for explicitly affording added value to patients (backed by HCP recommendation, if applicable), meticulous planning and preparation including early and continued stakeholder involvement, as well as post-marketing surveillance and risk management strategies, have proven to be key requirements for a positive outcome of a switch approach in a short- and long-term perspective.

Given the above mentioned trend towards more complex switches, correspondent requirements associated with the planning, realization, and successful implementation of a certain Rx-to-OTC switch are constantly growing. In the author’s view, the option of drug reclassification should thus be integrated in a drug’s life-cycle development as early as possible. As regards the challenges remaining, companies will have to find creative and viable solutions enabling them to tackle issues such as, for example, compliance under OTC daily-life conditions or dealing with the diversity of pharmacy systems within Europe. However, according to the author, the latter will only gain momentum, if an appropriate political, legal, and regulatory environment is in place. Within this context “data exclusivity” has been set up as an institutional tool in European legislation to foster and reward compelling and innovative Rx-to-OTC switch approaches. The following chapters will shed a critical light on

the role of data exclusivity provision within the context of Rx-to-OTC switches in Europe at the present time. Potential issues identified will subsequently be discussed and possible proposals for solution will be elaborated.

4 Data exclusivity as important success factor for Rx-to-OTC switches

The following section will begin with the description of data exclusivity within the context of prescription drugs. Essentials will subsequently be assigned to the situation of Rx-to-OTC switches (see Section 4.4 ff.).

4.1 Definition of data exclusivity^{9,10}

As the most valuable asset for a research based company is its research data, it is quite obvious that adequate protection of a company's research based data is vital to its owner (Dodds-Smith 1996). In addition to other forms of data protection like patents, data exclusivity represents an important form of intellectual property for innovators providing incentive to invest in the development and marketing of new product candidates (Grabowski 2008). Basically, pharmaceutical products can be protected against generic competition in two ways: by means of patents and/or data exclusivity (Adamini 2009). As overlapping and complementary forms of intellectual property (Adamini 2009; Grabowski 2008) both are awarded independently (Junod 2004).

Patents usually are applied for in the pre-clinical or early clinical phase of the development process and as a rule they are granted for "true" innovative inventions based on the criteria of novelty, utility, and non-obviousness giving the holder the right to exclude others from making, using, selling, or importing the protected product for the duration of patent protection.

In contrast, the instrument of data exclusivity recognizes a research company's substantial investments essential for regulatory approval by preventing generics from immediate accelerated market entry (Clift 2008). "Ideally, data exclusivity would delay abbreviated [generic] filings and patent challenges until innovators have had an opportunity to earn a positive return on the new therapeutic candidates [...]" (Grabowski 2008). In essential, by definition, "data exclusivity for a specified period prohibits a regulatory authority from affirming the

⁹ In fact, the term "data exclusivity" refers to the exclusive right to use proprietary information in support of an application for a defined period of time whereas the term "market(ing) exclusivity" refers to the exclusive right to market a product. The exclusivity period based on data exclusivity legislation is thus normally longer than the one based on market exclusivity legislation due to the necessity that competitive products first have to be authorized after expiry. Both terms, however, are encompassed by the term "data protection" (WSMI 2009).

¹⁰ The terms "marketing exclusivity", "market exclusivity", "new product exclusivity", "Hatch-Waxman exclusivity", "sui generic protection", "data exclusivity" and "data protection" are all found in the relevant US and/or EU legal literature. The US exclusivity system is mostly referred to as "market(ing) exclusivity" whereas both the terms "data exclusivity" and "data protection" are more frequently used in the EU system (Friedman 1999; Sanjuan 2006).

safety [and efficacy] of a bioequivalent generic by using the pre-clinical and clinical trials data submitted when a product was initially registered. Central to this approach is the idea that the initial sponsoring company paid for the trials and thus owns the data, though the trials were done for a public authority and for a public purpose” (Adamini 2009). Data exclusivity comes into force with approval once the safe and effective use of the concerned drug candidate has been proven. Compared with patents, it is generally associated with less administrative and procedural burden (Junod 2004).

As mentioned above, pharmaceutical companies have the possibility to call upon patent and data exclusivity in a cumulative way due to the fact that they are granted independently from each other. Hence, after a drug’s patent expiration the provision of data exclusivity might ensure further protection difficult to be challenged by reason of its mediation by authorities (Junod 2004).

4.1.1 The notion of reliance

As depicted above, data exclusivity prevents second applicants for a certain period of time from relying on original data of the reference drug generated for the sake of demonstrating safety and efficacy. In the US as well as in Europe, “reliance” is understood as direct or indirect “use” of the pioneer’s proprietary data. In practice, a second entrant’s reliance would be only indirect as it is liberated from generating the same data as the originator in order to prove safety and efficacy of a similar drug seeking marketing approval (Junod 2004).

As a consequence, unlike patent right protecting the product itself, data exclusivity is not a right that pioneer firms can invoke directly against generic firms (Sharma 2007). That is, if during the limited period of data exclusivity a second entrant generates its own data supporting the safety and efficacy of its own drug, the entrant is not banned by data exclusivity. The entrant is thus able to get marketing approval on the basis of his own data – a long and highly costly process though which is usually avoided in favor of market entrance after the period of exclusivity has expired (Gorlin 2000; Junod 2004). Moreover, next to the mere economic and practical reasons, objections are to be raised from an ethical point of view, as it is deemed unethical to replicate the testing of drugs both on animals and humans (Sanjuan 2006).

Of note is, however, that in the case of an abridged so-called “informed consent” application both the US and the EU entitle a second applicant with the right of referring to and relying on the originator’s data before the data exclusivity period has expired (Junod 2004).

4.2 Data exclusivity in practice

The protection of regulatory test and study data is considered as a relatively new form of independent intellectual property rights. In the mid-1990s it was first recognized internationally and has since been legally required by both the North Atlantic Free Trade Agreement (NAFTA, Article 1711) and Article 39.3 of the World Trade Organization’s (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (“TRIPS Agreement”) (Pugatch 2004). The provisions intend to protect undisclosed pharmaceutical test data from

so-called new chemical entities (NCEs) that required “considerable effort” to be generated against disclosure and “unfair commercial use” in order to provide incentives for the development of innovative pharmaceutical products (Gorlin 2000; Sanjuan 2006). Unfortunately, many countries currently still fail to provide accordant data exclusivity with non-compliance ranging from total absence to an effective scope which is only limited (Gorlin 2000).

Even if not mandatory based on its correct interpretation (Sharma 2007), industry groups and certain developed countries, such as the US and the EU, have argued that TRIPS Article 39.3 charges countries with the setup of a data exclusivity regime as a form of time-limited intellectual property right with both of them having adopted data exclusivity regimes for medicinal products even prior to the TRIPS Agreement (see Subsections 4.2.1 and 4.2.2) (Clift 2008; Sharma 2007). Interestingly, these models do not fall under the category of trade secrets though, as they are rather an inseparable part of the regulations concerning the approval of pharmaceutical products (Pugatch 2004).

4.2.1 Data exclusivity in the United States

Until 1984, a trade secret protection regime quite limited in scope constituted the only US protection for an applicant’s unpublished safety and efficacy data (Sanjuan 2006). In 1984, data exclusivity was introduced with the “Drug Price Competition and Patent Term Restoration Act” amendment – commonly named after its sponsors (i.e., “Hatch-Waxman Act” (Clift 2008)). It is now codified in FD&C Act Section 505 (i.e., Title 21 U.S. Code (U.S.C.) § 355 ¹¹, respectively (Pugatch 2004)). Related implementing regulations are provided by § 314 of Title 21 of the Code of Federal Regulations (CFR) (Dickinson 1999). In principal, there are two main categories of marketing or data exclusivity to be granted depending on the kind of drug application (Junod 2004):

- a five-year period of data exclusivity can be obtained for drug products based on NCEs, meaning the drug does not necessarily have to constitute an innovation or represent a significant therapeutic advance, but must contain an active moiety never approved by the FDA ever before alone or in combination (Sanjuan 2006).
- a three-year period of marketing exclusivity is awarded for drugs already approved for which essential clinical test data were submitted to support new or supplemental new drug applications (e.g., new indications, changes affecting active ingredients, strength, dosage form, route of administration, etc.). However, an important limitation of this kind of exclusivity is that it only protects these specific “additions” without the uses or indications already established.

Specific conditions have to be fulfilled by a pharmaceutical company to benefit from this three-year market exclusivity, such as, for example, the conduct or sponsoring of clinical trials essential for the approval of the application (at least 50 % of study costs). In this regard, the FDA has set up only vague definitions of the kind of data to deliver

¹¹ cf. <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec355.pdf>, last accessed 2013-08-05

except for the fact that “significant innovations” and clinical investigations “vital to the application or supplement” are required (Junod 2004; Sanjuan 2006).

In contrast to the five-year exclusivity, during the three-year exclusivity period the FDA is allowed to receive and review further applications (often in the form of so-called “abridged applications” implicating that the applicant does not have to replicate the original data but can refer to these). In case of a positive decision, approval will become effective immediately after expiry of the three-year exclusivity period offering second applicants the opportunity to directly enter the market.

Both types of exclusivity often are combined, that is, a five-year data exclusivity is often followed by a three-year period when it is about to expire. Consequently, the total period of exclusivity is maximized by this sequential addition. In terms of eligibility, it is the FDA which autonomously decides whether the conditions for exclusivity are met (Junod 2004).

4.2.2 Data exclusivity within the European Union

Within Europe, the origin of data exclusivity dates back to 1987 and has been a Community affair ever since. Before that time, the EU data protection regime basically was made up of a trade-secret regime considerably varying from country to country (Sanjuan 2006). Historically, a system of data exclusivity was introduced to allow some form of protection to research-based pharmaceutical companies in EU member states, such as Spain or Portugal, not endowing pharmaceuticals with any patent protection until 1992 (Junod 2004). Provisions on data exclusivity were first included in EU Directive 87/21/EEC, affording six years of data exclusivity to the majority of pharmaceuticals as of the issue of the first marketing authorization in any EU member state and ten years for biotechnology and high-technology medicinal products. In 2001, precursor directives were consolidated in a single Community Code, Directive 2001/83/EC, governing the current EU data exclusivity regime and amended in 2004 by Directive 2004/27/EC (Adamini 2009; Garland 2007). The 2004 amendments with the objective to strengthen EU competitiveness in the pharmaceutical industry (CMS 2007) constitute a “compromise package” resulting from lengthy negotiations among the European Parliament, the Commission, and the Council initiated in 2001 within the so-called 2001 Pharma Review process (Junod 2004). Data exclusivity was a key topic of the review with the main objective to harmonize national differences in length among EU member states (Adamini 2009; Junod 2004) against the background of striking a balance between the interests of brand-name industry, on the one hand, and generic industry, on the other (Bogaert 2005). Whereas the latter strove for minimization of the period of data exclusivity, the brand-name industry – appealing to the US exclusivity system - lobbied for a harmonized upward-extension as well as a broadening towards secondary uses or other variations (Junod 2004).

The most significant changes and compromises introduced for implementation include the following:

- “8+2+1 formula” for new drugs

This term refers to the fact that new drugs approved within the EU either via cen-

tralized or decentralized procedures will be able to benefit from eight years of data exclusivity as of their first marketing authorization with generics prohibited from relying on corresponding original data until this period has expired. A new term - “market exclusivity” - was introduced at the same time alluding to the prevention of generic firms during two additional years from marketing a generic product although their (abridged) applications may already be processed after expiration of the eight-year period of data exclusivity. Hence, generic market entrance is not possible before ten years of marketing the originator’s drug product have passed, but there is a two-year window during which bioequivalence testing may be carried out. In case of “new therapeutic indications” with significant clinical benefit in comparison to existing therapeutic options, market exclusivity might be extended by one additional year if applied for during the eight-year period of data-exclusivity (Adamini 2009; Garland 2007; Junod 2004). Importantly, contrary to the US system, this extension of market exclusivity is to cover the product as a whole (i.e., both “new” and “old” uses) (Generics Bulletin 2004). Another crucial distinction from the US system, where a three-year exclusivity may be granted for new uses/applications, etc. of a drug, is the EU’s 2004 legislative assignment that all variations and line extensions of an initial marketing authorization as well as any other additional strengths, pharmaceutical forms, administration routes, etc. granted to the holder of the initial authorization are considered to belong to the same “global marketing authorization” and, therefore, these changes are not awarded any data protection (Bogaert 2005; Sanjuan 2006).

- “Bolar Scheme”

Whereas in the US generics are enabled to conduct research before the relevant patent has expired, this was not possible in the EU until 2004 due to patent infringement. In order to put the EU system in line with the US regime, the 2004 Directive now allows for generic makers conducting their own specific studies viewed as necessary with respect to approval of a certain drug marketing authorization, even during the lifetime of the relevant patent to enable them to demonstrate bioequivalence prior to patent expiry (Adamini 2009; CMS 2007; Garland 2007; Junod 2004).

- Definition of “generic medicinal product”

Directive 2004/27/EC for the first time comprises an explicit definition of a generic medicinal product with respect to the terms “active substance” and “pharmaceutical form” (Bogaert 2005), as the hitherto valid concept of “essential similarity” raised important questions due to its vague formulation (Kingham 2000). According to Article 10(2)(b) a generic medicinal product “has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, [...] whose bioequivalence [...] has been demonstrated [...]. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly [...] with regard to safety and/or efficacy. [...]”. This definition offers further, although still not ultimate, clarity (Bogaert 2005; Junod 2004) as to

when a drug qualifies for the abridged procedure in case of expiration of a pioneer drug's exclusivity period (Adamini 2009; Garland 2007).

- “European reference product” and “Historical reference principle”
The new provision of “European reference product” allows generic applications to refer to products licensed in any other member state (Generics Bulletin 2004). Additionally, the “Historical reference principle” authorizes generic companies to equally develop similar products of original pharmaceuticals that had previously been (i.e., had been approved for at least eight years) but are no longer on the EU market (Adamini 2009; Bogaert 2005).

However, despite of the effort to bring about further clarification, Bogaert and Michaux identified major outstanding issues in their analysis of the reviewed legal framework (Bogaert 2005) with one of them being, for example, the lack of clarity if an abridged marketing authorization can be granted during the aforementioned period of market exclusivity. The current provisions only state that a generic product is not to enter the market during that time. Sound reasons are in favor of this authorization to only be valid at the end of the market exclusivity, yet this issue is not without ambiguity. If it is granted before, control mechanisms will be required to prevent marketing steps to be taken.

4.3 The rationale of data exclusivity provision

When developing a drug, originator companies often have to cope with high-risk, temporal, and costly investments in connection with innovations that result in completely new drugs or the further development of an already existing drug. Research intensive pre-clinical and clinical study investigations often lasting over several years are needed to generate the data required by regulatory authorities for first time approval. Additionally, in many cases the delay between patent filing and final regulatory approval of a marketing authorization correspondingly reduces the number of years of protection remaining for the product to recoup associated investments (Clift 2008). In contrast, generic pharmaceutical manufacturers can achieve marketing approval of a certain drug without the need of engaging in similar significant research and development expenditures. Innovators, therefore, seek to obtain the broadest patents for their drug to be protected against generic invasion.

On the other hand, more and more drug products are developed these days without being eligible for patent protection due to the lack of a “true” innovative character. Many of them rather represent line extensions or other variations (e.g., fixed dose combinations, etc.) according to a product's life-cycle management. In this case, non-patent data exclusivity plays an important role for the pharmaceutical industry (Junod 2004), as it constitutes a valuable alternative means to protect proprietary data and interests against unauthorized use and disclosure.

The Organization for Economic Co-operation and Development (OECD), among others, strongly encourages the award of data exclusivity periods due to the following reasoning: “Data exclusivity recognizes the innovator's investment in conducting the rigorous pharmaceutical, toxicological and clinical trials necessary to establish the safety and efficacy of new

drugs before they can be provided to patients” (Garland 2007). “The central justification for data exclusivity is that, as with patents, the longer an innovator company enjoys protection from price competition (i.e., market exclusivity), the greater its incentive to innovate” (Adamini 2009). “Without a data exclusivity period, there would be little incentive to invest in developing and marketing new product candidates with few remaining years of patent protection or with uncertain forms of protection” (Grabowski 2008).

Data exclusivity nowadays is thus seen as a principal instrument to maintain pharmaceutical research and development by extending market protection for new indications, pharmaceutical forms, and other variations¹² in order to reward pharmaceutical companies for investments taken in hand for approval (Junod 2004).

4.4 Data exclusivity for Rx-to-OTC switches

The present chapter will deal with legal conditions for and practical examples of data exclusivity provision for Rx-to-OTC switches.

4.4.1 Legal framework in the US

In the US, based on the provisions deduced from the aforementioned Hatch-Waxman Act and implemented in § 314 of Title 21 of the Code of Federal Regulations (q.v. 21 CFR 314.108), switch applications might be eligible for a three-year period of marketing exclusivity (see also Subsection 4.2.1) provided that new clinical data considered essential by the FDA is available and investigations are conducted or sponsored by the applicant (Cullen 2007; WSMI 2009). Importantly, as not all data are automatically viewed as essential, these data have to prove significance for the approval of the switch application either regarding safety and efficacy/effectiveness of the drug itself, or with respect to diagnostic measures, for example (Fish 2010). As mentioned before, FDA guidelines - like those of the EU - do not identify or arrange for a mechanism of how to conform to its quite indefinite requirements (Junod 2004). However, contrary to the EU, exclusivity has already repeatedly been granted to Rx-to-OTC switch applications in the US and published switch application documentation might thus give a clue on the kind of data potentially relevant within the context of exclusivity provision in the US.

4.4.2 Practical examples of data exclusivity application for Rx-to-OTC switches in the US

The following two case studies will serve to depict the conditions of data exclusivity assignment within the context of Rx-to-OTC reclassification in the US.

Levonorgestrel 0.75 mg (Plan B[®], Duramed Research Pharmaceuticals). The supplemental new drug application (sNDA) for Plan B[®] (levonorgestrel 0.75 mg tablets) was first submitted to the FDA under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act in

¹² unless coming under an existing “global marketing authorization” within the EU and therefore not eligible for data protection (see also Subsection 4.2.2)

April 2003. After rejection of this application by the FDA in May 2004 based on “inadequate sampling of women under 16” (Johnson et al. 2006), Plan B[®] was at last successfully reclassified to OTC on August 24th, 2006, for women of the age of 18 or older after agreement on certain commitments to be followed by the applicant.

Plan B[®] is an emergency hormonal contraception drug to prevent pregnancy commonly also known as “morning after pill” containing the active ingredient levonorgestrel, a hormonally active second generation synthetic progestogen (Camp et al. 2003; Trussell and Cleland 2007). Even though any drug product comprising other forms of the same active moiety as the drug under consideration had already been approved under Section 505 of the FD&C Act, this particular form of the active moiety for which the application was submitted had not previously been approved by the FDA. Three years of exclusivity were claimed in line with the application for changing the drug’s legal status. Due to the list of published studies demonstrating safety and effectiveness not being sufficient and satisfactory for approval, the applicant submitted two new clinical investigations deemed essential for approval that had not been relied upon by the agency before and that did not duplicate the results of other investigations relied on by the agency to demonstrate the effectiveness of a previously approved drug product (i.e., did not re-demonstrate something the agency considered to have been demonstrated in an already approved application). Both studies fall under the definition of “behavioral studies” with the first one being a label comprehension study testing consumers’ understanding of the product label (cf. also Subsection 3.5.3) and the second one demonstrating actual use in a simulated OTC setting (actual use trial) with repeat use, occurrence of pregnancy and adverse events as secondary objectives. Both studies have been published in the relevant literature (Raymond 2002; Raymond 2003).

According to the effective legal requirements (q.v. Subsection 4.4.1), the applicant had been identified as sponsor of the respective studies. Therefore, the FDA granted three years of exclusivity for the OTC approval of Plan B[®] (levonorgestrel 0.75 mg tablets) based on the provisions laid down in the Code of Federal Regulation.

Orlistat 60 mg (alli[®], GlaxoSmithKline) In June 2005, the pharmaceutical company GlaxoSmithKline submitted a sNDA for alli[®] (orlistat 60 mg capsules) to the FDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act requesting its nonprescription use for weight loss in adults of 18 years and older when used with a reduced-calorie, low fat diet, and an exercise program.

Orlistat, also known as tetrahydrolipstatin, is a lipase inhibitor acting locally in the intestinal tract. As saturated derivative of lipstatin, a potential natural inhibitor of pancreatic lipase, it was primarily designed to partially prevent dietary triglycerides from hydrolysis and absorption by binding to pancreatic lipase in the small intestine (Schwartz et al. 2008). Caloric intake is thus reduced, especially as orlistat is strongly recommended for use in combination with a calorie-reduced diet.

The application was approved on February 7, 2007, for use as recommended after commitment to and completion of FDA required actions based on its review of the original submission (e.g., accomplishment of a label comprehension and self-selection study including subsequent

adaptation of the labeling, etc.). The study data handed in partly cross-referenced to the original application of orlistat 120 mg capsules, published literature data, and was complemented by new study data intended to simulate OTC usage.

Within its application, GlaxoSmithKline also requested a period of exclusivity of three years under 21 CFR 314.108(b)(4)(iv). This claim was based on two clinical investigations considered essential for approval - a weight loss study in primary care setting of four months duration and an AUS simulating OTC setting of three months duration. Both investigations had not been relied upon by the FDA to demonstrate effectiveness of a previously approved drug product and examinations did not duplicate the results of any investigation previously referred to by the agency for supporting potency of a formerly approved drug product. In the actual use trial which was conducted in co-operation with 18 community pharmacies and which was published in 2008, customers were to decide on the appropriateness of orlistat 60 mg for self-treatment with only very little pharmacist assistance. Consumers gave their consent to participation in the study about the purchase of the product in a “real-world setting” and were then followed-up during three months by regular telephone interviews being asked about product use, occurrence of AEs, use of educational material, doctor/pharmacist interaction, multivitamin use and satisfaction with the product (Schwartz et al. 2008). Overall, 237 participants purchased and made use of the product. Approximately 80 % of subjects took account of the educational material placed at their proposal and found it useful. The same percentage indicated being satisfied with treatment effect. In conclusion, orlistat 60 mg proved to be an appropriate weight loss treatment in OTC environment. The weight loss study was a double-blind, randomized, placebo controlled, parallel group, phase III clinical efficacy study in a primary care setting of four months duration. It is unclear why study duration was limited to four months. Subjects ($n = 195$ placebo t.i.d.¹³ vs. $n = 196$ orlistat 60 mg t.i.d.) were overweight with a body mass index (BMI) of 25-28 kg/m². Interestingly, 94 % of study participants were female. Average age was about the same in both placebo and verum groups (46.5 yrs and 45.8 yrs, respectively). Overall, results were not different from pooled results of other efficacy studies submitted and statistical significance versus placebo was only given with respect to a 3 % and not to a 5 % weight loss (FDA 2006b).

Nevertheless, the applicant had been identified as sponsor of both studies and was granted three years of exclusivity for the classification of alli[®] (Orlistat 60 mg capsules) as OTC drug product based on the aforementioned study data.

4.4.3 Legal framework in the EU

In the EU, a draft version of Directive 2004/27/EC amending Directive 2001/83/EC primarily envisioned a data protection period of three years for marketing authorizations of drug products envisaging a change of classification, but this was reduced to one year at the final stage of approval (WSMI 2009). Finally, the following wording has been passed in Article 74a, Directive 2001/83/EC, introduced by Article 54, Directive 2004/27/EC:

“Where a change of classification of a medicinal product has been authorized on the basis

¹³ t.i.d. = “ter in die” (Lat.) meaning “three times a day”

of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.”

This means that generic versions of the switched product can be marketed if the legal requirements to submit an abridged application are met (q.v. Subsection 4.2.2). However, in contrast to the reference product it will not be available OTC but prescription-only during one year after the switch of the originator’s pharmaceutical product (Bogaert 2005).

As is the case for every European legislative directive, the new legislation approved by the European Commission had to be transposed into national law, namely until October 30, 2005, at the latest. The provision applies in relation to the results of tests or trials which form the basis of valid applications for reclassification received on or after January 1, 2005, including both variation applications and applications for new reclassified marketing authorizations.

The one-year data exclusivity period under Article 74a is a stand-alone period of protection. It can be granted independently from any other periods of data protection (European Commission 2006a). However, in the UK, for example, the MHRA as competent authority has decided that the principle of additional exclusivity as applied by various exclusivity provisions within the reviewed legislation is affirmed only once per global marketing authorization (see also Subsection 4.2.2). The one-year period of data protection starts from the date of the issue of the authorization or variation affecting the reclassification, not the date on which the pharmaceutical product is first placed on the market. Only one year after the date of grant of the authorization or variation the competent authority of the concerned member state is allowed to refer to the originator’s data when examining a reclassification application by another applicant for the same substance, whereas applications referring to these data will not be scrutinized during the period of data exclusivity (MHRA 2005).

A so-called “Notice to Applicants” (NTA) has been prepared by the European Commission in consultation with member states to give some guidance on the procedures related to the receipt of a reclassified marketing authorization. Correspondingly, “a report justifying that [the] application includes significant pre-clinical tests or clinical trials which have been carried out in relation to this change of classification” has to be submitted. This report should be not more than five to ten pages of length and include:

- a summary of the tests and/or trials conducted in relation to the switch of classification as well as
- a justification why these tests and/or trials should be considered as significant.

Related study reports and literature references should be inserted in the relevant places of the dossier and cross-referenced to accordingly. A reference to the “Guideline on changing the classification for the supply of a medicinal product for human use” is equally requested (European Commission 2008).

4.4.4 Practical examples of data exclusivity application for Rx-to-OTC switches in Europe

Three recent Rx-to-OTC reclassifications within Europe - two centralized and one national - will be analyzed below with particular attention regarding eligibility of the data submitted in order to award protection through data exclusivity.

Orlistat 60 mg (alli[®], GlaxoSmithKline) As previously mentioned (cf. Subsection 3.5.1), the central European Rx-to-OTC switch application of orlistat 60 mg hard capsules indicated for “weight loss in adults who are overweight ($BMI \geq 28 \text{ kg/m}^2$) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet” under the alli[®] brand was the first to be approved by the EMA in January 2009 based on a CHMP recommendation after review of data on quality, safety and efficacy and careful benefit-risk evaluation in the proposed indication and dosage strength (EMA 2009a).

Before the switch, the product as presented on the European market as a prescription product consisting of orlistat 120 mg hard capsules. The active substance used in the requested 60 mg line extension is identical to the one of the already approved alli[®] 120 mg capsules (Xenical[®]). As the latter already had been authorized via central procedure, reclassification of alli[®] 60 mg was automatically eligible for assessment through the central Community procedure.

Besides quality specifications and details regarding non-clinical aspects (which could be derived from existing Rx data) generally required in the case of (new) drug applications, the applicant submitted some clinical studies supporting efficacy/effectiveness of the proposed dosage strength of 60 mg in the target indication. Whereas three pivotal studies originated from the initial Rx marketing authorization application of orlistat 120 mg in which 60 mg also had been tested in comparison, two additional supportive studies included data on the real-life use of orlistat 60 mg. These behavioral studies were conducted in the US, where orlistat 60 mg already has been OTC since 2007. Based on study data, both refinement of target indication/population from $BMI \geq 25 \text{ kg/m}^2$ to $\geq 28 \text{ kg/m}^2$ and labeling changes had to be carried out by the applicant to ensure a satisfactory effect as well as appropriate self-selection by the target population. Apart from that, clinical data was considered relevant and sufficient to support the extension of the marketing authorization in the proposed indication. In terms of safety, five studies were handed in for the initial application of orlistat 120 mg as prescription drug including data regarding the lower strength, as well as three additional US studies with orlistat 60 mg capsules. Furthermore, post-marketing experience worldwide was evaluated. Given the cumulative safety experience of orlistat 120 mg and post-marketing experience of orlistat 60 mg in the US, the CHMP finally agreed upon its favorable safety profile compared to 120 mg (less withdrawals due to AEs in pivotal studies) after having suggested some additions to the product information (i.e., amendments in the section of contraindications and AEs as well as advice with intake). As far as pharmacovigilance is concerned, a detailed so-called risk management plan (RMP) was added including proposed pharmacovigilance activities (i.e., routine actions and scheduled cumulative review of AE reports, so-called Periodic Safety Update Reports (PSURs)) as well as risk minimization activities (routine activities, warnings in product information) depending on the

characteristics of identified risks. No additional risk minimization activities were required based on consideration by the CHMP. Residual concerns regarding an increased risk of delayed diagnosis and treatment of underlying conditions as well as potential for incorrect use were addressed through demonstration of the results of consumer surveys showing a high rate of patient physician interaction in the target population and data from the US experience with alli® 60 mg as a nonprescription medicine. Finally, after the applicant's proposal of further strengthening information on the labeling and package leaflet by incorporation of a medical reference for a general health check and consultation in the case of co-morbidities, the CHMP recommended the classification of alli® 60 mg to "medicinal product not subject to medical prescription".

Additional clinical studies (one weight loss, i.e., clinical efficacy study, and one actual use trial, as well as two consumer surveys from the US and Europe, respectively) were submitted with the intention to claim one year of data exclusivity. The CHMP reviewed the data taking into account the provisions of Article 74a of Directive 2001/83/EC, as amended, and concluded it not to be relevant and thus not eligible for one-year data exclusivity. Both the weight loss and the AUT were identical with those exclusivity had been granted for in conjunction with the Rx-to-OTC reclassification in the US. According to the CHMP, both studies were not considered relevant and necessary for demonstration of both efficacy and safety of the reduced strength. This opinion was based on the inaptness of studies to provide additional value and insights due to study designs, on the one hand, and already existing study and post-marketing data, on the other. Original clinical study data from the initial Rx marketing authorization for orlistat 120 mg had already confirmed the preservation of efficacy under the reduced strength of 60 mg with at the same time fewer and less severe undesirable adverse effects recognized. Forthcoming clinical study data as well as post-marketing data for orlistat 120 mg and 60 mg from the US have further supported the overall safety profile rendering the generation of new safety/efficacy data for the respective switch application of orlistat 60 mg superfluous. However, the reason why the submitted consumer surveys were not eligible to be considered in light of exclusivity provisions was not clarified (EMA 2009a). Of note, instead, important insights into its "appropriate safe and effective use in a nonprescription setting" obviously were expected from the applicant's commitment to survey both EU alli® users' demographic and clinical characteristics as well as their individual usage patterns (EMA 2009a).

In conclusion, based on a comprehensive review of data on quality, safety, and efficacy, the CHMP, by majority, considered the benefit-risk balance of alli® 60 mg favorable for OTC usage in the proposed indication and therefore recommended an extension of the marketing authorization. However, taking into account the exclusivity provision of Article 74a, Directive 2001/83/EC, as amended, the CHMP did not consider the clinical data submitted by the applicant as significant and essential for the respective reclassification, due to their inability to yield additional relevant findings.

Pantoprazole 20 mg (Pantoloc Control®, Nycomed) The agent pantoprazole belongs to the pharmacological class of proton pump inhibitors - substituted benzimidazoles which act

by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (“proton pump”) of the gastric parietal cell. As terminal stage in gastric acid secretion, inhibition of proton pumps results in effective and lasting reduction of acid production. Therefore, PPIs are considered the most potent substance class for acid inhibition to date and have displaced H₂-blockers as therapeutic standard medication to treat acid-related disorders including gastro-esophageal reflux disease (cf. Subsection 3.5.1).

The pan-European switch of Pantoloc Control[®] 20 mg gastro-resistant tablets with the active ingredient pantoprazole 20 mg indicated for “short-term treatment of reflux symptoms (e.g., heartburn, acid regurgitation) in adults” was the second switch within Europe based on a central application and was approved in June 2009. Eligibility was grounded on the demonstration of “interest of patients health at Community level” due to the fact that the wish for an optimal self-treatment of heartburn is universal and valid for patients across the whole Community. A harmonized nonprescription pantoprazole product would enable Community-wide access as well as consumer protection, based on harmonized labeling avoiding diverted markets. The request was based on a so-called “hybrid application” meaning that it referred to already approved products but that - compared to these - changes in the therapeutic indication were applied for supported by the results of appropriate non-clinical and/or clinical trials (EMA 2009b). Overall treatment duration without doctor consultation was suggested to be limited to four weeks and in case of continuous therapy to two weeks, respectively. Product quality characteristics were tested and demonstrated satisfactory. Concerning non-clinical aspects, a comprehensive overview of pharmacological, pharmacokinetic, and toxicological aspects was provided based on published information and data available for the reference product such that, in accordance with the evaluating committee, no additional data had to be provided in support of the application. Moreover, no bioequivalence data were required, as the medicinal product applied for and the reference product are identical in regards to qualitative and quantitative composition as well as manufacturing itself.

In relation to clinical aspects, however, appropriate clinical data supporting the proposed change in indication had to be submitted. Heartburn and acid regurgitation are considered as cardinal symptoms of GERD and 17 clinical studies were filed including the treatment of symptoms in patients with GERD as primary or secondary endpoint. In these studies the use of pantoprazole 20 mg, either compared to placebo or another PPI/H₂-blocker, within the first 14 days of symptomatic treatment of GERD at any stage, was investigated. Apart from showing the superiority of pantoprazole 20 mg to the placebo and the H₂-antagonists, and the non-inferiority to other PPIs as well as pantoprazole 40 mg and 80 mg at most time points, results demonstrated an onset of clinical effect within seven days (up to 80.6 % symptom relief after day seven) more or less independent of the initial GERD stage. The latter is crucial with a view towards self-medication, where the severity of GERD is not explicitly determined as treatment generally is performed prior to medical endoscopic diagnosis. A self-medication setting was also mimicked by one study which encompassed patients exclusively based on the presence of reflux symptoms without endoscopic examination. No dose-finding studies were performed. Likewise, no clinical studies or study analyses were performed in special populations in support of the application. In response to the CHMP’s request for study data

of pantoprazole 10 mg as lowest available dosage strength, one accordant study was identified pointing out to, however, 20 mg as more consistent and satisfactory in terms of symptom relief. In turn, the CHMP then acknowledged and agreed on the efficacy/effectiveness and safety of the 20 mg dose as being appropriate for the proposed indication in a nonprescription status.

Safety was evaluated based on reviewing the applicant's worldwide clinical trial database and post-marketing surveillance data concluding with a benefit-risk consideration for nonprescription status. As far as safety in special populations is concerned, special safety and pharmacokinetic studies were performed during Rx drug development reassured that pantoprazole is safe in elderly and renal- or liver-impaired patients. Neither children nor women during pregnancy or lactation are included in the target group of the current OTC application. In light of the long safety record in Europe since its introduction in 1994, the CHMP agreed that the nonprescription application of pantoprazole 20 mg does not require a risk management plan. Moreover, it is based on a reference product which has been widely used in Rx setting and mandates no additional risk minimization activities in terms of direct danger. "Indirect danger" of potential masking of underlying serious conditions was considered minimal in relation with adequate product information. Results from a published actual use study with OTC omeprazole from the US (Fendrick 2004) were used to show appropriate self-assessment and self-selection. User-tested package information leaflet and labeling were judged adequate with respect to the safe and effective use of the medicine including appropriate guarding for potential misuse. Overall, the CHMP concluded the documented use of pantoprazole 20 mg as relevant for the proposed indication and thus considered its supply as nonprescription medicine appropriate.

Referring to Article 74a of Directive 2001/83/EC, as amended, the applicant requested one year of data exclusivity on the basis of 6 unpublished studies out of the 17 studies handed in. Significance of this new study data for assessing a change of classification was ascribed to the fact that they all recorded reflux-related symptoms at least once during the first 14 days of treatment. The applicant further substantiated the justification by pointing out the demonstration of efficacy/effectiveness with respect to the proposed indication and posology in a nonprescription setting as well as emphasizing selected studies showing early onset of relief from reflux symptoms (54.0 % - 80.6 % after day seven). Overall, the applicant considered that the new data from these studies "added significant support to the classification as nonprescription product as it provided both effect and relevance to the assessment" (EMA 2009b). The applicant's claim on data exclusivity was addressed by the CHMP with the following observations: overall study results were either comparable to those of already published studies thus not adding additional significant value to the application or lacked in effectiveness data after two weeks of treatment, showing only data for day 28 or even after. In a nonprescription setting, however, patients would be self-referring to their physician, if no symptomatic relief was obtained after 14 days of therapy, making the study design of limited value for self-medication issues. Another shortcoming regarding the study design of the respective studies was the comparison of pantoprazole 20 mg with omeprazole 10 mg which is usually applied as maintenance and not starting dose in the treatment of reflux

disease and therefore not therapeutically equivalent. Additionally, similar results, i.e. non-inferiority compared to other PPIs, were already shown elsewhere in the published literature. Therefore, the CHMP concluded that “none of the 6 above-mentioned studies provide data to support the proposed indication and treatment duration that could not be derived from the other 11 studies provided with the application” and accorded the studies no genuine impact on the classification of the product as “medicinal product not subject to medical prescription” (EMA 2009b).

All in all, after review of data on quality, safety, and efficacy/effectiveness, the CHMP considered by consensus that benefits of Pantoloc Control® outweigh risks in the proposed indication of short-term treatment of reflux symptoms thus being favorable as nonprescription product and that granting of the marketing authorization, therefore, was to recommend. As for alli® though, the CHMP did not judge data submitted by the applicant with reference to Article 74a, Directive 2001/83/EC, as amended, to be of additional significant value in support of the change of classification and thus declined its one-year data exclusivity application.

Tamsulosin hydrochloride 0.4 mg (Flomax Relief® MR, Boehringer Ingelheim) In the UK, reclassification of the active ingredient tamsulosin from POM to P status was recently approved for the first time worldwide by the UK’s competent authority MHRA.

Based on a UK national procedure, Boehringer Ingelheim applied for P status of tamsulosin hydrochloride 0.4 mg under the name Flomax Relief® MR, indicated for the treatment of lower urinary tract symptoms (LUTS) in the common male condition of benign prostatic hyperplasia (BPH) in men aged 45 to 75. The application was submitted as an abridged application according to Article 10.1(c) of Directive 2001/83/EC cross-referencing to an already existing Rx marketing authorization of Flomax® MR and combined the application for a new product license with a reclassification application (MHRA 2009).

Tamsulosin is a selective $\alpha 1$ -receptor-antagonist preferentially targeting $\alpha 1A$ -adrenoceptors in the prostate versus $\alpha 1B$ -adrenoceptors in the aortic tissue (Wilde and McTavish 1996). Subsequent relaxation of smooth muscles in the prostate and the urethra result in relieving obstruction and improving urinary flow rate. Thus, symptomatic relief is usually achieved within 7-14 days of treatment.

Based on its cross-reference to an already approved product, no new pre-clinical or clinical data were submitted. During the process of reviewing the application, in addition to a public consultation, the Commission on Human Medicines (CHM) was asked for advice and finally argued in favor of the reclassification. The positive vote was based on several arguments. First of all, the benefit-risk ratio of the respective substance was considered positive due to its proven satisfactory pre-clinical and clinical safety as well as efficacy profile. Second, the applicant proposed only symptoms to be assessed and treated in the pharmacy, whereas the condition itself (i.e., BPH) is to be diagnosed and confirmed at subsequent general practitioner (GP) review. The applicant had developed a comprehensive pharmacy model including training materials on lifestyle advice, patient monitoring, etc., revised by relevant professional pharmacy organizations. A pharmacy questionnaire had been developed for

patients" symptom assessment (based on an international symptom score) supporting an adequate treatment choice. Continuation of treatment may only occur on recurrent interaction of the patient with the pharmacist and GP encouraging men to sign up with one specific pharmacy which may thus help monitor treatment success. As mentioned in the public assessment report, this kind of model was supported by study data "showing that the in-pharmacy assessment, including a suitable questionnaire, ensures that the supply of a product is consistent with current guidelines" (MHRA 2009). Third, next to a disease awareness and patient support program, the applicant had developed a so-called "Men's Health Pack". A booklet proposed to be placed in the product packaging in addition to the patient information leaflet was designed in order to inform about the pharmacy supply scheme, allow for self-assessment of symptoms (through a copy of the symptoms questionnaire) and educate on lifestyle measures as well as disease management. Moreover, a medication/registration card to share with the GP should enhance patients' linkage to their pharmacy and their medicating GP. Finally, the applicant proposed to, and was advised by, the CHM to conduct a "post-authorization compliance program" for follow-up monitoring of men's compliance with the pharmacy protocol under real-life conditions as well as registration of potential adverse events to be reported to the CHM/MHRA every six months within a period of two years (MHRA 2009).

Furthermore, it is important to note that UK's switch of tamsulosin for treatment of BPH symptoms was not only the first of its kind worldwide with respect to the active substance and indication, but also unique when it comes to the provision of data protection. It was the first Rx-to-OTC switch in Europe which was granted one year of data exclusivity in accordance with Article 74a of Directive 2001/83/EC, as amended, for data submitted in support of the reclassification. Data exclusivity was granted with approval of the Rx-to-OTC switch on December 3, 2009, and hence officially expired on December 2, 2010. Based on the fact that according to the public assessment report no new pre-clinical and clinical study data were handed in and no such data could be detected or traced on the relevant internet sites of the responsible regulatory authority (MHRA) after expiration of the one year's data protection period, the author of the present work postulates that exclusivity presumably was not granted on grounds of any new pre-clinical or clinical study data available at the time of reclassification, yet supposedly on the basis of the comprehensive supportive data and material submitted by the applicant instead. As can be derived from the above, this mainly includes a complex pharmacy supply model as well as disease awareness and management programs, next to comprehensive patient and pharmacist education measures. Obviously, without backing by these collateral measures the switch of tamsulosin for the treatment of LUTS could not have been approved, as Article 74a rules that data exclusivity must only be granted based on significant data interpreted as "relevant and necessary for the change in classification" (European Commission 2006a). Moreover, hypothetically, the applicant's commitment to delivering post-authorization data verifying the proposed pharmacy supply scheme under real-life conditions and concurrently monitoring potential AEs may also have contributed to this reward of data protection.

From a regulatory perspective, this precedent UK switch of tamsulosin is thus to be seen

as success in regards to the reclassification request itself, but even more so when with a view towards it being the first and only positive approval of data exclusivity provision for a Rx-to-OTC switch within Europe to date.

4.4.5 The rationale of data exclusivity provision for switch products

In principle, the same idea that is fundamental to data exclusivity provision for the development of prescription drugs (see Section 4.2) is underlying the one for switch products. As well, the main intention of this incentive tool is to encourage companies to undertake necessary investments in essential data generation to successfully pursue and establish new switches of well-established drugs with a favorable safety and efficacy profile (WSMI 2009). In particular, when applying for the release of a certain substance or drug from prescription-only status (especially if “first in class”), a new or modified set of tests and/or trials usually is necessary to confirm effectiveness and safety of a reduced strength, posology, and/or a new indication intended for OTC status. For example, the generation of data pointing out that the significant therapeutic benefit for the target group in its intended use might require considerable effort and investment from pharmaceutical companies. Most notably, in light of future switches being increasingly complex in nature, resources to be spent on switch projects should not be underestimated. As can be derived from reclassification examples depicted above (cf. Section 4.4 ff.), apart from the demonstration of a product’s safe and effective use in OTC setting, the development of clear and comprehensive guidance to both HCPs and consumer/patients as well as comprehensive post-marketing pharmacovigilance and risk management systems seem to be increasingly relevant prerequisites – depending on the characteristics of the potential switch candidate and the targeted disease. Against this background, a certain period of data exclusivity obviously is key to a successful Rx-to-OTC switch, as it allows the originator company the possibility to accordingly prepare and settle into the OTC market in the absence of a prompt invasion of “me-too” products from generic competitors that usually do not engage with similar efforts when entering the market. Moreover, the development of a brand is generally considered as the main potential competitive advantage of being first-to-market but is as well accompanied by “substantial and ongoing investment”. Within this context, the “copying of brand trade dress” (so-called “passing-off”) by competitors was mentioned as a particular concern where the “protection of investment” (e.g., by awarding data exclusivity) is likewise of interest (AESGP 2011). As mentioned before (see Section 2.3), Rx-to-OTC switches may implicate significant public health benefits and economic savings due to easier and faster access to effective treatment or preventive therapy options eventually resulting in cost and time savings for health care systems and society in general. Adequate incentives are needed to motivate pharmaceutical manufacturers to undertake accordant investments necessary to provide well-established, safe, and effective therapeutic options to a broader target group whose therapeutic benefit thereby can be maximized. Since Rx-to-OTC switch products in general are not “novel” and therefore not eligible for patent protection, data exclusivity represents an alternative incentive to be afforded to companies initiating and conducting a costly, time-consuming and often also risky switch project.

4.5 Summary and conclusion

Just like patent protection, data exclusivity constitutes a fundamental intellectual property right. It has internationally been acknowledged and legally required since the mid-1990s by important trade agreements – that is, the North Atlantic Free Trade Agreement and the World Trade Organization’s TRIPS Agreement.

In essence, data exclusivity is provided independently from patent law and bans regulatory authorities from relying on proprietary data for assessing an abbreviated generic drug application during a specific period of exclusivity (in case of switch products three years in the US and one year in Europe). Respective provisions are laid down in corresponding legal frameworks, such as: FD&C Act Section 505 (i.e., more specifically, 21 U.S.C. § 355, implemented in 21 CFR 314.108) and Article 74a, Directive 2001/83/EC, as amended by Directive 2004/27/EC, for Rx-to-OTC switches in the US and in Europe, respectively. Accordingly, applicants are granted exclusivity based on the submission of “significant” data from pre-clinical tests (EU) or clinical trials (US, EU) meaning they need to be considered crucial in regards to a positive reclassification decision. However, in contrast to the US, with the reclassification of tamsulosin in 2009 in the UK there has been only one precedent example of successful regulatory appliance of legal provisions within Europe to date.

In general, the rationale behind data and/or market(ing) exclusivity provision is the attempt to stimulate resource intensive development of high value medication in the absence of eligibility for patent protection by a delay of generic invasion. Most notably in light of augmenting requirements and investments associated with drug research and development, the existence of such incentive tools is regarded to be of major importance.

As implicated by a trend to more complex switches and indicated by recent practical examples, a similar increase in requirements and preconditions is to be asserted with a view to Rx-to-OTC switch approvals. Therefore, in the author’s opinion adequate incentive tools likewise need to be in place that foster the accelerated and broader access to safe and effective switch products targeting patients with unmet medical needs, thereby eventually providing a significant benefit to public health. Yet, based on the fact that switch products occur only late in a drug’s life-cycle, they naturally are hardly ever able to come up with criteria to be fulfilled for patent protection (i.e., novelty, utility, and above all non-obviousness). Against this background, according to the author, data exclusivity provides a valuable alternative means of protecting comprehensive proprietary data to be generated within the context of an Rx-to-OTC switch over a certain period of time after reclassification. More specifically, depending on the complexity of a specific switch proposal, the author considers it as an important success factor for originator companies to be motivated to develop and provide a comprehensive framework (including: e.g., post-marketing surveillance, drug product supply, risk management, etc.) necessary for successful implementation and establishment in the market.

However, unfortunately, on the grounds of the hitherto existing all but one negative examples of data exclusivity application within Europe, the author concludes its current practicability to be rather limited.

4.6 Legal framework of data exclusivity provision for Rx-to-OTC switches in the EU at status quo – a critical analysis

On a European basis, the only basic approach to interpretation of the current legislation on data exclusivity for switch products is given in part III of the “Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use”. According to this guideline, pre-clinical tests and/or clinical trials are considered “significant” if they are “relevant and necessary to the change of classification” (European Commission 2006a). As reflected by the aforementioned examples of data exclusivity application for switch products in the EU (see Subsection 4.4.4), this interpretation is, however, not at all concrete and does not provide detailed information on what kind of data might comply with Article 74a and the switch guideline, respectively. Therefore, from a legal perspective the term “significant” as it is used in Article 74a of Directive 2004/27/EC, as well as the terms “relevant” and “necessary” as used in the EU “Guideline on Changing the Classification” constitute so-called “indeterminate legal terms” lacking a clear, unambiguous interpretation, concretion, and implementation within this specific context. Moreover, a clear definition and outline of data requirements regarding “pre-clinical tests”, but especially “clinical trials” is missing. Requested data categories, criteria, standards, and quality aspects are likewise unmentioned. In fact, based on the above mentioned, it could even be argued that the current interpretation of Article 74a of Directive 2004/27/EC is rather a “hindrance” instead of being adjuvant with a view to the provision of data exclusivity when transferring a drug from prescription to nonprescription status. Of course, it has to be borne in mind that the provision of data exclusivity implies both a huge political and economic dimension due to the fact that exclusivity certainly prevents (generic) competition and thus price erosion for a limited period of time – a situation which is not always welcomed.

Within this context it is important to note that the legal clarity of the EU Directive and subsequent amendments have been fairly influenced by political considerations resulting in the fact that certain issues such as the grant of data exclusivity are still vague and therefore much debated as many formulations and provisions are incomplete (WSMI 2009). Experts also state that the award of exclusivity for switch products throughout the world still is largely insufficient to justify and safeguard further investment within this therapeutic movement (AESGP 2011).

Based on the aforementioned, the author has developed two main hypotheses regarding the issue of data exclusivity provision for Rx-to-OTC switch products within Europe which will be analyzed in detail and discussed below.

4.6.1 *Hypothesis 1: The current EU legal framework makes it virtually impossible to reach data exclusivity for Rx-to-OTC switches based on the given criteria and data categories.*

As can be understood from the above, within the context of interpreting Article 74a of Directive 2004/27/EC regarding data exclusivity provision for Rx-to-OTC reclassifications, the current switch guideline does indeed stress the importance of confirmatory pre-clinical test or clinical study data with respect to a drug’s safety and efficacy profile in case of any modi-

fication (i.e., dosage strength, pharmaceutical form, duration, or modalities of treatment, as well as indication, etc.). Furthermore, “significant” data as a basic requirement for eligibility for data exclusivity currently is interpreted and defined as “relevant and necessary to the change of classification”.

However, this interpretation of the respective legal specification implicates all or nothing. Its concept remains rather indeterminate and no guidance is given with respect to specification and interpretation of relevant data categories, criteria and requirements. Hence, it is not astonishing that apart from one precedent case in the UK (switch of tamsulosin), successful Rx-to-OTC switch applications claiming data exclusivity based on the EU’s actual legal framework and its interpretation are still being awaited.

Against this background and in the author’s opinion, the currently changing nature of Rx-to-OTC switches in terms of both indications and drug products directing towards an increasingly autonomic self-management of people’s health should definitely be reflected by the setup of accordant criteria and data categories for the provision of data exclusivity within future reclassification processes. Besides, requirements for data exclusivity in the context of Rx-to-OTC switches should finally be in analogy with the general evolution of switch criteria, described in Section 3.2, where the focus of regulatory assessment obviously was complemented by or has even shifted from the mere evaluation of substance and product properties towards the demonstration of a patient’s safe and effective use of a switch product for the treatment or management of a certain condition.

Moreover, according to the author, the current one-year data exclusivity period for Rx-to-OTC switches in Europe is to be challenged based on the considerations above. A period of one year in the author’s opinion seems to be rather short for successfully settling or - depending on the scenario – establishing a new (sub)category in the market.

Thus, in summary, further clarity, transparency, amendment, and adaptation is needed on the current interpretation of the legal provisions for data exclusivity to be granted to future switches. Only if there is a common understanding of what set of data, etc. seems to be appropriate in order to be eligible for data exclusivity, will this “incentive tool” work as such, leading to the second main hypothesis of the present work which is depicted below.

4.6.2 Hypothesis 2: Available criteria and data categories have to be specified and new ones have to be developed to enable the provision and receipt of data exclusivity for Rx-to-OTC switches.

Specific characteristics and trends in the Rx-to-OTC switch movement, the definition and implication of data exclusivity as well as current European legal provisions and interpretations within this context were analyzed in the previous chapters. As discussed above, the present existence of exclusivity criteria and data category requirements for switch products is rather questionable and incomplete especially with respect to future self-medication with switched OTC products. Against this background, next to the discussion, interpretation, and specification of current data categories, further potential eligibility criteria as well as data categories will have to be elaborated upon, analyzed, and discussed explicitly focusing on appropriateness, feasibility, and applicability aspects with regards to data exclusivity

provision for Rx-to-OTC switches targeting the setting of self-medication.

5 Case study analysis: Rx-to-OTC switch of clotrimazole for the treatment of vaginal candidiasis

For the purpose of verification of the aforementioned hypotheses (cf. Subsections 4.6.1 and 4.6.2), the reclassification of clotrimazole for the treatment of vaginal candidiasis was retrospectively analyzed comparing pre-clinical and clinical data categories available at its registration as prescription medicine with those at its subsequent Rx-to-OTC switch. The primary objective was the identification of potential major gaps in data requirements and data generation (i.e., availability) for each submission. In theory, if existent these gaps could then serve as reference points for new data to be generated within the context of an Rx-to-OTC switch potentially eligible for the provision of data exclusivity.

Clotrimazole is a tritylimidazole derivative (triphenylimidazolylmethane) which was synthesized at the Bayer Research Center in 1967 as the first member of a new class of substances showing effective antimycotic activity (Clayton 1977; Plempel 1982). It was registered and marketed in 1973 for the first time primarily on the grounds of treating vaginal and skin infections caused by yeasts and dermatophytes (Sawyer et al. 1975). *In vivo*, the drug is highly effective against the *Candida* species (Clayton 1977) and seems to have some antibacterial property (Sawyer et al. 1975). Products with the active ingredient clotrimazole have since been marketed by its originator Bayer under the Canesten® brand. Many delivery and therapy forms are available, by now ranging from its application as powder, solution, or cream to (vaginal) tablets depending on the respective indication it is used for.

Clotrimazole has been available OTC as of 1977 for the treatment of skin infections immediately after expiration of the automatically triennial obligation to be marketed as prescription drug effective at that time (according to § 35a, German Medicines Law, 1961). In contrast, after automatically having been available as prescription only for three years, clotrimazole was classified to stay Rx within the indication of vaginal infections according to § 35, German Medicines Law, 1961. Hence, it has only been available for self-treatment of vaginal candidiasis as of 1993 when it was switched from Rx to OTC status for this indication. Today, in Germany all Canesten® products, aside from the six-day-therapy of vaginal mycosis, are available without prescription.

5.1 Excursus: overview of the development of the German Medicines Law

As mentioned above (q.v. Chapter 5), in Germany the first Canesten® drug products were registered in 1973 (application submitted in 1971) and switched for the treatment of vaginal yeast infection in 1993. In order to understand the legislative framework that governed these processes and its development to present in Germany, a short overview of the development of the German Medicines Law is depicted in Table 5. An institutional national Medicines

Law was first introduced in 1961. One major difference from the Medicines Law as it is effective today is the fact that drug substances, so-called proprietary products (“Arzneispezialitäten”), had not to be authorized by a special approval procedure but simply to be listed on a specific index (“Spezialitätenregister”) based on a standard form being filled in with required details. After several changes and amendments the most important of which was the “thalidomide amendment” in 1964 as reaction to the well-known thalidomide¹⁴ disaster, the German Medicines Law was extensively reformed in 1976. A comprehensive approval procedure in compliance with existent legal requirements and guidelines has since become compulsory for the authorization of a new drug. The reformed Medicines Law came into effect in 1978 and has since formed the fundament of the current German Medicines Law of which the 16th amendment has become effective in 2012.

¹⁴ Thalidomide is a hypnosedative drug introduced in the 1950s and taken as a sleeping aid under the brand Contergan[®]. It was withdrawn from the world market (after it had been reclassified to prescription status in some German federal states, cf. Subsection 3.5.2) in late 1961 due to its potential to cause infant limb defects. Interestingly, thalidomide was never marketed as sleeping aid in the US, as the FDA had objected to the lack of chronic toxicity studies (Kirk and Friedrich 2001). However, the active substance thalidomide has since been selectively reintroduced for use in autoimmune and inflammatory conditions (Tseng et al. 1996) and might play a potential role in inhibition of tumor angiogenesis (Seitz 2001).

Table 5: Overview of the development of the German Medicines Law (based on Blasius 2003; Gall 2009)

German medicines law	Up to 1961	1961 (introduction)	1976 (reform, effective as of 1978)
Characteristics	<ul style="list-style-type: none"> • No consistent national Medicines Law • Some regulations for certain substances only (e.g., vaccines, etc.) 	<ul style="list-style-type: none"> • Law on the marketing of drugs • Introduction of manufacturing permission: requirements regarding development, manufacturing and marketing • Introduction of index-listing of so-called proprietary products, but <i>not</i> of generic products: <ul style="list-style-type: none"> – no obligation regarding efficacy and safety trials for originator drugs to be listed – for substances and formulations not commonly known a report regarding kind and amount of potential side effects was required only • Definitions and terminologies • 17 changes until drug law reform in 1976 	<ul style="list-style-type: none"> • New structured and stricter law on the marketing of drugs and legal basis of the current German Medicines Law (adapted to European legislation) • Introduction of authorization of drug products and generic products: <ul style="list-style-type: none"> – approval procedure (document review) for all except homeopathic drug products – proof of quality (GMP), efficacy, and safety • Stricter monitoring of drug marketing: <ul style="list-style-type: none"> – stricter requirements for packages and leaflets – development of an information system for documentation, evaluation and management of adverse events (graduated plan procedure)

Continued on next page...

Table 5 – Continued

German medicines law	Up to 1961	1961 (introduction)	1976 (reform, effective as of 1978)
			<ul style="list-style-type: none"> • Introduction of absolute liability of pharmaceutical manufacturer and safety regulations for study participants (e.g., insurance, etc.) • Further refinement of definitions and technologies • Implementation of European guidelines (European Economic Community (EEC)) • 16 amendments up to date

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Table 5 – Continued

German medicines law	Up to 1961	1961 (introduction)	1976 (reform, effective as of 1978)
Major changes and amendments	<ul style="list-style-type: none"> • First drafts for a separate national Medicines Law in 1928, 1931, 1933, and 1938, yet without implementation 	<ul style="list-style-type: none"> • 2nd Amendment 1964 (“Thalidomide amendment”): <ul style="list-style-type: none"> – requirement to report pre-clinical and clinical evaluation for substances and formulations not commonly known according to respective scientific knowledge (§ 21, 1a+b) – general prescription-only availability of substances and formulations not commonly known lasting for (at least) three years (§ 35a, 1-4) 	<ul style="list-style-type: none"> • 2nd Amendment 1986: <ul style="list-style-type: none"> – clinical evaluation imputed to surveillance by authorities under obligation to submit clinical investigation plan • 7th Amendment 1998: <ul style="list-style-type: none"> – implementation of additional authorization procedures according to European regulations: CP and MRP • 12th Amendment 2004: <ul style="list-style-type: none"> – implementation of European guidelines: Good clinical practice (GCP) regulation replaces requirement to disclose towards authorities by approval procedure through ethical review committee – clinical drug assessment required in children and adolescents if intended to be authorized for use in these patient groups – Periodic Safety Update Report (PSUR): requirement to extensively document and disclose any (suspected) adverse event

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Table 5 – Continued

German medicines law	Up to 1961	1961 (introduction)	1976 (reform, effective as of 1978)
			<ul style="list-style-type: none"> • 14th Amendment 2005: <ul style="list-style-type: none"> – implementation of DCP – omission of § 49, i.e., discontinuation of the requirement of new substances automatically being classified Rx, but also automatic reclassification to OTC (if applicable) – implementation of European guidelines (e.g., “Guideline on traditional herbal medicines”)

5.2 Gap analysis: original registration vs. Rx-to-OTC switch of clotrimazole (Canesten[®]) for the treatment of vaginal candidiasis

Based on a short overview of the legislative environment, data categories available at both the time of its original registration for the therapy of vaginal mycosis and the corresponding Rx-to-OTC switch of clotrimazole, respectively, will be analyzed below.

5.2.1 Legislative environment

The development of the German Medicines Law has been and is still in large part guided and influenced by the European legislative environment. On a legal basis, several directives and regulations have been ground-breaking. Some of them judged to be of major relevance are listed in Tables 6 (e.g., Directive 65/65/EEC, “Clinical Trials Directive”, or “GCP Directive”) and 7, respectively.

In parallel, big institutions such as the WHO or OECD have developed and released important guidelines to be considered in a drug development process. Standard references and quality requirements, for example, have been established by the European Pharmacopoeia (Pharm. Eur.). These guidelines as well as the legal requirements mentioned above (e.g., “Good Manufacturing Practice” (GMP), “Good Laboratory Practice” (GLP), “Good Clinical Practice” (GCP), etc.) are primarily based on the so-called “Declaration of Helsinki” of 1964 which was adopted by the 18th General Assembly of the World Medical Association (WMA)¹⁵ and contains ethical principles essential for medical research involving human subjects.

The biggest guideline compilation with respect to drug authorization requirements is by now represented by the so-called ICH Guidelines (“International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use”). Its evolution is mainly due to the effort of harmonizing guidelines and requirements for the registration of pharmaceuticals against the background of the establishment of one single (European) market for pharmaceuticals. Based on independent discussions about harmonization possibilities, Japan and the US joined the initiative and shortly thereafter the ICH was born (April 1990)¹⁶. Today, more than eighty guidelines are provided in four main categories, namely: efficacy, safety, quality, and multidisciplinary guidelines. Major ICH guidelines have also been implemented in national and international legislation.

Table 8 gives an overview of selected relevant guidelines which have been developed over the years. As Canesten[®] for the treatment of vulvovaginitis (in the following discussion its actual brand name “Canesten[®] GYN” will be used) is analyzed in the present work, the date of its original registration in 1963, its switch from prescription to nonprescription status in 1993, and the situation today (2012) were used as time frames for the tabular overview.

¹⁵ cf. <http://www.wma.net/en/30publications/10policies/b3/>, last accessed 2013-01-06

¹⁶ cf. <http://www.ich.org/about/history.html>, last accessed 2013-01-06

Table 6: European legislative framework (as amended) relevant for the authorization process of medicinal products for humans in 1973 (original registration of Canesten®), 1993 (Rx-to-OTC switch of Canesten®), and at present (selection)

1973	1993	2012
<ul style="list-style-type: none"> • Directive 65/65/EEC¹⁷ 	<ul style="list-style-type: none"> • Directive 75/318/EEC¹⁸ • Directive 75/319/EEC • Directive 92/26/EC (“Classification Directive”)¹⁹ • Directive 93/41/EEC 	<ul style="list-style-type: none"> • Directive 2001/20/EC (“Clinical Trials Directive”) • Directive 2001/83/EC • Directive 2003/94/EC (“GMP Directive”)²⁰ • Directive 2005/28/EC (“GCP Directive”)²¹
	<ul style="list-style-type: none"> • Regulation (EEC) No 2309/93 	<ul style="list-style-type: none"> • Regulation (EC) No 726/2004

¹⁷ first European pharmaceutical directive providing quality guidelines for the development and manufacturing of drugs, pharmacovigilance guidelines and three criteria for the registration of new drugs – safety, quality, and therapeutic efficacy (Schmucker 2006)

¹⁸ approximation of the laws of member states relating to analytical, pharmaco-toxicological, and clinical standards and protocols in respect of the testing of proprietary medicinal products

¹⁹ Cranz 1999

²⁰ GMP = “Good Manufacturing Practice” relates to international regulatory requirements regarding the manufacturing and control of products in health care, food, and cosmetic sectors (Bliem 2004)

²¹ GCP = “Good Clinical Practice” represents an international ethical and scientific quality standard with respect to the design, conduct, record, and reporting of trials with participation of human subjects (EMA 2002)

²² “Richtlinie über die Prüfung von Arzneimitteln” announced by German Federal Health Minister Käte Strobel – first directive in Germany for the assessment of drugs on the basis of European legislation and guidelines, respectively

²³ “Arzneimittelprüfrichtlinien”

²⁴ “Grundsätze für die ordnungsgemäße Durchführung der klinischen Prüfung”

²⁵ “Verordnung über die Anwendung der guten klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen”

²⁶ “Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen”

Table 7: German national legislative framework (based on EU provisions) relevant for the authorization process of medicinal products for humans in 1973 (original registration of *Canesten*[®]), 1993 (Rx-to-OTC switch of *Canesten*[®]), and at present (selection)

1973	1993	2012
<ul style="list-style-type: none"> • German Medicines Law 1961 including amendments until 1973 • Directive regarding the evaluation of drugs (1971)²² 	<ul style="list-style-type: none"> • German Medicines Law 1976 including amendments until 1990 • Drug evaluation directives (cf. § 26 German Medicines Law)²³ • Principles on the Conduct of Clinical Trials (1987)²⁴ 	<ul style="list-style-type: none"> • German Medicines Law including amendments until 2012 • Drug evaluation directives (1995) • Regulation regarding GCP with respect to the Conduct of Clinical Trials with drugs intended for human use (GCP Regulation 2004)²⁵ • Announcement regarding the clinical evaluation of drugs in humans (2006)²⁶

Table 8: Relevant guidelines with respect to the authorization process of medicinal products for humans in 1973 (original registration of *Canesten*[®]), 1993 (Rx-to-OTC switch of *Canesten*[®]), and at present (selection)

1973	1993	2012
<ul style="list-style-type: none"> • Declaration of Helsinki (1964)²⁷ • EC Guidelines (various)²⁸ • WHO GMP Guidelines (endorsed 1969)²⁹ • European Pharmacopoeia (Ph. Eur., 1st edition)³⁰ 	<ul style="list-style-type: none"> • EC GMP Guideline (first published 1989) • EC GCP Guideline (operational as of 1991) • OECD GLP principles (first published 1992) • European Pharmacopoeia (Ph. Eur., 2nd edition) 	<ul style="list-style-type: none"> • EMA (CPMP/CHMP) Scientific Guidelines • ICH Tripartite Guidelines^{31, 32} • WHO GCP Guidelines (first published 1995) • OECD GLP principles (updated 1997) • European Pharmacopoeia (Ph. Eur., 7th edition) • ISPE GPP Guidelines³³ • IEA GEP Guidelines³⁴

5.2.2 Overview of data (categories) required for and available at original registration and Rx-to-OTC switch

Against the legislative background illustrated above, data requirements and data available, respectively, at the time of the original registration of Canesten[®] and at the time of its Rx-to-OTC switch for the treatment of vaginal mycosis were analyzed and compared in order to identify potential disparities and gaps.

For comparability reasons the different data categories of the so-called Common Technical Document (CTD) provided by the ICH as a standard set of specifications for (new) drug application dossiers and consisting of five different modules³⁵ were used as basic guidance to structure this gap analysis. Furthermore, as specific preconditions have to be fulfilled before a substance and/or indication will be allowed to be switched to self-medication, OTC specific requirements and data categories were equally included in the analysis.

In order to check the availability of different data categories according to the requirements at the respective time points of Canesten[®]'s original registration and its reclassification to OTC, all relevant documentation (i.e., dossiers, pre-clinical test and clinical study reports, publications, etc.) still retrievable and either published or unpublished was screened and

²⁷ a set of ethical principles for medical research with the participation of human subjects which was developed by the World Medical Association and adopted in 1964 in Helsinki, Finland (cf. <http://www.wma.net/en/30publications/10policies/b3/17c.pdf>, last accessed 2013-01-20) and is “the most widely accepted guidance worldwide on medical research involving human subjects” today (Christie 2000)

²⁸ later published by the EMA which was founded in 1995

²⁹ GMP guidelines recommended and issued by the World Health Organization (WHO) since 1969 to support quality assurance of pharmaceutical products

³⁰ based on the Convention developed by the Council of Europe on the Elaboration of a European Pharmacopoeia in 1964 (Convention on the Elaboration of a European Pharmacopoeia, 1964, cf. <http://conventions.coe.int/Treaty/Commun/QueVoulezVous.asp?NT=050&CL=ENG>, last accessed 2013-01-24); single reference work for the signatory states of the Convention on its elaboration, providing a legal and scientific basis for standard quality control during the development, production, and marketing processes of medicines (q.v. <http://www.edqm.eu/site/background-50.html>, last accessed 2013-01-24)

³¹ ICH = “International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use”, unique initiative that has brought together since 1990 the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States initially focusing on the development of harmonized ICH Tripartite Guidelines regarding criteria and documents required for approval and authorization of new medicinal products intended for use in ICH regions (cf. <http://www.ich.org/about/vision.html>, last accessed 2013-01-21), > eighty guidelines and annexes in the four categories efficacy, safety, quality and multidisciplinary guidelines (Kuhnert 2011); implemented in European legislation as well as EMEA scientific guidelines

³² including the EU switch guideline (European Commission 2006a) which has been adopted in 1998 (cf. Section 3.3)

³³ International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practice (GPP), issued 1996, revised August 2004 & April 2007 (q.v. http://www.pharmacoepi.org/resources/guidelines_08027.cfm, last accessed 2012-07-21)

³⁴ International Epidemiological Association (IEA) European Federation. Good Epidemiological Practice (GEP) – IEA Guidelines for proper conduct of epidemiological research. November 2007

³⁵ module 1= administrative and prescribing information; module 2 = overview and summary of modules 3 to 5; module 3 = quality (pharmaceutical documentation); module 4 = safety (toxicology studies); module 5 = efficacy (clinical studies)

evaluated according to its classification based on the different data categories. A summary of the analysis is provided in Table 9.

As can be derived from this tabular overview, in principle the main data categories of pre-clinical, but also clinical drug development phases were in existence back in 1973. The main differences between then, 1993 (i.e., the time of the Rx-to-OTC switch of Canesten® GYN), and today are in scientific and technological progress, on the one hand, and the advancement of ethical principles and considerations, on the other.

To give an example with respect to pre-clinical data, genotoxicity testing has among others been added to the range of toxicological evaluation due to increasing scientific knowledge and the development of newer and increasingly sensitive analytical and diagnostic tests. Besides, on the grounds of a growing pool of drug substances aimed at widely varying target molecules associated with more and more different metabolic pathways, naturally more extensive evaluation of drug interaction potential has been required and performed over the years and has set a high standard for current drug evaluation.

When it comes to ethical aspects, based on a continued evolution of existent guidelines and the addition of new ones (e.g., regarding GLP, GMP, GCP, ICH guidelines, etc.), requirements regarding the conduct of clinical studies, for example, have constantly risen. Provisions regarding study population, size, design, documentation, etc. are clearly specified and not least determined by the legislative environment. However, back in 1973, basic principles of randomization control, blinding, and comparison with existing therapeutic alternatives were already valid and required by legislation - even though not yet that formalized (cf. Tables 6, 7, 8 and 9).

Due to the availability of comprehensive data generated for Canesten®'s registration as a prescription drug and during its post-marketing phase meeting the basic requirements for drug application as effective in 1973 and still valid in 1993 in its kind, the Rx-to-OTC switch of Canesten® GYN was primarily a bibliographic one (i.e., referencing existing pre-clinical test and clinical study data). Thus, based on 1993 general data requirements for both the application of a new drug as well as an Rx-to-OTC switch of an existing drug (the European Commission's switch guideline was yet not in place), no additional pre-clinical or clinical data had to be or were, respectively, generated. Instead, existing data was reviewed, analyzed, evaluated, and summarized by a scientific expert according to current scientific knowledge. In view of a substance and/or indication to be registered OTC or to be switched from prescription status to nonprescription safety, efficacy/effectiveness, and self-assessment under OTC conditions deserve special attention and evaluation. Whereas none of these categories were relevant at the time of the original Canesten® registration as prescription drug, it has become important for its Rx-to-OTC switch. For this purpose and in the absence of a specific guideline (like today's EU switch guideline) existent (post-marketing) Rx data were evaluated with respect to conditions relevant for intended OTC usage. Market research instruments were employed to collect patient data regarding knowledge, attitudes, and behavior as well as treatment options used in association with vaginal candidiasis and to judge the ability of self-diagnosis as well as the potential for mis- or abuse. A two-step survey design provided qualitative insight through a small pilot study, whereas quantitative information was gained

via questionnaires sent to a representative study population of women from all over Germany who had had a preceding vaginal infection (data on file). This kind of enquiry was probably able to provide decision makers with an anticipated “feeling” of how the disease would be diagnosed and treated under daily conditions of OTC usage. The fact that it demonstrated that women suffering from repeated infection seem to self-diagnose correctly due to familiar symptoms and that most of them do not consult their doctor right away (mainly not until after one week) was certainly pivotal to the decision of switching Canesten[®] GYN to OTC so as to offer the possibility of immediate access to treatment. Therefore, from a retrospective point of view, the basic idea behind this kind of data might have been able to qualify for data exclusivity, if it had been existent at that time, and might be seen as seminal (at least with regards to content) to the definition of respective data categories today.

Aside from market research instruments specific study designs are available nowadays, such as “actual use” or “self-selection” studies in order to investigate correct self-diagnosis, compliance, effectiveness, and safety, etc. in a nonprescription setting and anticipate actual OTC usage (q.v. Subsection 9.3.3). However, as these study designs – at least the way they are conducted in the US - do not represent clinical trials in a classical sense (like phase I-III studies) and study objectives are different from typical post-marketing surveillance studies (phase IV) generally required throughout pharmaceutical development (Bradford et al. 2010), acceptance of such “real-world data” by regulatory authorities still significantly varies. One reason might be that the validity of observational research study data (cf. Chapter 7) considerably differs as definite standards regarding study design and statistical evaluation have not yet been determined. In contrast, as label comprehension is an important prerequisite for correct and compliant self-medication in general, “label comprehension” or “readability” tests have been recommended for several years, though not yet common at the time of the Rx-to-OTC switch of Canesten[®] GYN.

5.3 Summary and conclusion

The case study of Canesten[®] GYN was retrospectively analyzed in order to determine potential differences between data requirements and data available at the time of its original registration as prescription drug in 1973 compared with the situation of its reclassification to OTC in 1993. To this end, the concomitant development of relevant legislations and guidelines both at a national and European level was taken into account disclosing that the main advancements over time are to be found in scientific and technological progress as well as ethical aspects, yet that fundamental principles in the main data categories of pre-clinical and clinical drug development phases were already existent back in 1973.

In conclusion, the showcase of Canesten[®] GYN demonstrates that unless the term “significant” is further substantiated and “pre-clinical tests” as well as “clinical trials” in the absence of precise specification are interpreted other than in a conservative (i.e., classical) way, the availability of usually extensive pre-clinical and clinical data from a drug’s original Rx registration in practice virtually leaves no room for novel data generation eligible for the award of data exclusivity to a certain Rx-to-OTC switch. Moreover, it can be postulated that this holds even true for older substances (such as clotrimazole in the example used

here) which for the most part already comply with basic scientific and ethical demands in pre-clinical and clinical research.

Instead, market research data that had been generated for the support of a change of classification of Canesten® GYN provided valuable insight into patients' ability to self-diagnose and presumably constituted a crucial component in the final reclassification decision. Besides, epidemiological study data demonstrating patients' ability to correctly self-select and/or self-medicate in an OTC setting could possibly have further complemented the existing Rx data pool in the Canesten® GYN case with respect to self-medication issues. Yet, if such data could have qualified for data exclusivity from the (retrospective) perspective of the current legislation is not clear on the basis of its insufficient specification and indistinct, or rather absent, interpretation at present.

Table 9: Overview of data requirements and data availability at the time of the original registration and the Rx-to-OTC switch of Canesten® for the treatment of vaginal mycosis (actual brand name “Canesten® GYN”) compared to current requirements

		1973	Canesten® original registration	1993	Canesten® GYN Rx-to-OTC switch (bibliographic)	Now (2012)
Preclinical requirements						
Pharmacology						
	Primary pharmacodynamics	x	x	x	∅ (Ref. to existent Rx data)	x
	Secondary pharmacodynamics (not required for core safety assessment)	∅	∅	∅	∅ (Ref. to existent Rx data)	(x)
	Safety pharmacology	x	x	x	∅ (Ref. to existent Rx data)	x
	Pharmacodynamic interactions	(x)	∅	x	∅ (Ref. to existent Rx data)	x
Pharmacokinetics						
	Analytical methods and validity reports (if available)	x	x	x	∅ (Ref. to existent Rx data)	x
	Resorption, distribution, metabolism, elimination	x	Only single dose	x	∅ (Ref. to existent Rx data)	x
	Pharmacokinetic drug interactions	x	x	x	∅ (Ref. to existent Rx data)	x
	Other preclinical studies	∅	∅	(x)	∅ (Ref. to existent Rx data)	(x)
Toxicology						
	Single dose	Acute	Acute	x	∅ (Ref. to existent Rx data)	x
	Repeated dose (depending on duration of clinical investigation)	Subacute, chronic	Subacute, chronic	x	∅ (Ref. to existent Rx data)	x
	Genotoxicity (in vitro, in vivo incl. toxicokinetic evaluation)	∅	∅	?	∅ (Ref. to existent Rx data)	x
	Carcinogenicity (long-, short-, or medium-term studies, other studies)	x	x	x	∅ (Ref. to existent Rx data)	x
	Reproductive and developmental toxicity (fertility and embryonic development, embryo/fetal development, pre- and postnatal development (with offspring dosed/evaluated))	x	x	x	∅ (Ref. to existent Rx data)	x
	Local tolerance studies	x	x	x	∅ (Ref. to existent Rx data)	x
	Other toxicity studies (antigenicity, phototoxicity, metabolites, dependence, impurities, etc.)	∅	∅	?	∅ (Ref. to existent Rx data)	x
Documentation						
	(Tabulatory) summary of preclinical study results including description of test systems and methods used	x	x	x	Short (bibliographic) summary/overview of pharmacological properties -> monograph?!	x
	Discussion and conclusion of all relevant preclinical study data regarding safety of drug under investigation to evaluate benefit-risk ratio for human clinical testing in intended indication(s)	x	x	x	x (Discussion with respect to self-medication)	x

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Table 9 – Continued

General						
	Evaluations based on current scientific knowledge regarding methodology, biometrics, and ethical requirements	Basic	x	x	x	Advanced (max. validity, min. bias/confounders)
	Relevant guidelines: GLP, etc.	∅	∅	x	∅	x
	Use of different animal species (males and females)	x	x	x	∅ (Ref. to existent Rx data)	x
	Examination of different (inteded) forms of administration	x	x	x	∅ (Ref. to existent Rx data)	x
Additional						
	Discussion of advantages against therapeutic alternatives	x	x	x	∅	
Clinical requirements						
Clinical phase I + II						
Human pharmacodynamic studies						
Healthy subjects/patients	Primary pharmacodynamics	x	x	x	∅ (Ref. to existent Rx data)	x
	Secondary pharmacodynamics (not required for core safety assessment)	∅	∅	∅	∅ (Ref. to existent Rx data)	x
	Pharmacodynamic interactions	(x)	∅	x	∅ (Ref. to existent Rx data)	x
Human pharmacokinetic studies						
Healthy subjects/patients	Resorption, distribution, elimination, metabolism, excretion	x	x	x	∅ (Ref. to existent Rx data)	x
	Bioavailability/Bioequivalence	x	x	x	∅ (Ref. to existent Rx data)	x
	Pharmacokinetics of active metabolites	x	x	x	∅ (Ref. to existent Rx data)	x
	Pharmacokinetic interactions	x	x	x	∅ (Ref. to existent Rx data)	x
	<i>In vitro</i> - <i>in vivo</i> correlation studies	x	x	x	∅ (Ref. to existent Rx data)	x
	Dose-response (dose finding) studies	x	x	x	∅ (Ref. to existent Rx data)	x
	Dose dependency and time course of pharmacokinetics	x	x	x	∅ (Ref. to existent Rx data)	x
	Initial tolerability	x	x	x	∅ (Ref. to existent Rx data)	x

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Clinical phase III + IV						
Efficacy and safety						
	Controlled clinical trials pertinent to the claimed indication, including special (at risk) populations, comparison with therapeutic alternatives	RCTs recommended (no specific study protocol regarding size/kind of study population, etc.)	x	x	∅ (Ref. to existent Rx data)	Detailed study protocol required (based on Clinical Trials Directive/ICH/GCP)
	Uncontrolled clinical trials	Not recommended	x	x	∅ (Ref. to existent Rx data)	x
	Post-marketing experience	∅	∅	x	x (Ref. to existent Rx data)	x
Documentation						
	Background and overview	x	x	x	x	x
	(Tabulatory) summary of clinical study results	x	x	x	x (Ref. to existent Rx data)	x
	Comparison and analyses of results across studies, also regarding sub-populations	x	x	x	x (Ref. to existent Rx data.)	x
	Persistence of efficacy and/or tolerance effects	x	x	x	x	
	Analysis of clinical information relevant to dosing recommendations	x	x	x	x	x
	Drug exposure: overall safety evaluation plan, narratives of safety studies, overall extent of exposure	∅	∅	?	x (Ref. to existent Rx data)	x
	Adverse event analysis by organ system	x	x	x	x	x
	Clinical laboratory evaluations of vital signs, physical findings, etc. related to safety	x	x	x	x	x
	Safety in special population groups and situations (e.g., drug interactions, pregnancy, overdose, abuse, effect on ability to drive, withdrawal/rebound)	x	x	x	x	x
	Inclusion/exclusion/discontinuation criteria	x	x	x	x (Ref. to existent Rx data)	x
	Description of methodology, study design etc. (e.g., statistics: level of significance, study subject selection, management of missing data, etc.)	x	x	x	x (Ref. to existent Rx data)	x
	Case report forms and individual patient listings	x	x	x	∅ (N/A)	
General						
	Submission of complete documentation and all results (on request)	x	x	x	∅ (N/A)	x
	Evaluations based on current scientific knowledge regarding methodology, biometrics, and ethical requirements	Basic	x	x	x	Advanced (max. validity, min. bias/confounders)
	Relevant guidelines/legal requirements: Clinical Trials Directive, GCP Directive, ICH guidelines	∅	∅	∅	∅	x
	Examination of different (intended) forms of administration	x	x	x	x	x

Continued on next page...

Table 9 – Continued

Quality information						
Technical details and specifications regarding drug substance, excipients and drug product (e.g., reference standards / materials, stability, etc.), and manufacture	x	x	x	x (Ref. to existent Rx data)	x	
Relevant guidelines: GMP	(x) Not yet in legislation	(x)	x	∅ (N/A)	x	
Administrative information						
Product information: Summary of Product Characteristics (SPC), labeling, and package leaflet	x (w/o SPC)	x (w/o SPC)	x	∅	x	
Results of readability tests	∅	∅	∅	∅	x	
Information about experts used for review/evaluation	x	x	x	x	x	
Environmental risk assessment	∅	∅	∅	∅	x	
Pharmacovigilance: risk management plan (RMP), etc.	∅	∅	∅	∅	x	
OTC specific requirements						
Efficacy and safety						
Ability of self-diagnosis	∅ (N/A)	∅ (N/A)	x	x (Market research data)	x	
Efficacy and safety of dosage form(s) intended for OTC usage (e.g., evaluation of strength, indication, route of administration), comparison with therapeutic options already available OTC	∅ (N/A)	∅ (N/A)	x	x (Ref. to existent Rx data: RCTs, epidemiological studies)	x	
Risk of masking underlying serious diseases	∅ (N/A)	∅ (N/A)	x	x (Market research data, etc.)	x	
Potential of overdose/abuse	∅ (N/A)	∅ (N/A)	x	x (Clinical expert review)	x	
Clinical expert review on potential OTC usage	∅ (N/A)	∅ (N/A)	x	x	x	
OTC drug exposure/post marketing experience (if available, e.g., from other countries)	∅ (N/A)	∅ (N/A)	x	(x) Only overview of classification status worldwide	x (Sales, patient exposure, PSUR data, etc.)	
Label comprehension: readability test	∅ (N/A)	∅ (N/A)	∅	∅	x	
Self-selection	∅ (N/A)	∅ (N/A)	∅	∅	(x)	
Actual use: efficacy, safety, compliance, overdose/abuse	∅ (N/A)	∅ (N/A)	∅	∅	(x)	

6 Qualitative research: expert opinions at a glance

The primary insight gained from the aforesaid Canesten® GYN case study is an obviously quite limited practicability of the existent indefinite legal framework regarding data exclusivity provision for Rx-to-OTC switches based on conservative interpretation. The following chapters are therefore dedicated to the specification of existing and elaboration of, respectively, potential new criteria and/or data categories with the intention to further substantiate (data) requirements for the grant of data exclusivity for Rx-to-OTC switch products. Within this context national (i.e., German) and international experts as well as stakeholders within the field of self-medication, and in particular the Rx-to-OTC switch process, were selected and interviewed on the basis of a qualitative written questionnaire. The present chapter will focus on the analysis and discussion of qualitative research results gathered from these interviews.

The questionnaire was developed in order to get information about and insight into various experts' opinions on the kind of data categories and criteria they would consider relevant for the provision of data exclusivity within the context of an Rx-to-OTC switch of a drug and/or indication formerly only available by prescription. It was comprised of 24 questions (multiple choice and open format) and was subdivided into six main parts: a short introduction, a general part related to the topic, and four more or less specific parts comprised of questions which basically reflected the ideas emerging from the evaluation of relevant literature and case study analyses.

Of note, potential weaknesses of the interview questionnaire have to be kept in mind: the questionnaire was developed for the purpose of collecting qualitative interview data from selected stakeholders in the field of self-medication with regards to their knowledge and opinion on the provision of data exclusivity for Rx-to-OTC switches in Europe and hence no statistically significant outcomes can be drawn. The majority of questions were composed based on the author's preliminary thoughts and considerations related to the definition and relevance of specific data sets potentially qualifying for data exclusivity. Against this background, the fact that some questions might be of a slightly suggestive nature has to be considered as a potential limitation. Moreover, the rather individual nature of Rx-to-OTC switch cases, which was attempted to account for by differentiating at least three possible scenarios³⁶ illustrated by either real or fictive examples, displays another potential drawback in this investigation, as some questions and answers might be better applied to one scenario than to another. The need of specific questions to be discussed on a case-by-case basis has thus to be kept in mind with regards to data analysis and interpretation. Last but not least, the author acknowledges potential bias due to some advocacy groups being "overrepresented"

³⁶ scenario A: new OTC substance, known OTC indication; scenario B: new OTC substance, new OTC indication; scenario C: known OTC substance, new OTC indication

in terms of interview partners as compared to others. Nonetheless, expert interviews were conducted with at least one representative of each stakeholder group in some way involved in the process of Rx-to-OTC switching (i.e., regulatory authorities, patients, pharmacists, physicians, the pharmaceutical industry as well as third party payers).

6.1 Interview results

In a first step, national and international experts well-known in the arena of self-medication and Rx-to-OTC switch were contacted by mail, phone, or at congresses and asked for their willingness to act as interview partner. Further contact persons were subsequently recommended or identified via desk research. Altogether, 13 experts were interviewed and ten of them filled in the written questionnaire they had been provided with regarding the issue of “Rx-to-OTC switches and data exclusivity provision”.

Overall, most expert interviews confirmed and highlighted the fact that data exclusivity, which usually actually affords a temporary market exclusivity, is getting increasingly important for not only the growth of self-medication in general, but also the expansion in new therapeutic areas not yet established within self-medication. However, many experts also pointed out a probably indispensable conflict of interests between industry and political decision makers rendering the tool of data exclusivity less attractive and desirable. Moreover, probably most important as regards the potential value and impact of the present work, individual expert discussions as well as questionnaire results clearly show that there is no common opinion with respect to the interpretation and implementation of Article 74a of Directive 2004/27/EC among experts representing the different interest groups involved in Rx-to-OTC switches. Instead, notwithstanding the high interest they expressed, the topic seems to be rather new to many experts and corresponding views and opinions currently are, if at all existent, rather rudimental and diverse. Altogether, conversation partners frequently alluded to the multiple political considerations influencing an individual Rx-to-OTC switch decision. This is also reflected by individual answers and a lower response rate regarding particular questions given in the questionnaire. More specifically, as to the substantiation of the legislation (i.e., its interpretation and specification) feedback for the most part was only limited mainly due to lacking knowledge and associated self-effacement in providing substantial input.

The main results are depicted in the following: first of all, when asked about comprehensibility, precision and relevance with a view towards requirements or criteria, respectively, for data generation, the existing legal framework regarding the provision of data exclusivity for Rx-to-OTC switches (i.e., Article 74a, Directive 2004/27/EC) was mostly judged to be in the range of 2-3 within a 6 point scale (1 = very good, 6 = very bad) or no opinion was expressed. With respect to the current duration of the exclusivity period, one year was regarded as “too short” by the majority of respondents (cf. Figures 7 and 8). On the contrary, the period was considered as “too long” by one survey participant.

In the next section the legal postulation of pre-clinical test data as potential data category for the generation of data with a claim on data exclusivity had to be assessed under the aspect of appropriateness for Rx-to-OTC switching. Figure 9 shows a slight majority in

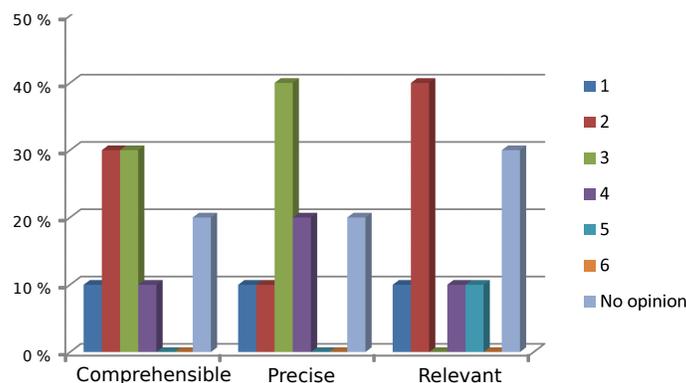


Figure 7: Judgment of the existent legal provisions regarding data exclusivity (Article 74a, Directive 2004/27/EC); 1 = very good, 6 = very bad (n = 10)

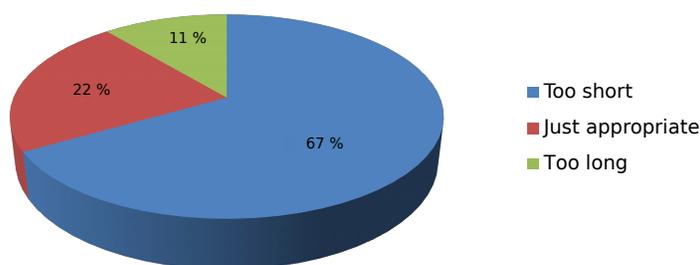


Figure 8: Assessment of the length of the exclusivity period currently granted for Rx-to-OTC switches within Europe (n = 9)

terms of pre-clinical test data being “not necessary” and/or “not appropriate”, respectively. However, almost two thirds of the experts asked could imagine a re-analysis of already existing pre-clinical Rx data that had been generated for Rx authorization with respect to OTC critical aspects as potentially relevant (meaning at least supportive) with a view towards data generation eligible for exclusivity (cf. Figure 10). Among positive judgments, the following aspects were named for pre-clinical investigation on the grounds of potential OTC relevance:

- drug interactions with both Rx and OTC drugs,
- overdosing,
- acute/chronic toxicity,
- pharmacokinetics,
- new fixed combinations,
- new routes of administration,

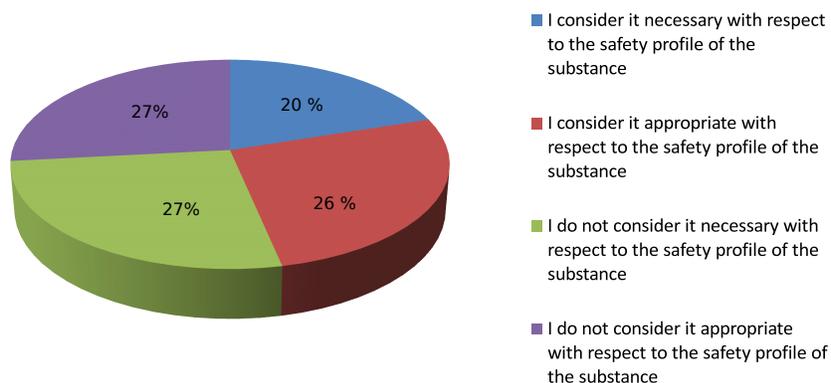


Figure 9: Evaluation of the appropriateness of pre-clinical test data for a claim on data exclusivity within the context of Rx-to-OTC switches ($n = 12$ entries)

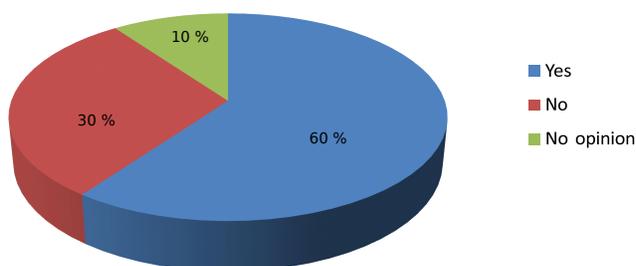


Figure 10: Potential relevance of the re-analysis of existent pre-clinical Rx data under OTC pertinent aspects for the provision of data exclusivity in case of Rx-to-OTC switches ($n = 10$)

- new excipients,
- cancerogenicity.

The idea of a potential re-analysis of already existing clinical Rx data under OTC pertinent aspects for anticipation of self-medication practice found even more encouragement when it comes to clinical data as basis for the provision of data exclusivity for Rx-to-OTC switches and experts showed more or less mutual consent in this case (see Figure 13). Against the background of such a data re-analysis, safety/pharmacovigilance, size and kind of study population were judged as most significant design and outcome parameters, respectively, and were thus rated with “1” (on a 6 point scale with 1 = very important and 6 = not important at all) by most of the experts, followed by the analysis of special patient groups and compliance parameters as shown in Figure 11.

Another concept that was integrated into the expert questionnaire and suggested as a further potential category that the provision of data exclusivity for Rx-to-OTC switches could be built on is the generation of data by conducting actual use studies, self-selection studies, and/or label comprehension studies as subcategories of the former. The study concept has

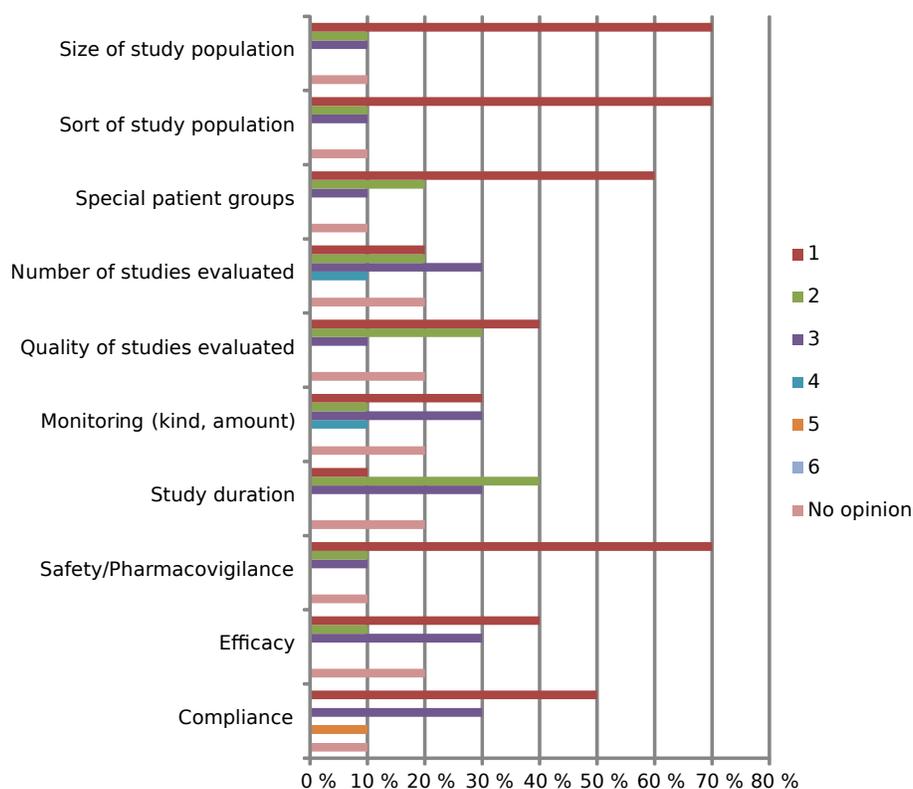


Figure 11: Assessment of the significance of different design and outcome parameters within the context of a potential re-analysis of existing clinical Rx data under OTC relevant aspects; 1 = very important, 6 = not important at all (n = 10)

been widely used in the US in a mainly simulated OTC setting providing OTC-like data to support the Rx-to-OTC switch or OTC registration of respective medications and/or indications. Figure 12 shows that this kind of study concept was ascribed a comparable relevance within Europe (large majority of positive votes) when it comes to the generation of data of informative value regarding potential OTC usage.

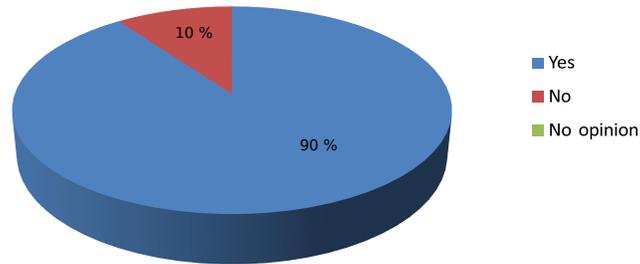


Figure 12: Estimated relevance of the generation of OTC-like data for an envisaged Rx-to-OTC switch for the provision of data exclusivity within Europe (n = 10)

Among supporters of such a study concept, data referring to “label comprehension” and especially “actual use” were assessed as most significant against the background of entitlement to exclusivity (see Figure 14).

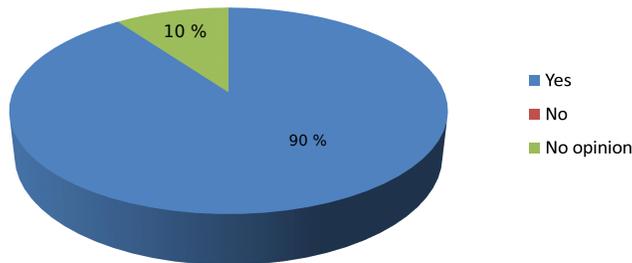


Figure 13: Potential relevance of the re-analysis of existent clinical Rx data under OTC pertinent aspects for the provision of data exclusivity in the case of Rx-to-OTC switches (n = 10)

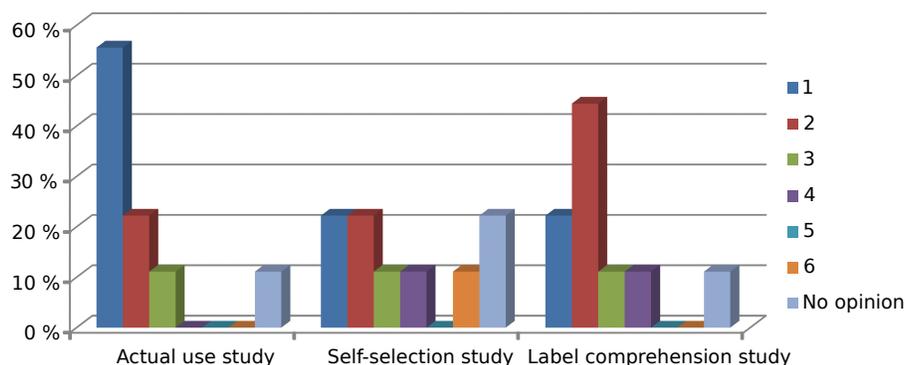


Figure 14: Generation of OTC-mimicking data: evaluation of different subtypes in the context of their potential significance for the provision of data exclusivity for Rx-to-OTC switches ($n = 9$)

Furthermore, experts were asked to rate different study parameters (depicted in Figure 15) according to their significance for the design of such studies depending on the switch scenario to be considered; that is, Rx-to-OTC reclassification of a substance (scenario A), an indication (scenario B), or both (scenario C). Out of all parameters, “representativeness” was judged to be of highest importance particularly in the case of a new OTC indication (B), but also for a new OTC substance in a known OTC indication (A), and to a lesser extent for both a new OTC substance and OTC indication (C). Furthermore, the “selection of study population” as well seems to play a major role for a new OTC indication treated with a known OTC substance (B). “Randomization” is another feature in study design obviously highly appreciated, even more for scenarios A and B than for C. This is followed by the parameters “special patient groups” to a little larger extent in scenario B than in A and C as well as “follow-up”, judged more important for scenario C than for A and B. Residual assessments can be derived from Figure 15 below.

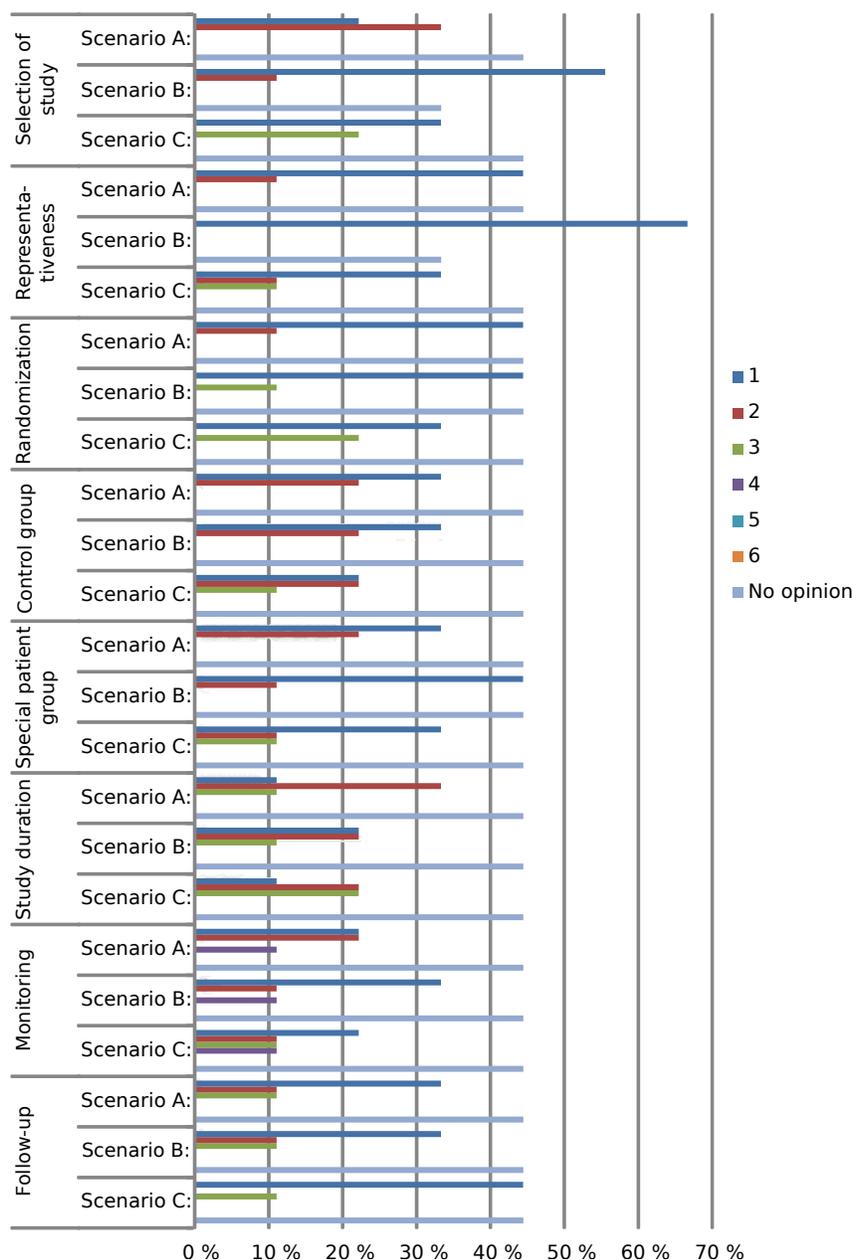


Figure 15: Assessment of different study (design) parameters against the background of the generation of relevant data for a claim on data exclusivity in the case of Rx-to-OTC switches; scenario A: new OTC substance, known OTC indication, scenario B: known OTC substance, new OTC indication, scenario C: new OTC substance, new OTC indication (n = 9)

The next part of the questionnaire focused on the concept of so-called “collaborative care”. As has already been discussed above, apart from classical switches (i.e., the reclassification of easily self-diagnosable diseases and potential treatment options) the removal of

indications within the scope of prevention or therapy of (semi-)chronic conditions initially requiring medical diagnosis and subsequently managed by patients independently is another model conceivable within the context of the evolution of the self-medication sector including Rx-to-OTC switch movement. Survey participants were asked if they considered data demonstrating self-diagnosis ability and autonomous therapy management by patients after an initial doctoral diagnosis as basically appropriate to qualify for data exclusivity. As depicted in Figure 16 below, the majority of experts questioned could – where appropriate – imagine data demonstrating the functioning of collaborative care under OTC conditions to qualify for the grant of data exclusivity.

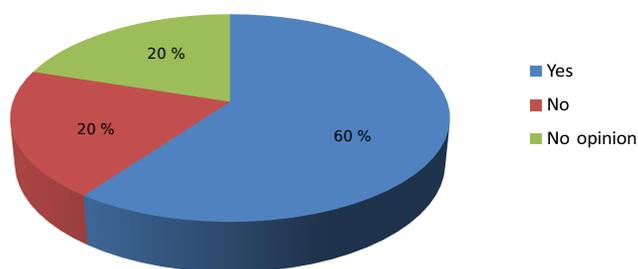


Figure 16: Expert opinions on the possibility of the general qualification of data verifying so-called “collaborative care” under OTC conditions (n = 10)

Within this context the development of an adequate method or algorithm, respectively, that enables patients to correctly self-assess and subsequently self-treat their symptoms was rated best and preferred by the majority of experts in terms of its potential significance for data exclusivity, followed by the development of a measurement device easily operated by patients themselves (see Figure 17).

More specifically, data from actual use studies either with or without specialized personnel demonstrating patients’ correct self-assessment and effective therapeutic self-management of their conditions or disease prevention were estimated to potentially be able to contribute to data exclusivity provision for a respective Rx-to-OTC switch. Besides, data investigating and showing increased compliance due to measurement devices or activities developed to assist patients in therapeutic self-management based on the specific Rx-to-OTC switch of either a certain drug substance, indication, or both were partly attributed exclusivity potential (cf. Figure 19).

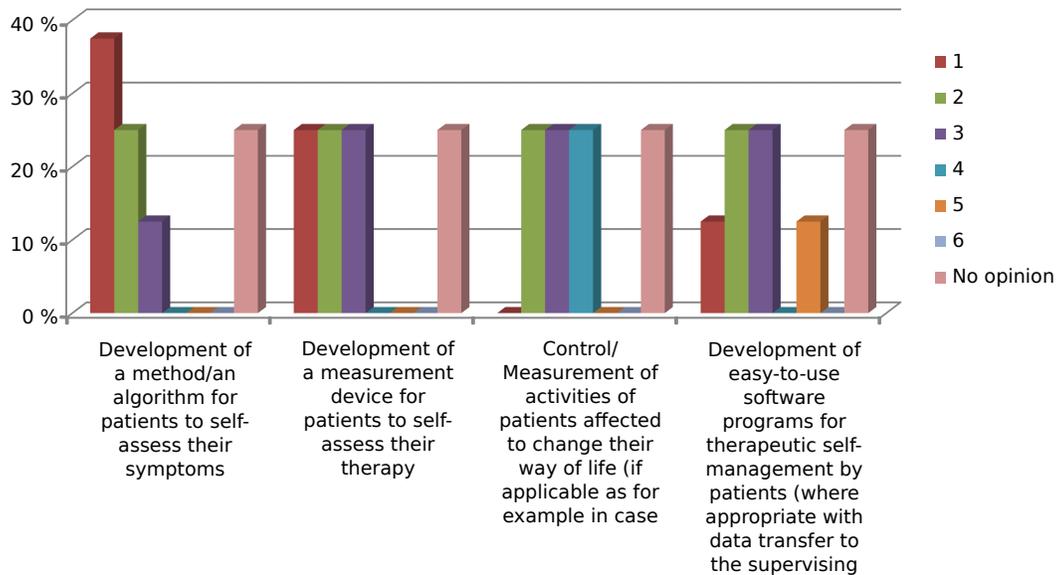


Figure 17: Evaluation of different therapy management aspects regarding their appropriateness in contributing to data exclusivity; 1 = very good, 6 = very bad ($n = 8$)

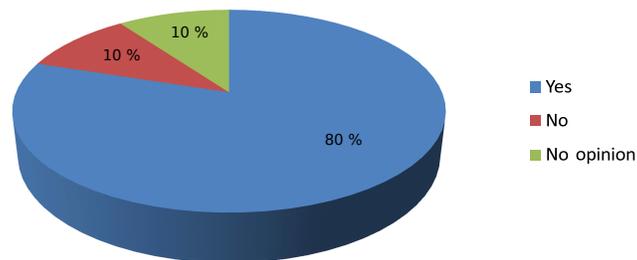


Figure 18: Relevance of a comparison with therapeutic alternatives already available OTC by means of a clinical study or the like (e.g., phase IV) in reference to a potential claim on data exclusivity ($n = 10$)

Another important aspect to investigate within the context of an envisaged Rx-to-OTC switch might be the comparison with existing OTC therapy alternatives in terms of, for example, a clinical safety/efficacy study. As shown in Figure 18, this opinion is at least held by the plural among experts who consider safety/pharmacovigilance and the kind of study population as the most important parameters in such a setting, succeeded by the size of study population, including special patient groups, as well as efficacy and compliance as downstream parameters (cf. Figure 20).

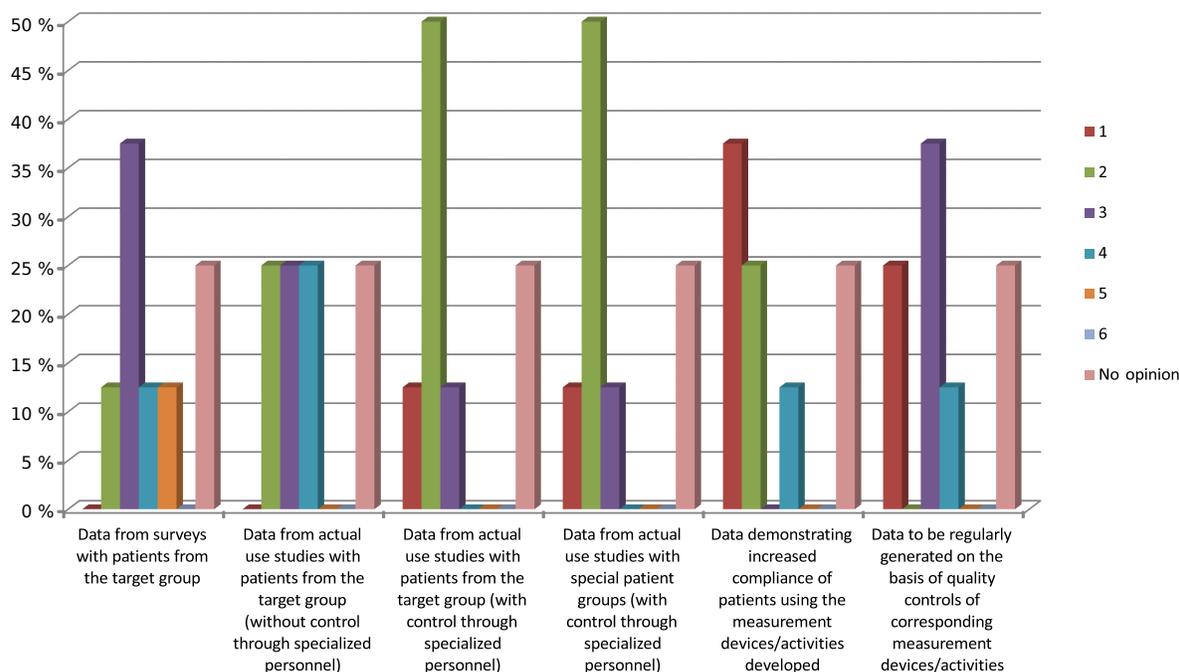


Figure 19: Assessment of (partial) exclusivity potential of different data categories demonstrating patients’ diagnostic self-assessment and/or therapeutic self-management of (potential) OTC conditions or disease prevention, respectively; 1 = extremely relevant, 6 = not relevant at all (n = 8)

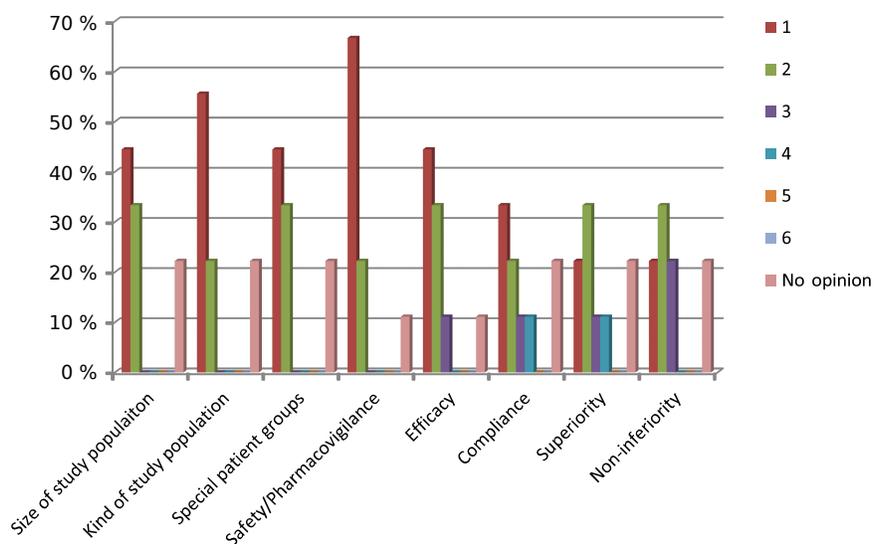


Figure 20: Role of different study parameters of a comparative (clinical) study with a switch candidate and an existing therapeutic alternative regarding a potential demand for data exclusivity for the respective Rx-to-OTC switch; 1 = very important, 6 = not important at all (n = 9)

Additionally, the generation of non-interventional study (NIS) data in the sense of a classical AUS, but under specific constraints (so-called “conditional release”) was suggested to experts in order to be assessed for possible eligibility for exclusivity. This means, that study details including design, outcome measures, etc. could be discussed and agreed upon with the accordant decision making bodies ante switch to be then put into practice post switch in order to collect data and insights concerning efficacy/effectiveness, safety, usage pattern, as well as patient satisfaction, etc. under daily-life conditions of self-medication. Most experts could imagine such a situation and presumably would accept this kind of study data as adjuvant in a claim on data exclusivity, although one third of them opposed this possibility or did not have an opinion on this issue (see Figure 21).

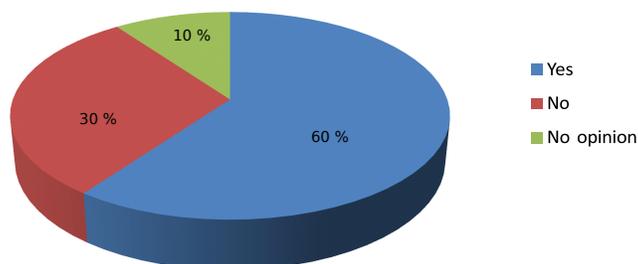


Figure 21: Expert opinions on a so-called “conditional release” concept as potential data basis for data exclusivity with the requirement of actual use (i.e., real-life) data generation (non-interventional study) post switch (n = 10)

Without doubt, comprehensive and detailed educational measures including specific training programs for HCPs and patients, brochures, interactive information services, etc. play a key element during the establishing phase of a Rx-to-OTC switch, especially in case of more complex and intensive conditions in terms of management as well as monitoring. Experts were thus asked to judge “informational and educational measures” as another possible data category at least partly accounting for the provision of data exclusivity. As depicted in Figure 22, more than half of the experts interrogated estimated comprehensive educational material and activities for target groups involved in a certain switch as valuable in regards to a claim on data exclusivity. Informational and educational material got the highest rating in this regard, followed by a demand for elaborated training programs and regular quality checks (q.v. Figure 23).

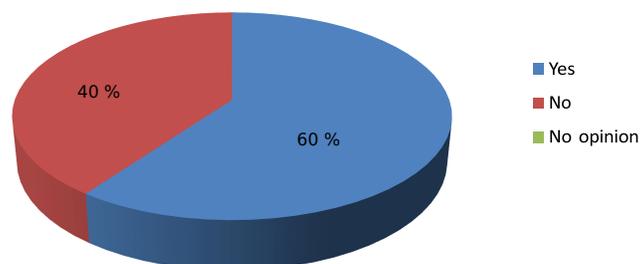


Figure 22: Experts' judgment of comprehensive informational and educational material within the context of a Rx-to-OTC switch as possible basis for data exclusivity provision ($n = 10$)

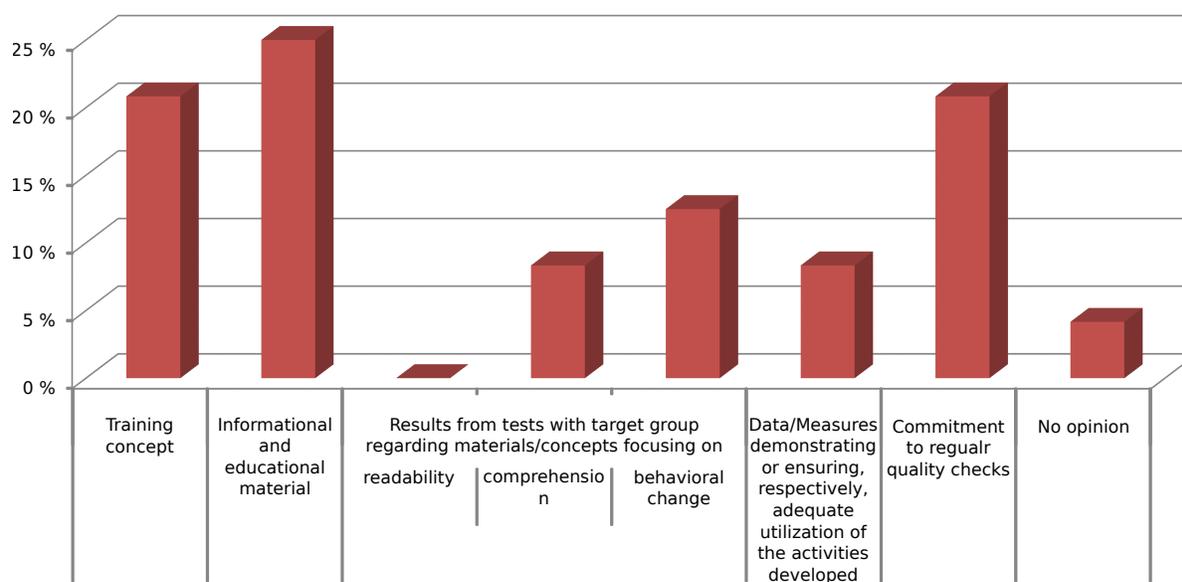


Figure 23: Estimation of the potential relevance of different aspects related to information and education for a potential claim on data exclusivity ($n = 24$ entries)

The last section of the questionnaire consisted of two questions regarding pharmacoeconomic aspects in terms of a potential increase in public health value associated with a specific Rx-to-OTC switch. Again more than half of the experts could imagine pharmacoeconomic analyses preferably investigating non-monetary parameters such as improvement of quality of life, for example, as partly suitable for a demand for data exclusivity, whereas the remainder mainly does not believe such data being adequate in order to be accepted by regulatory authorities (see Figures 24 and 25).

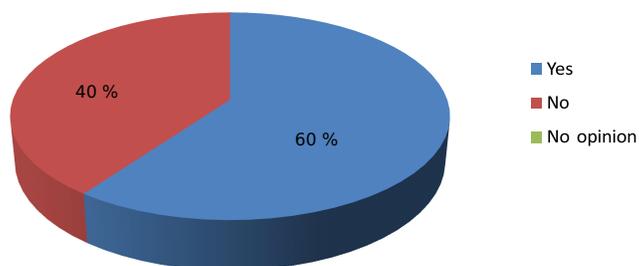


Figure 24: Respondents' opinion on the appropriateness of pharmacoeconomic data with regards to entitlement to data exclusivity (n = 10)

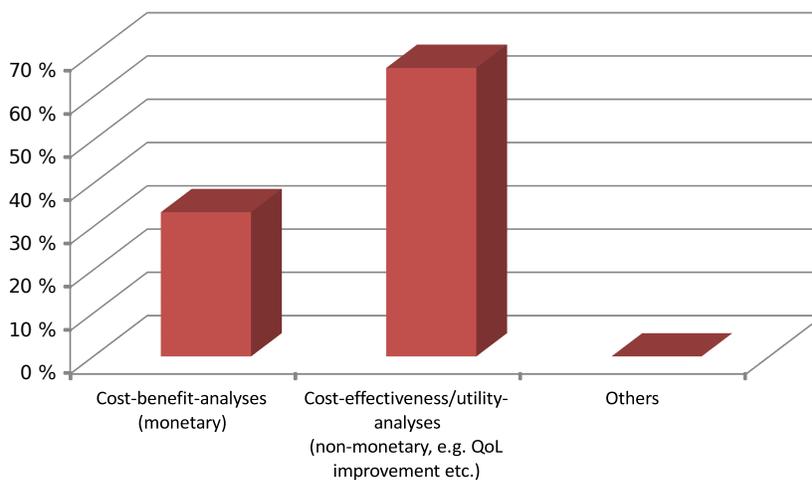


Figure 25: Rating of monetary/non-monetary pharmacoeconomic analyses according to their potential to be used within a claim on data exclusivity for Rx-to-OTC switches (n = 6)

6.2 Summary and conclusion

In order to specify and substantiate the currently rather indefinite legal framework related to data exclusivity provision for Rx-to-OTC switch products, national (i.e., German) and international experts regarding the reclassification of medicines had been selected for participation in qualitative interviews based on a written questionnaire. From an overall perspective, knowledge of and insight in corresponding legal provisions was rather scarce. Nevertheless, the tool of data exclusivity was highly appreciated with a view to the future evolution of the self-medication sector.

More specifically, as can be derived from interview results, the relevance of the existent data category of “pre-clinical tests” with a view towards appropriateness for data exclusivity provision for switch products is considered to be rather low by the majority of experts, if not explicitly focusing on OTC critical aspects. OTC relevant design and analysis parameters (study population, safety/pharmacovigilance, representativeness, etc.) were similarly stressed when referred to the second data category currently available for a claim on data exclusivity (i.e., clinical trial data) at best newly generated or otherwise re-analyzed from Rx. Particular importance was thereby ascribed to data emanating from studies conducted in either a real or in an OTC-like setting to investigate label comprehension, self-selection, and overall actual use (e.g., if applicable) compared to therapeutic alternatives available.

Moreover, informational and educational material as well as devices facilitating self-management, such as drug monitoring and compliance within the context of more complex drug therapies potentially to be reclassified OTC were judged to (at least partly) be accounted for (e.g., as additional data category) with respect to eligibility for data exclusivity provision.

Based on the aforementioned, the author concludes that the generation of any kind of data mimicking, as much as possible, conditions of the targeted OTC setting and/or supporting safe and effective OTC usage is of the utmost importance in regards to potential eligibility for data exclusivity provision. Of note, according to the nature of self-medication (i.e., no medical intervention), the generation of OTC-like data is inevitably linked with a merely observational, non-interventional study design. The quality and validity of this kind of study data are, however, often challenged by the medical community rendering its potential with respect to data exclusivity qualification rather arguable.

Thus, in addition to the expert input gained regarding the potential significance of different study parameters in terms of reevaluation of respective pharmacoepidemiological study data and associated eligibility for data exclusivity, statistical approaches to enhance the validity of observational study data were identified via literature research. These will be briefly presented and one of them will be subsequently applied to a practical example in the following Chapter 7.

7 Data validity in observational research: a statistical approach to reduce potential biases

As can be concluded from the qualitative interview results depicted above (q.v. Chapter 6), an important role regarding data exclusivity provision, in the context of Rx-to-OTC switches, is attributed to the generation of observational OTC-like study data in the case of adequate quality provided. However, as to the latter, there is a continuous discussion among experts with the validity of non-randomized observational study data often being doubted.

Based on a short overview of the characteristics and advantages/disadvantages of both randomized controlled trial as well as non-randomized observational study research, the present chapter is, therefore, dedicated to the discussion of the possibilities to enhance the validity of observational study data. On the grounds of a potential role regarding eligibility for data exclusivity provision within the context of Rx-to-OTC switches, applicability will subsequently be demonstrated through a practical example.

7.1 Randomized vs. observational (non-randomized) study research

Several principal methods of study research are available with an important distinction between so-called randomized controlled trials (RCTs), mainly conducted in a more or less experimental setting and non-randomized studies including quasi-experiments, natural experiments and non-interventional observational studies (i.e., prospective or retrospective cohort or case-control studies) (Britton 1998).

“Evidence-based medicine” (EBM) classifies studies into grades of evidence based on research architecture with internal validity (i.e., correctness of the results) as the criterion for hierarchical rankings (Concato 2000; Concato 2004). According to this approach, RCTs are considered as the gold-standard (Britton 1998; Schaefer 2007) providing the highest grade of evidence and quality information, most often serving as the foundation to regulatory decision making on drug approval or labeling, etc. (Brass 2010). On the contrary, observational studies usually fall into intermediate levels (Concato 2000; Concato 2004). Over the past years there were recurrent debates about the merit of observational versus randomized studies with criticisms primarily aiming at a claimed overestimation of intended (i.e., treatment effects) (Benson 2000; Britton 1998; Ray 2003). Instead, successes are attributed to “the study of unintended effects – adverse effects of environmental factors, of behavior, and of constitutional characteristics” (Miettinen 1983). Recent systematic review analyses, however, have come to the conclusion that neither RCTs nor non-randomized studies seem to give larger or smaller treatment effects and that variation in results occurs equally within both RCTs and non-randomized studies each mainly reflecting a high variability in study design and analysis (Benson 2000; Britton 1998; Concato 2000; Concato 2004).

In fact, both research designs have their own benefits and limitations when it comes to internal and external validity of study results. “The difference goes back to the respective core problems in these two types of studies – confounding in non-experimental research and ethics in experimentation” (Miettinen 1983).

As to internal validity, the absence of any type of bias due to potential confounders, all observational studies have a fundamental deficit with their design not being an experimental one. Within this setting, any differences in outcome between treatment and control groups may possibly be due rather to systemic differences in baseline characteristics of the two comparison groups instead of resulting from the effectiveness of the therapeutic intervention (Britton 1998). By contrast, randomized treatment assignment in experimental RCTs provides the basis for reliably unbiased causal estimates of treatment effects (Pocock 2000), as subjects compared should, at best, only differ in their exposure to the intervention under evaluation. The main benefit of randomization is, thus, that it is able to balance known and, in particular, unknown potential confounders (Concato 2004). This allows for high internal validity of study results and renders RCTs indispensable in drug development with respect to the elementary study of intended therapeutic effects.

On the other hand, external validity indicating generalizability of results is often comprised in RCTs due to strict eligibility criteria for study participants and high levels of exclusion (e.g., special patient populations such as elderly, women, ethnic minorities, etc.). This restriction in study population may lead to a lack of representativeness impairing the generalizability of treatment results to the target population (Britton 1998; Concato 2004). A much broader range of patients, also generally containing representatives of populations at risk, is often included in non-randomized studies (Concato 2000), thus much better representing the “real-world conditions” of medical practice (Rubin 1997). Hence, although on the expense of the power to detect drug effects, such a naturalistic study setting allows for better generalizability of study results (Brass 2010).

The criterion of large patient populations is also one of the rationales underlying the usage of observational data to monitor for drug toxicity, including rare serious adverse events, or to study risk factors for disease and prognostic indications, which are all hard to detect within a small population. Moreover, observational studies generally are more or less easy and cheap to conduct while at the same time offering timeliness of data. In situations where RCTs are impossible or unethical, they constitute the only alternative for gathering important study data (Benson 2000; Pocock 2000).

In general, all types of studies are located on a continuum ranging from irrelevant to relevant with respect to answering specific research questions. Real-world studies typically lie somewhere in the middle, whereas representativeness is more probable within non-experimental, observational studies and control over existing, potentially confounding variables usually is easier and higher within randomized experimental studies (Brass 2010; Rubin 1974).

7.2 Observational research and the estimation of causal treatment effects

In theory, referring to clinical and therapeutic research, the provision of evidence of efficacy requires: a study (= experimental conditions), in a cohort (= repeated observations of many

patients), with a control cohort (= comparison), and a randomly generated assignment of patients to test or control cohort (= randomization) independent of all the other factors. Against this background the concept of a randomized controlled clinical trial seems to be the only reliable study research design (Kiene 1998).

However, within the wider context of “therapeutic causality” it is concluded elsewhere that non-experimental studies apart from investigating unintended (e.g., safety) effects (see Section 7.1 above) are likewise able to provide evidence of efficacy³⁷ and infer causal treatment effects (Concato 2000; Kiene 1998; Rubin 1974). For example, Concato even holds the opinion that well-designed observational studies are able to “produce results similar to those of RCTs when similar criteria are used to select study subjects” and that “the popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of health care professionals” (Concato 2000).

7.2.1 Potential biases and confounders in observational research

As mentioned before, the major disadvantage and limitation regarding the validity of study results from non-randomized, observational study research is the inevitable presence of confounding factors that make these studies prone to bias. “Confounding” generally occurs, when a variable is related to both exposure and outcome variables for the association of interest with the exposure variable depicting the confounding variable, rather than actually causing the outcome (Concato 2004).

By far most cited and most obvious is a systematic effect called “selection bias” which encompasses many subtypes of potential biases some of which are mentioned exemplarily below. The term generally refers to the distortion of a statistical data analysis due to the method of collecting samples. Without controlling for this kind of bias, any conclusions drawn from the study may be kind of false. Selection bias might occur, if a patient’s particular treatment is deliberately chosen rather than randomly assigned. Consequently, the risk of systematic differences in outcomes not to be due to the treatment itself is high (Pocock 2000), as selection bias may confound real differences causal to treatment. To give a practical example, selection bias can be introduced when the base where study participants are sampled from indirectly depends on exposure variables in an unknown way. If study control subjects are selected by telephone, for instance, potential candidates not having a phone are automatically excluded irrespective of their eligibility (Wacholder 1992a). Selection bias may also be introduced by practitioners or even patients themselves when deciding on treatment (treatment preference). If treatment assignment is dependent on the indication, an effect called “confounding by indication” might occur. Hence, in a non-randomized study design, selection or treatment allocation bias will complicate the assessment of drug therapy as there might be definite prognostic reasons for favoring one treatment over another, which will be deceptive in the comparison of coarse outcomes (Britton 1998).

³⁷ i.e., rather “effectiveness”, as studies observing real-world conditions are concerned in this case (see Section 2.1)

“Chronology bias” comes into play if risk associated with a certain treatment varies with time. For example, time dependent risk may be a consequence of physiologic adaptation during prolonged treatment periods or may be associated with medications that display both beneficial and adverse effects with different induction periods (Ray 2003). This effect is closely linked to the risk of “prevalent user bias” indicating that prevalent users of chronic medication (who already took the type of medication under evaluation prior to study entry) can introduce two types of bias – first of all a potential underestimation of events occurring early in treatment phase and secondly the inability to account for disease risk factors that may be changed by the study drugs (Concato 2004; Ray 2003). Study analyses including prevalent users are also more susceptible to influences of “adherence bias”, as long-term users obviously seem to be more adherent to therapy. “Even for drugs whose physiologic effects do not vary with duration of therapy, including prevalent users may amplify adherence bias. This bias is thought to underlie the findings from analyses of data from several randomized controlled trials in which better adherence to placebo has been associated with a 30-60 percent reduced risk of death from cardiovascular disease and fewer episodes of fever or infection in cancer patients [...]. It is thought that adherence is a marker for a constellation of unmeasured factors, some of which may be time dependent, associated with better prognosis” (Ray 2003).

A scenario that holds true for many medications and in particular those used for prevention is known by the term “healthy user effect”. As individuals willing to participate in preventive studies tend to be healthier and also more health conscious, more affluent, better educated, and demonstrate higher treatment compliance, treatment benefits might be overestimated in this patient population. Therefore, these factors potentially interacting with treatment intervention must be adequately measured and controlled for with study analysis so as to eliminate systematic differences between the study group and the remainder population (Britton 1998; Concato 2004; Ray 2003).

Several other biases are addressed elsewhere, e.g., by Wacholder in his analysis of selection of controls in case-control studies (Wacholder 1992a; Wacholder 1992b; Wacholder 1992c).

7.2.2 Dealing with biases and confounders in observational research

Some of the most relevant biases are depicted in Subsection 7.2.1 above. In theory, an indefinite number of confounders is existent in observational research, possibly leading to biased research results. In effect, it is impossible to actually control every single variable, especially, if confounding covariates are unobserved and unmeasured.

Nevertheless, if observed, major systematic bias and confounding effects can be taken into account and reduced or even eliminated. Of note, however, as a general requirement to this, some essential assumptions are to be adopted. These are based on the theoretical framework of the counterfactual account of causality which was first formalized and extended to non-experimental study designs in the 1970s by Donald B. Rubin (Holland 1986; Rubin 1974). Key to this framework is the definition of causal effects through potential outcomes (Tsiatis 2006). It theorizes that individuals assigned to either treatment or control group have a potential outcome in all states (i.e., both the observed and the unobserved state). Each

subject in the treatment group has an observable outcome in the treatment state and an unobservable counterfactual outcome in the control state. The contrary holds true for subjects in the control group (Winship and Morgan 1999). These potential outcomes are also referred to as counterfactual random variables, as it is impossible to observe them simultaneously (Tsiatis 2006). Within this context, in theory, the causal treatment effect for each subject is defined as the difference between the two potential outcomes in the treatment and control states. Yet as pointed out above, it is impossible to observe and hence to directly calculate the causal treatment effect at a subject-specific level.

Notwithstanding the aforementioned, the estimation of the average causal treatment effect at the population-level, which equals the expected value of the subject-specific causal treatment effect, may be feasible under certain assumptions (Tsiatis 2006; Winship and Morgan 1999). The first assumption is the so-called “Stable Unit Treatment Value Assumption” (SUTVA) meaning that “the observed response for [a certain] individual in the sample should not be affected by the response of the other individuals in the sample” (Tsiatis 2006). The second assumption refers to the so-called “strongly ignorable treatment assignment” implicating that any assignment to either treatment or control group is unconfounded conditional on the observed covariates (i.e., there are no unmeasured confounders) (Yanovitzky 2005). If so, the assumption that treatment assignment is independent of potential outcomes given the observed pre-treatment variables may be reasonable. Of note, although not testable, the latter is key to being able to estimate the average causal treatment effect in observational study research (Tsiatis 2006). The third assumption is that the probability of being assigned to either treatment or control is unlikely to be zero or one for all subjects conditional on the observed confounders. That is, confounders have to relate to potential outcomes and thus have to be selected accordingly (Tsiatis 2006; Yanovitzky 2005).

Based on the aforementioned assumptions, the relevant literature describes various methodologies and techniques with a view towards practical application and dealing with potential confounders in observational research. Examples are: covariance adjustments based on multivariate regression, stratification (subclassification), or matching (D’Agostino 1998; Qin 2008; Rosenbaum 1983; Rubin 1973; Rubin 1979; Zanutto 2006).

Another technique which has become increasingly popular within recent years is based on the estimation of so-called propensity scores (Glynn 2006; Seifert 2009). Propensity score methodology was introduced by Rosenbaum and Rubin who define a subject’s propensity score as “conditional probability of assignment to a particular treatment given a vector of observed covariates” (Rosenbaum 1983). More specifically, as depicted in Figure 26 on the right, the propensity score is a single-number summary of the set of observed covariates from which it was estimated with a value always between 0 and 1 (Qin 2008; Yanovitzky 2005). Importantly, if treatment is strongly ignorable given a specific set of observed covariates as described above, it is also strongly ignorable given the propensity score as conditional function of these covariates. Therefore, at any value of the propensity score “the difference between the treatment and control means is an unbiased estimate of the average treatment effect” at that particular value of the propensity score (Rosenbaum 1983).

In conclusion, if respective assumptions are acknowledged, it is thus possible to limit calcula-

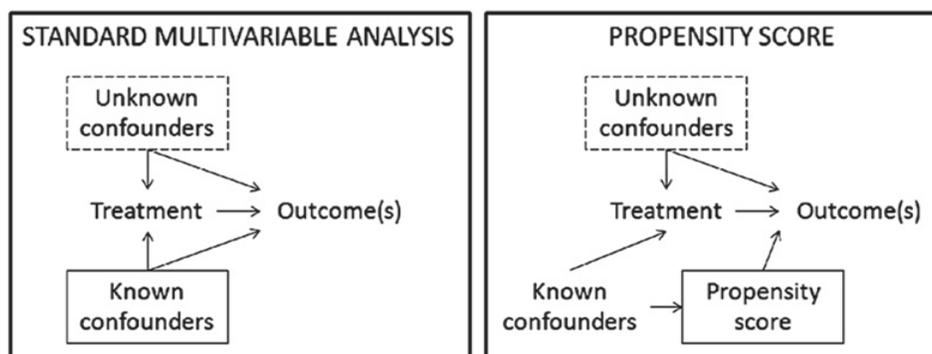


Figure 26: Basic idea underlying standard multivariable and propensity score analysis, respectively. As demonstrated by the continuous line, known confounders in contrast to unknown confounders (dotted line) can be adjusted for (from Biondi-Zoccai et al. 2011)

tion to the use of propensity scores when estimating average causal treatment effects within observational study research.

7.2.3 Practical illustration of the theory

Based on the above mentioned property of propensity scores theoretically being adequate to estimate causal treatment effects in non-randomized observational studies, propensity score methodology will now be applied to a practical example.

The example is about the comparison of two therapeutic options for the therapy of vaginal mycosis, with one option considered as “treatment” and the other one as “control”. Thereto the following outcome variables were investigated:

- pruritus, burning sensation, redness, swelling, increased discharge, pain at urination, pain at sexual intercourse (multiple selections possible)

as well as

- duration until considerable improvement of these symptoms.

The latter was measured in days and/or minutes. Symptom intensity was measured before treatment and one, two, three, and seven days thereafter on a scale ranging from 0 to 3 with 0 = none, 1 = little, 2 = modest, and 3 = severe.

Additionally, the following 13 covariates were determined as potentially outcome-relevant pre-treatment characteristics:

- age, body weight, body size, duration of symptoms before treatment (days), impairment of daily activities prior to treatment, impairment of quality of life prior to treatment, predispositions (stress/mental strain, (post)antibiotic therapy, cortisone therapy, diabetes mellitus, immunosuppression, adolescence, menopause, and others), previous

vaginal infection, pregnancy, acute status, previous therapy, macroscopic status, and microscopic status.

The most frequently reported symptom was pruritus. Taking this as an example, the following outcome variables were considered:

- duration until symptom improvement
- difference between intensity of pruritus on day one of therapy and intensity at baseline before beginning of the therapy
- difference between intensity of pruritus on day three of therapy and intensity at baseline before beginning of the therapy

i.e., for pruritus, the outcome variable was “symptom score on day one (day three) after applying one of the options (i.e. treatment or control, respectively) – symptom score before applying one of the options”. Small values therefore denote good performance.

The first step in employing a covariate adjustment in an observational study is to select a set of potential confounders. The 13 variables listed above were assumed to have a possible relation to both outcomes and treatment assignment and were thought to cover all or at least the major part of such covariates. Furthermore, since patients were assigned to the treatment or control group independently of each other and since they reported the results independently of each other at the end of the study, it seemed reasonable to assume that the individual response of one patient was not affected by the response of any other patient and that therefore the SUTVA held. Thirdly, the common support was checked and taken into account in the computations.

The estimators used in the example can be described as follows: let T be an indicator of observed treatment exposure ($T = 1$ if treated, $T = 0$ if control), let Y be an outcome variable, and X be a vector of covariates. Let n_1 be the number of treated objects, n_0 the number of controls, and $n = n_1 + n_0$. Let $p_i = 1, 2, \dots, n$ be the propensity scores. The unconditional (“naive”) average treatment effect (ATE) is

$$ATE_{uncond} = E(Y|T = 1) - E(Y|T = 0), \quad (\text{i})$$

where $E(\cdot)$ denotes expectation (average), which for observational studies in general is biased. The unbiased, covariate-adjusted average treatment effect is

$$ATE_{covadj} = E_X [E(Y|T = 1, X) - E(Y|T = 0, X)]. \quad (\text{ii})$$

Expression (i) was estimated by

$$\widehat{ATE}_{uncond} = \frac{1}{n_1} \sum_{i=1}^n T_i Y_i - \frac{1}{n_0} \sum_{i=1}^n (1 - T_i) Y_i. \quad (\text{iii})$$

As mentioned above (see Subsection 7.2.2), there are several ways to estimate (ii). In the example study inverse probability weighting with estimator

$$\widehat{ATE}_{covadj} = \frac{\sum_{i=1}^n \frac{T_i Y_i}{p_i}}{\sum_{i=1}^n \frac{T_i}{p_i}} - \frac{\sum_{i=0}^n \frac{(1-T_i) Y_i}{1-p_i}}{\sum_{i=0}^n \frac{1-T_i}{1-p_i}} \quad (\text{iv})$$

was used. Lunceford and Davidian compared some commonly used estimators of the average treatment effect and found that (iv) performed well (Lunceford and Davidian 2004).

In the example study there were 461 patients with complete data for the covariates, of whom $n_1 = 204$ were treated and $n_0 = 257$ were controls. The propensity scores were estimated for these 461 patients on the basis of a logistic model and kept fixed.

An available case analysis was conducted with respect to the outcome variables. Depending on the outcome variable, the proportion of available cases laid between 83.3 % and 94.1 % for the treated and 87.2 % and 95.7 % for the controls. The computations were conducted both for the “naive” estimator (iii) and for the covariate-adjusted estimator (iv). Results are depicted in Table 10.

The main reason for presenting these data is to give a viable real-life example that bias in observational studies can be reduced with the application of appropriate methods. Mathematically, the bias of an estimator of a population parameter θ is the difference of the expectation of the estimator and the true value of the parameter in the population, i.e.,

$$\text{bias of an estimator of } \theta = \text{expectation of the estimator} - \theta.$$

Here θ corresponds to the average treatment effect. The values of the unconditional (naive) ATE-estimators for the three outcome variables (formula (iii) above) are displayed in column six of Table 10. The bootstrap was used to assess the bias of these estimators as described below (Efron and Tibshirani 1993).

The covariate-adjusted average treatment effects presented in column three of Table 10 corresponding to formula (iv) above are (approximately) unbiased if the fundamental assumptions (SUTVA, no unmeasured confounders) are fulfilled. They can therefore be considered as the “true” values of the ATE. It remains to determine the expectation of the ATE-estimators in column six of Table 10.

For this purpose 10,000 independent bootstrap samples were drawn from the data. For each such sample the average treatment effect was evaluated according to formula (iii). Finally, the bootstrap expectation of these estimators was approximated by the average of the 10,000 ATE-values. Results are shown in column seven of Table 10, the corresponding bias values in column eight. Column nine contains the bias in percent of the true value given by the formula

$$\text{Bias } \% = \frac{|bias|}{|true\ value\ of\ parameter|} * 100, \quad (\text{v})$$

where $|\cdot|$ means absolute value, which gives a better impression of the size of the bias. It can be seen that the naive estimators were biased between 5.7 % and 23.4 %. Without adjustment, the naive values could therefore lead to wrong decisions.

7.3 Summary and conclusion

Randomized controlled trials are considered as gold standard within evidence-based medicine. They mainly differ from non-randomized observational studies by generally exhibiting high internal validity (i.e., the presence of potential confounders being minimal due to randomized study design). In contrast, non-randomized observational studies often are exposed to known and unknown biases, yet on the other hand, exhibit high external validity (i.e., generalizability of results). Moreover, observational study research is of relevance when it comes to the investigation of “real-world” conditions in prescription and particular nonprescription setting. However, within this context its appropriateness to study intended effects and draw causal inferences (i.e., therapeutic effectiveness) has been the subject of debate for many years. Whereas opponents claim the control of potential confounders and biases to be rather impossible, proponents hold the opinion that well-designed and well-analyzed observational trials are able to bring about results essentially similar to those of RCTs.

As to the presence of observable confounders, statistical techniques are available which are able to minimize their biasing impact under certain assumptions. One method being increasingly used in observational study research is the so-called propensity score technique. By definition, a propensity score represents a person’s probability of being allocated either to treatment or control group depending on his or her observed covariates. According to the theoretical framework of the counterfactual account of causality, the average causal treatment effect can be determined based on estimated propensity scores, thereby reducing any correlation between treatment and outcome which is not due to the treatment itself, thus, enhancing the validity of the data.

In order to demonstrate the practicability of this theoretical approach, propensity score technique was retroactively applied to an exemplary set of observational non-interventional study data.

In conclusion, non-randomized observational study research is regarded indispensable in complementing randomized controlled trial results by delivering important real-world data. This holds particularly true for the assessment of therapeutic safety, effectiveness and practice within the setting of self-medication typically lacking close medical supervision. According to the author, the approach to enhance the validity of such data by applying appropriate statistical techniques, such as - in particular - propensity score analysis should therefore be considered as crucial quality criterion within its assessment of eligibility for data exclusivity as part of an Rx-to-OTC switch application.

Table 10: Example of the comparison of two therapeutic options (i.e., treatment and control) for the therapy of vaginal mycosis: average treatment effect (ATE) for selected variables based on estimated values and bias. (*) Bootstrap estimator on the basis of 10,000 resamples; (**) symptom intensity measured on the scale 0, 1, 2, 3 with 0 = none, 1 = little, 2 = modest, and 3 = severe

Outcome variable	Covariate-adjusted			Unconditional (naive)						
	Group-specific mean		ATE	Group-specific mean		ATE				
	Treatment	Control		Treatment	Control	Estimated value	Expected value (*)	Bias	Bias % of (3)	
	1	2	3	4	5	6	7	8	9	
		= (1) - (2)			= (4) - (5)		= (7) - (3)			
Time to improvement (hh:mm, any ailment)	36:10	42:08	-05:58	35:13	41:54	-06:25	-06:26	-00:28	7.76	
Pruritus: decrease of symptom intensity (**)	one day after medication	-1.0190	-0.8020	-0.2170	-1.0339	-0.8297	-0.2042	-0.2046	0.0124	5.71
	three days after medication	-2.2809	-2.0756	-0.2053	-2.2765	-2.1205	-0.1560	-0.1573	0.0480	23.38

8 Results

Major findings and conclusions from the literature and qualitative interview research, as well as the Canesten® GYN case study analysis, referring to the applicability of the existent EU legal framework in regards to the data exclusivity provision for Rx-to-OTC switches (Article 74a, Directive 2004/27/EC) will be depicted in the following in conjunction with Hypotheses 1 and 2 initially developed within the present work (see Section 4.6).

8.1 Confirmation of Hypothesis 1

Based on a critical analysis of the European legal framework at present regarding the provision of data exclusivity within the context of the transfer of pharmaceuticals from prescription to nonprescription status, it was hypothesized that there is rather little chance to receive data exclusivity for a certain Rx-to-OTC switch with given the unspecific legal requirements (i.e., Article 74a, Directive 2001/83/EC, as amended, and its interpretation in the “Guideline on changing the classification for the supply of a medicinal product for human use”) currently prevailing throughout Europe (cf. Hypothesis 1, Section 4.6). Both a retrospective case study analysis of the Rx-to-OTC switch of Canesten® GYN (see Chapter 5) as well as the results of personal interviews with experts from different interest groups involved in Rx-to-OTC switching (cf. Chapter 6) contribute to the confirmation of this assumption (i.e., to the adoption of Hypothesis 1), respectively, due to the following reasons:

- absence of a concrete definition, substantiation, and interpretation of the terms “significant” as well as “relevant” and “necessary” found in the legal text (Article 74a) and its correspondent guideline (European Commission 2006a),
- availability of extensive pre-clinical test and clinical trial data from Rx-registration of even also older substances which in their majority meet basic scientific and ethical data requirements still valid for drug applications today,
- no detailed definition of “pre-clinical tests” and “clinical trials” as data categories (i.e., standard/quality requirements, etc.).

As to the first issue mentioned, the insufficient specification of the relevant terms referring to eligibility of data for data exclusivity (i.e., “significant”, etc.) for Rx-to-OTC switches was acknowledged by the majority of experts interviewed and is at least to some extent also reflected by the results of the respective survey. None of the attributes “comprehensible”, “precise”, or “relevant” was rated “very good” (c.f. Section 6.1, Figure 7).

Second, with respect to the point of “availability of extensive pre-clinical test and clinical trial data” the Canesten® GYN example shows that even for old substances like clotrimazole

in this case, which was registered for the first time several decades ago, the original data submitted for registration seems fairly complete. Although ethical requirements and scientific knowledge as well as technological methods have certainly arisen and developed over time, demanding increasingly complex and intricate study research, both ethical research principles and scientific criteria and requirements have already existed for many years (in Germany as of the beginning of the 1970s, cf. Section 5.1). Therefore, comprehensive pre-clinical tests and clinical trials had already been necessary for the registration of older substances such as clotrimazole, as was illustrated by the exemplary gap analysis of Canesten® GYN documentation (which is of course only an example and not representative by force, yet might still hold true for other substances as well). Moreover, as large parts of the tests and trials conducted have been available to the scientific public for a long time, they mostly have no news value and thus do not contribute to eligibility for data exclusivity as such.

Another hurdle to overcome in the generation of new data within this context is obviously the deficient specification of the terms “pre-clinical tests” and especially “clinical trials”. If, for example, “clinical trials” are to be interpreted in the “classical” sense (phase I-III or post-marketing phase IV), similar studies certainly had to already have been carried out for and during Rx registration as demonstrated by the retrospective analysis of the Canesten® GYN case. However, contrary to the setting of self-medication, studies up to phase III are of interventional character (i.e., conducted according to a predefined study protocol), whereas phase IV studies need participants to be insured. Thus, in general the execution of such studies is rather complex and complicated and, hence, hardly to be realized under OTC-like conditions. The latter was though determined as an important characteristic in Rx-to-OTC switch data generation for the application of data exclusivity by most of the experts interrogated.

In consequence, as largely confirmed by the qualitative interview results, the scope for the generation of novel data eligible for data exclusivity within an Rx-to-OTC switch is rather limited taking the current European legal framework as an orientation guide. The potential success of a certain data exclusivity request seems to be unique to a restricted number of cases (see also Subsection 9.3.1) and in the current situation (i.e., the absence of distinct and rigorous criteria applied to data submitted) a positive judgment seems to fairly depend on regulatory arbitrariness.

8.2 Confirmation of Hypothesis 2

Likewise, Hypothesis 2 which was developed on the grounds of Hypothesis 1 (q.v. Subsection 4.6.2) and refers to the demand for specification of existent and the precise definition of new criteria and data categories potentially qualifying for data exclusivity, is accepted based on the following reasons:

- guidance on Article 74a included in the current “Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use” published by the European Commission in the sense of a detailed interpretation and definition of specific requirements is rather limited,

- accordingly, precise information on Article 74a is equally missing on EU national levels (except for formal implementation in national law),
- usefulness and meaningfulness of “pre-clinical tests” currently named as potential data category for a claim on data exclusivity for Rx-to-OTC switch candidates, i.e. drugs very late in their life-cycle, is questionable.

As mentioned earlier (see Section 4.6), when looking at the current European switch guideline only a small section (part III) is dedicated to interpreting and specifying the legal provisions of Article 74a (European Commission 2006a). Although some categorical aspects with the potential for data exclusivity qualification are named here, crucial hints cannot be found on how to reach “significance” of data as pre-requisition for the provision of data exclusivity acceptable for evaluating authorities. The section concludes with the apparent key message: “To be considered ‘significant’, the pre-clinical tests and/or clinical trials must be relevant and necessary to the change in classification” (European Commission 2006a). Yet, this statement rather leaves too much room for interpretation than really providing substantial information for applicants, thereby all the more generating the impression of an arbitrary decision to be taken by competent authorities.

Presumably, more or less as a result of the imprecise definition of requirements on a European level (i.e., within Article 74a of Directive 2004/27/EC) virtually no detailed definition is available (besides technical implementation in national law) in the various EU member states with the UK as the only exemption. The MHRA as competent regulatory authority in the UK has issued a “Guidance on the Application for Exclusivity for Change in Legal Status of a Medicine” (MHRA 2005) (cf. Section 4.6). Unfortunately, this guidance equally lacks a precise concretion of how data claiming exclusivity should look like in detail, yet while focusing on clinical trial data at least it points out to some outcome parameters and study designs, respectively, that might be beneficial with regards to exclusivity (MHRA 2005). Interestingly, an expanded version is announced in this guidance “with further examples of ‘tests’ or ‘trials’ that may justify exclusivity following agreement of European guidance and in the light of experience gained [...]”. But no update has been released so far, probably not least due to a deficient number of precedent cases.

As regards the inclusion of “pre-clinical tests” as a potential data category currently mentioned in Article 74a and its interpretation towards the possibility of demanding exclusivity, the eligibility of such data for Rx-to-OTC switches is to be questioned with respect to their relevance being rather moderate for switch candidates usually very late in their life-cycle and used in a setting of self-medication (see Section 9.2). Even though few ideas referring to pre-clinical tests are mentioned in the respective section of the European switch guideline, no further specification is given on what they should be like (European Commission 2006a). Correspondingly, as demonstrated by expert interview results, controversial views or “no opinion at all” are held by experts on this issue with the majority considering this data category as less useful and reasonable for Rx-to-OTC switches. Nevertheless, some scenarios potentially coming under this category were hypothesized and discussed (see Section 6.1, Figure 9 and Subsection 9.2.2).

Yet, overall, in regards to a possible entitlement to exclusivity the tenor of nearly every

expert interviewed irrespective of the relative advocacy group, was to focus on clinical trial data ideally gathered under OTC real-world conditions (e.g., including educational measures, etc.) rather than pre-clinical test data. At the same time, a detailed definition of clinical trials to be conducted for this purpose was affirmed to be missing and thus was postulated in unison.

8.3 Summary and conclusion

As a result of both literature review, as well as qualitative interview research, both hypotheses 1 and 2 can be confirmed to be valid.

In particular, as the applicability of the current legal framework regarding the provision of data exclusivity for Rx-to-OTC switches (i.e., Article 74a, Directive 2004/27/EC and its corresponding switch guideline) was demonstrated to be rather limited; they have to be substantiated by both the concretion of existing and the elaboration of potential new criteria and/or data categories serving as a sound and realistic basis for the provision of data exclusivity to future Rx-to-OTC switches.

Within this context the generation of OTC relevant data such as, for example, non-interventional, observational study data in an OTC-like setting is concluded to be crucial from the qualitative research results of the present work. Respective proposals and conceptions with a view towards eligibility criteria and data category specification will therefore be analyzed and discussed in the following.

9 Discussion of results

Both Hypothesis 1 and Hypothesis 2 presented in the present work (i.e., the need to further specify existent and possibly elaborate on new criteria and data categories in regards to data exclusivity provision for Rx-to-OTC switches due to inadequate precision and thus limited applicability of Article 74a of Directive 2004/27/EC) could be confirmed in the previous chapters. Against this background, apart from the discussion and clarification of existent data categories, the possible introduction of new data (sub)categories and criteria will be analyzed and debated in the following discussion. At the same time, qualitative results gathered from individual expert interviews based on the questionnaire developed and depicted in Section 6.1 will add to the discussion.

First of all, it has to be pointed out that within this process the objective to bring about acceptable, realizable, and transparent proposals that deserve the grant of data exclusivity as an incentive instrument based on a common understanding is of the utmost importance. Future reclassifications from prescription to nonprescription status will inevitably take place and stakeholders, in particular regulatory authorities and political decision makers, will be confronted with the task to get on with and eventually support this movement, provided that a clear public health gain argues for it.

Many of the qualitative interview respondents confirmed the assumption that the application of “data exclusivity” as incentive instrument currently does not seem to be appreciated/supported from a political point of view – at least in Germany, but presumably in other EU countries as well. The fact that, as discussed earlier (cf. Section 4.6 and Chapter 8), information and further guidance on specification, interpretation, and implementation of legal provisions in Article 74a, Directive 2004/27/EC, are missing, is indicative of this supposition. Thus, in order to ensure the application of “data exclusivity provision” as an instrument to foster innovative and enlarged self-medication to cope with people’s aspiration towards increased autonomous health-management and easier access to adequate therapy options, a precise guidance referring to the generation of data of informative and essential value within the context of Rx-to-OTC switches has to be elaborated. In particular, subcategories and definite criteria have to be set up with attention paid to the aptitude of potential new data categories and/or criteria being acceptable for all stakeholders as well as being accomplishable under “real-world” conditions. In particular, it has to be kept in mind that as pointed out to by William Soller, member of the Self Care Collaboration³⁸, in his recently published guiding principles addressing Rx-to-OTC switches, new self-medication options based on Rx-to-OTC switches have to be “driven by a principle of simplicity of design” with complexity of risk minimization activities, etc. reduced to a minimum (Soller 2012a).

³⁸ “A group of academic-based health professionals with interests in Rx-to-Nonprescription switch and related conditions of use” (Soller 2012b).

9.1 Definitions and interpretation of terminology

Based on the aforementioned, in the first instance it is considered essential to define, specify, and interpret the indefinite legal terms used in Article 74a in order to be able to provide a basis for the setup of specific data exclusivity criteria and data categories within the context of Rx-to-OTC switches.

Apart from the unspecific categorical terms “pre-clinical tests” and “clinical trials” which will be discussed below (see Sections 9.2 and 9.3), as noted before the associated term “significant” is also devoid of further specification as well, albeit considered as an evident “key word” (cf. Section 4.6 and Chapter 8). Against this background, an attempt to define and interpret “significant” within the context of data exclusivity for Rx-to-OTC switches follows, which is based on the author’s individual judgment and considerations. The basic meaning of “significant” as an adjective is defined in Oxford dictionary as follows³⁹:

- “sufficiently great or important to be worthy of attention; noteworthy,
- having a particular meaning; indicative of something,
- statistics relating to or having significance”.

Within the context of statistics the latter refers to a mere mathematical definition, which is not expected to be intended in Article 74a, as “significance” would then only depend on a certain mathematical value (e.g., a specific p-value⁴⁰), regardless of study objectives, outcome parameters etc. Therefore, referring to the former definitions which are more likely within the context of Rx-to-OTC switches, in the author’s opinion any data might be “significant”, if it is able to demonstrate that treatment with a former Rx-only drug in either a former Rx or an already established OTC indication can be associated with obvious safe and effective use under OTC conditions implying a positive benefit-risk ratio. Moreover, the element of “novelty” is another factor that most presumably will have to be accounted for in this interpretation of “significant”. More specifically, as demonstrated by practical examples of data exclusivity applications within the context of recent European Rx-to-OTC switches (see Subsection 4.4.4), a genuine and possibly relevant impact of data eligible for exclusivity will only be given if not evident from study results which are at the basis of the general switch application and most often are already disclosed. Furthermore, according to the author’s view, switch-specific data should be regarded as “relevant” if above all - with respect to a broad and usually less or even uncontrolled self-medication – generalizability of data is possible and appropriate. Thus, efficacy/effectiveness and safety data should not only be convincing from the perspective of controlled, experimental study conditions, but also from utilization under real-world conditions anticipating the envisaged OTC-setting. More specifically, the latter might comprise different data categories ranging from actual use data to health education or risk minimization measures. Hence, as also reflected by expert

³⁹ cf. <http://oxforddictionaries.com/definition/english/significant?q=significant0>, last accessed 2012-10-27

⁴⁰ The so-called p-value determines the probability of obtaining a result at least as extreme as the one that was actually observed, assuming that the null hypothesis is true (Goodman 1999).

interview results (q.v. Section 6.1, Figure 15), next to standard quality requirements (e.g., methodology, data analysis, etc.) representativeness with a view to the target population, indication, dosage, and setting should play a major role within data's "significance" and "relevance" evaluation.

9.2 Pre-clinical test data

The relevance of pre-clinical test data as one possible data category currently anchored in the European legal framework with respect to data exclusivity for Rx-to-OTC switches will be reflected on and discussed below.

9.2.1 Practical relevance up-to-date

By definition, pre-clinical development is a stage of research the purpose of which is to taper candidate selection for subsequent clinical evaluation in humans. Pre-clinical test data as a kind of "basic" data usually are generated on a large scale at an early stage in a drug's life-cycle *in vitro* and in animal models. Investigations on drug metabolism, pharmacokinetics, toxicokinetics, drug action, drug targets, and drug-disease interactions help to generate exposure-response relationships for efficacy and safety which can eventually be extrapolated to humans (Lesko et al. 2000).

It might be hypothesized that the term "pre-clinical test data" has been deliberately included in the legislation by legislative bodies for the purpose of providing applicants with a broad range of possible data to be supplied for a claim on data exclusivity and not to categorically rule out pre-clinical data as an important data category in drug development in general.

However, based on the aforementioned (cf. Section 8.2), the author holds the opinion that the category of pre-clinical test data by classical definition seems to be of rather limited value with respect to eligibility for data exclusivity within the context of the transfer of medicines from prescription to nonprescription status. Most substances suitable for Rx-to-OTC reclassification are of long-standing in the Rx market having undergone several assessments in regards to completeness of data. The general availability of plenty of pre-clinical data originating from a drug's Rx-application, most of them available to the scientific community, and an adequate safety record accumulated during Rx-marketing minimize the practical relevance of another set of similar pre-clinical data for OTC usage. As the transfer of a substance from Rx to OTC generally does not include a basic modification of a substance's pharmacological properties, no additional value for a drug's application in nonprescription setting will be generated by pre-clinical tests unless taking into account OTC relevant aspects. Moreover, from an economic, but even more so from an ethical point of view, further pre-clinical (i.e., in particular animal, but also *in vitro*) testing would be rather unjustifiable bearing in mind that these tests in the majority of cases only provide general information on the drug substance itself less specific for its application in an OTC environment.

Thus, above all, confirmed by qualitative interview results (see Section 6.1), the author considers the likelihood of being able to generate new significant data in this category as rather low. In fact, a similar attitude is adopted by the UK's regulatory authority (MHRA) in its

“Guidance on the application for exclusivity for change in legal status of a medicine” from 2005. The only national interpretation and guidance on the issue of data exclusivity for Rx-to-OTC switches as addressed by Article 74a of Directive 2004/27/EC known to date states: “Additional pre-clinical i.e. animal toxicology or *in vitro* studies for products late in their life-cycle, may not have much practical relevance on a switch application, but the applicant is invited to give this due consideration” (MHRA 2005). In the US, to qualify for three years of Hatch-Waxman exclusivity, an application or supplement must contain “reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant”. Thus, by regulation, exclusivity is provided solely on the basis of clinical, but not pre-clinical, study data and the FDA thereby clearly interprets clinical investigations as investigations conducted on humans other than bioavailability studies (cf. FDA 2006a; FDA 2007).

9.2.2 Pre-clinical scenarios with potential relevance to Rx-to-OTC switching

Nevertheless, although not specified in the current legal provision, pre-clinical evaluation is estimated to be reasonable and required for OTC switches under specific circumstances, such as the investigation of interaction profiles with newly available drug substances having not yet been available during pre-clinical test phases of a switch candidate prior to its Rx registration. Moreover, as suggested in the current EU switch guideline, certain Rx-to-OTC switch scenarios could benefit from pre-clinical investigations, such as: the pharmacokinetic/pharmacodynamic and associated toxicity and efficacy profile of a switch candidate’s new delivery forms, new fixed dose combinations, or new route of administration. Details on specific parameters potentially relevant for exclusivity approval, however, are missing. A proposition of pre-clinical test evaluation/outcome measures based on experts’ opinions on potential scenarios that they could imagine to contribute to data exclusivity eligibility is shown in Table 11. The focus on safety and especially toxicity aspects thereby seems to account for possible remaining concerns related to switch candidates encountering less medical control in an OTC setting.

Besides, the retrospective analysis of existing pre-clinical test data under OTC relevant aspects was propounded as a data (sub-)category potentially eligible for exclusivity. Yet, even though estimated as possibly relevant by two-thirds of the experts interviewed (see Figure 10), the discussion with these experts revealed that this kind of data analysis could only (if at all) be of a supportive nature and would definitely have to be complemented by adequate clinical trial data before being able to be considered significant and thus eligible for data exclusivity. Therefore, the wording of the interpretive EU switch guideline obviously equally allowing for submission of combined pre-clinical and clinical data (“and/or”) is reasonable and important⁴¹. The concern about retrospective definition, identification, and derivation of respective outcome parameters in the pre-clinical assessment relevant for a specific Rx-to-OTC switch being intricate and disputable in terms of regulatory acceptance

⁴¹ In contrast, strictly speaking, the original legislative text (i.e., Article 74a, Directive 2004/27/EC) only allows for either data category: “Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, [...]”

Table 11: Scenarios and associated pre-clinical tests suggested by experts interviewed as possibly contributing to data exclusivity eligibility

Scenario	Pre-clinical Evaluation
New delivery form	Pharmacokinetics/Bioequivalence/Superiority
New route of administration	Pharmacokinetics/Bioequivalence/ Superiority
New strength/posology	Pharmacokinetics/Pharmacodynamics/Toxicity/ Efficacy
New fixed dose combination	Pharmacokinetics/Pharmacodynamics/Toxicity/ Efficacy
New excipients	Pharmacokinetics/Pharmacodynamics/Toxicity
Drug-drug interactions with new Rx-/OTC-substances	Pharmacokinetics/Pharmacodynamics
If applicable (e.g., old substance, etc.): Re-evaluation of cancerogeny/genotoxicity	Toxicity (using current standard methods)

might be at the bottom of this assumption.

Overall, in the author's opinion, pre-clinical test data are essential and relevant when it comes to the safety and usability of a certain drug substance, delivery form, route of administration, etc. and should therefore be required for and precede any clinical development and registration in both prescription and nonprescription settings. However, apart from the fact that most pre-clinical data is most often already available (and often published) to a large extent, according to the author's view this data, in the classical sense, cannot be considered appropriate to exclusively qualify for the data exclusivity provision, as it might be interpreted from the wording of the current legal text of Article 74a. This is due to the belief that this kind of data is indeed able to cover "basic" safety parameters (e.g., pharmacokinetics/pharmacodynamics/toxicity), but does not take into account specific OTC parameters which are of at least equal or even higher importance in light of unsupervised "real-life application" (e.g., patient behavior, etc.) within the setting of self-medication. Instead, if applicable, new or quasi-new (i.e., re-analyzed) pre-clinical data should on an individual basis rather be seen as an important, but not sole contributor to eligibility for data exclusivity.

9.3 Clinical trial data

"Clinical trial data" is the second largest data category mentioned in the EU's current legal framework (Article 74a, Directive 2004/27/EC) with respect to qualification for data exclusivity for Rx-to-OTC switches. As with the pre-clinical test data category presented above, the significance and applicability of the clinical trial data will be debated in the following.

9.3.1 Practical relevance at present

By conservative definition, clinical trials are at best to be conducted according to a detailed study plan in a randomized, controlled way throughout different phases of drug development (i.e., phases I-IV). More specifically, phase I-III trials are designed to investigate efficacy and safety in a controlled setting and given indication, whereas phase IV trials including several thousands of patients aim at the investigation of adverse events after market approval (i.e., post-marketing surveillance). Hence, taken as such this commonly used term comprises a number of subcategories which often differ (e.g., in terms of study design, data quality, etc.). In any event, clinical studies based on the aforementioned definition always imply the involvement of a physician for treatment decision thus minimizing their potential significance and relevance for Rx-to-OTC switches targeting self-medication, as results do not fully allow an evaluation about how treatment would be managed by patients themselves under OTC usage conditions (i.e., without a physician's intervention).

In general, clinical study evaluation includes testing of multiple dosages and dosage regimes of a specific drug finally resulting in the authorization and establishment of a so-called "therapeutic standard dosage". This is usually the one with the best benefit-risk ratio referring to a specific indication and patient population under defined circumstances (e.g., prescription environment). If proven safe and effective, other than the therapeutic standard dose might also be available. When it comes to the application of as yet to be approved (e.g., reduced strength/posology) of course, confirmation of efficacy/effectiveness and safety in the targeted indication and patient population appears to be essential. However, as described before, these data often may already be available or at least derivable from studies conducted for and during a drug's prescription authorization. As demonstrated by the *alli*[®] and *Pantozol Control*[®] cases (cf. Subsection 4.4.2), additional confirmatory study data with a lower dosage strength/posology may, therefore, not be regarded as significant as long as safety and efficacy/effectiveness data merely are reproduced and - compared to already existing Rx data - are not investigated in light of additional criteria essential for its targeted application in a self-medication environment.

Unfortunately, as already depicted above (q.v. Section 8.1), within the context of an Rx-to-OTC switch no precise specification and interpretation of the term "clinical trials" is given in the respective legal framework apart from the switch guideline quoting confirmatory clinical trial data with respect to another (e.g., lower) dose or a new or widened indication in terms of safety, efficacy, and actual use.

Two double-blind placebo-controlled multiple-dose phase III studies were identified via internet search on <http://www.clinicaltrials.gov> investigating efficacy and safety of an extended release formulation of ibuprofen 600 mg within a typical OTC indication (i.e., dental pain after extraction of third molar teeth)^{42,43}. Study medication was dosed at 0, 12, 24, and 36 hours. Apart from AE tracking, primary and secondary outcome parameters mainly

⁴² cf. <http://www.clinicaltrials.gov/ct2/show/NCT01266161?term=ibuprofen+extended+release&rank=1>, last accessed 2013-03-10

⁴³ cf. <http://www.clinicaltrials.gov/ct2/show/NCT00707057?term=ibuprofen+extended+release&rank=2>, last accessed 2013-03-10

included onset, intensity, and duration of analgesic treatment efficacy. Without knowing the specific background of these studies, according to the author, Rx-to-OTC switch efforts and considerations claiming data exclusivity on the specific pharmaceutical form as indicated above might be hypothesized.

However, if study design and results will ultimately qualify for data exclusivity is not predictable, as no information is provided in the EU switch guideline with regards to study details such as quality requirements (design, analysis, etc.) for a certain study to be judged as relevant and significant within the context of a certain Rx-to-OTC switch.

As can be derived from the aforementioned, the author holds the view that a merely conservative definition and interpretation of the legally indefinite, superordinate term “clinical trials” is not conducive in the context of Rx-to-OTC switches and should therefore be extended to take the characteristics of the target setting, namely OTC setting, into consideration (in terms of study design, population, endpoints, etc.). Against this background, different criteria and categories estimated to be relevant for the targeted OTC setting were suggested and discussed with selected national and international experts and stakeholders within self-medication (see Section 6.1). Correspondent proposals will be analyzed and discussed in detail in the following.

9.3.2 Re-analysis of existent data with respect to OTC usage

Actually, all qualitative interview respondents could imagine the re-analysis of clinical data already available from a drug’s registration as prescription therapy under OTC pertinent viewpoints. Yet, this is not really astonishing: the Canesten[®] GYN case (see Chapter 5) shows exemplarily that from a drug’s prescription history there are plenty of pre-clinical and clinical data available – not only generated for registration purposes, but also during Rx marketing. Therefore, a huge data base comprised of pre-clinical and clinical data related to a potential switch candidate usually is available at its originator. Especially data gathered after a drug’s Rx authorization throughout the post-marketing phase, such as non-interventional study data (cf. Subsection 9.3.3) are thinkable to be re-analyzed and re-structured under OTC relevant aspects (e.g., utilization patterns, effectiveness and safety profiles, etc.). When asked about the relevance of various design and outcome parameters with respect to the extrapolation of Rx data to potential future OTC usage, size and kind of study population were named as the most important design parameters along with safety/pharmacovigilance as the most significant outcome parameters (cf. Figure 11). The distinct analysis of data referring to special patient groups (e.g., elderly, patients with comorbidities, etc.) was also judged valuable in light of potential precautions to be taken within less supervised OTC usage. As each and every potential switch candidate might differ a lot regarding indication, target population as well as complexity, for example, specific analysis parameters as well as inclusion and exclusion criteria (e.g., the exact definition of special populations, etc.) will probably have to be determined on an individual basis (and are recommended to be also discussed with authorities). To be considered significant, data should in any account be analyzed and summarized according to current scientific and especially statistical knowledge

(i.e., be of adequate statistical power). If available, suitable OTC data with regards to the same or a similar indication might be integrated into the analysis as well. Corresponding Rx data could then be analyzed and discussed in light of anticipated OTC utilization patterns and characteristics.

Aside from the above mentioned, in the author's opinion the re-analysis of data typically comprehensively available from a drug's history as a prescription drug might also be estimable, if appropriate, with a view towards ethical considerations and efforts to avoid redundancy by duplication of data.

After all, however, it is of note that – between the lines - many experts expressed their doubts that this kind of data might exclusively yield data exclusivity for a certain Rx-to-OTC switch. Thus, in summary, the criterion of re-analyzing pre-clinical and/or clinical data was indeed largely considered as supportive, yet not exclusively sufficient. Instead, the necessity of data generation under daily-life conditions in the target setting of self-medication was more or less concordantly stressed by experts asked (cf. Figure 12). The following chapter will therefore deal with so-called behavioral study data as data (sub)category with high potential for data exclusivity eligibility in Rx-to-OTC switches.

9.3.3 Switch candidate under daily-life conditions: behavioral study data as potential “clinical” data category

“Over the last years, behavioral study research has become an integral part of OTC drug development programs as it provides essential insight in and helps predict consumer behavior” (Leonard-Segal 2009).

One of the most important questions of interest before making a new drug available in a new OTC indication is how the respective drug candidate will actually be used by patients in the absence of the more or less close medical supervision mostly found in an Rx setting. Safety parameters are without doubt at the forefront of important parameters to be analyzed within this context, followed by effectiveness. Besides pharmacy recommendation and patient utilization patterns (such as self-selection, label comprehension), actual use (including potential mis- or abuse, as well as compliance) will have to be evaluated in order to put the aforementioned outcome parameters into context. Determination of a new OTC drug's potential impact on patients' QoL could as well be worth a downstream evaluation.

In order to investigate a drug's utilization, safety, and effectiveness under real-world conditions, the study setting obviously has to be as naturalistic as possible (i.e., ideally of non-interventional and only observational character). Hence, an epidemiological rather than a conventional clinical randomized study design approach seems to be appropriate in case of behavior and actual use evaluation. Actual use trials – that is, “anticipatory observational trials in which designed operations are implemented to create a setting for use that does not currently exist (OTC sale of a current Rx drug)” and in which only the observation of subjects should more or less provide the forecast of behavior, could help in answering “what are the public health implications of removing HCP from the process of diagnosing the problem, prescribing the drug, and monitoring its use” (Bradford et al. 2010). By assessing the safety

of Rx drugs under usage conditions mimicking OTC, such studies could or rather should play a key role in the Rx-to-OTC switch application process. The ability of OTC consumers and/or patients to responsibly and correctly perform functions previously managed by a physician (i.e., self-diagnosis, self-selection, AE monitoring, etc.), as well as potential benefits and risks to public health are among key regulatory questions when considering the reclassification of a drug from prescription to nonprescription setting and should be able to be assessed by properly designed, conducted and analyzed non-interventional AUTs.

As to traditional research models commonly applied in Rx drug development, such as efficacy trials, phase IV studies, passive surveillance systems, etc., Bradford argues that they typically only answer part of or other questions than those relevant with respect to OTC usage and, thus, offer only limited data about the suitability of a certain switch proposal. Efficacy trials are carried out according to a predefined study protocol in a risk controlled environment and usually investigate a carefully selected population not taking the decision to self-medicate itself and thus presumably differing from the self-treating OTC population. In brief, experimental conditions complicate generalization. Passive surveillance systems (e.g., registries) and epidemiological studies might deliver useful signal detection, yet are less suited for determination of parameters, such as non-compliance due to only broad questions and long duration of adequate data collection. In contrast, phase IV post-marketing surveillance trials might come closest to the generation of data potentially relevant to Rx-to-OTC switches as they monitor actual drug use, however, with the disadvantage of being focused on real-life data in the prescription setting only. Yet, despite its anticipatory value for OTC setting being comprised, this data might possibly serve as a comparative database. In summary, whereas clinical research in the classical sense mainly provides insight into how a drug reacts physiologically in a person, observational (consumer) research helps elucidate how a person reacts behaviorally with the drug (Aker 2006). Against this background and based on the fact that a successful Rx-to-OTC switch from a scientific point of view mainly depends on a well-functioning patient behavior in a much less controlled self-medication setting, the author comes to the conclusion that the interpretation of the term or category “clinical trials” mentioned in Article 74a, Directive 2004/27/EC, should definitely encompass appropriate forms of non-interventional behavioral research data (provided that accordant quality criteria are fulfilled – see below).

As a consequence of the aforementioned, Bradford calls for specific design elements to be used in actual use trials which he considers to be “significantly different from efficacy trials” (Bradford et al. 2010). The following chapters deal with the discussion of such design elements within the context of legal considerations, general principles, and quality criteria to be adhered to within the context of observational research studies.

Excursus: non-interventional studies (NIS) – short overview of definition, classification, and quality criteria to date By definition, observational studies are conducted post-marketing and without external intervention. They are therefore also termed “non-interventional”. In contrast to randomized, controlled clinical trials, no specific investigational requirements such as a detailed protocol referring to a distinct investigation and/or therapy procedure

need to be predefined, as the idea is to conform to normal practice reflecting daily-life conditions (Günther 2001).

In general, observational studies intend to prospectively or retrospectively collect data regarding a certain drug and/or indication over a certain period of time (Kori-Lindner and Eberhardt 2010). There are different types of observational study designs which can be classified as either descriptive (e.g., case studies, cross-sectional studies (surveys), non-interventional studies, drug utilization studies, and ante/post comparisons) or analytical (e.g., epidemiological cohort studies, case-control studies, and registries) (Häcker 2010; Kori-Lindner and Eberhardt 2010).

The focus of the present work will be laid on characteristics and requirements of non-interventional studies as a commonly used instrument to investigate and monitor drugs and drug usage during the post-authorization stage. Within Europe, the “non-interventional study” has been legally and regulatory defined by the EU’s so-called “Clinical Trials Directive” (Directive 2001/20/EC)⁴⁴ referring to the application of “Good Clinical Practice” when conducting clinical trials. According to EudraLex Volume 10, Chapter 5 (status July 2009), however, the Directive itself in fact does not apply to non-interventional studies, as the individual risk for study participants should be much less than in interventional clinical studies. Moreover, medical activities representing routine practice are part of patients’ general medical surveillance measures and thus do not come under the Directive’s scope of application.

In Germany, the above mentioned EU Directive was implemented into national law in 2004. Section § 4(23) of the German Medicines Law gives a precise definition of the respective term “non-interventional study”⁴⁵. Interestingly, as discussed by Häcker, the German legal definition and interpretation differs from the European one in that not only treatment measures, but any specifications regarding treatment, diagnosis, and monitoring are interpreted as “interventional” and thus excluded. On the contrary, the epidemiological interpretation which is at the basis of the European definition of “non-interventional” includes specifications regarding data generation, documentation, and control for the sake of data quality assurance (Häcker 2010).

In 1998 the German regulatory authority (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)) published quality recommendations regarding the conduct of non-interventional studies which are based on recommendations of the German Association of Medical Informatics, Biometry, and Epidemiology (GMDS). These recommendations were updated in collaboration with the Paul-Ehrlich Institute (PEI) and a final version has been

⁴⁴ “A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data” (Article 2c, Directive 2001/20/EC).

⁴⁵ A study where “findings from the treatment of persons with drugs according to the terms of the marketing authorization are analyzed with epidemiological methods; thereby treatment, including diagnosis and control, does not follow any predefined study plan but only the medical practice” (§ 4 (23) German Medicines Law).

available since 2010 (BfArM & PEI 2010). Another set of practice-oriented recommendations was published in 2007 by the German Association of Research-based Pharmaceutical Companies (VfA 2007b) in order to enhance NIS transparency and quality (Häcker 2010). Besides, with respect to the epidemiological definition of non-interventional study research, the German national “Guidelines and Recommendations for the assurance of Good Epidemiological Practice (GEP)” of the German Working Group Epidemiology⁴⁶ (DAE 2000) as well as the “Guidelines for Good Pharmacoepidemiological Practices” of the International Society for Pharmacoepidemiology (ISPE 2007), and the “Strengthening the reporting of observational studies in epidemiology (STROBE) Guidelines” are to be noted (Häcker 2010; Schnetzler and Hayward 2011).

In summary, Table 12 provides an overview of basic quality criteria and recommendations propounded by the various groups as to the conduct of NIS. Representing a synopsis of the current scientific state of knowledge and practice they should serve as guidelines for planning and conducting an accordant NIS.

⁴⁶ now German Society for Epidemiology (DGEpi)

Table 12: Actual basic criteria and recommendations referring to the conduct of non-interventional studies in Europe and Germany, respectively

Study characteristics	Quality requirements
General	<ul style="list-style-type: none"> • Marketed and commercial drugs or medical devices • Diagnostic measures and procedures as well as treatment within current practice, i.e., no rules for HCPs and patients involved (non-interventional) • Ethics committee advice recommended • If applicable: informed patient information and consent (in case of data not treated anonymously) • If applicable: reward/reimbursement
Objectives	<p>Medical/Scientific objectives:</p> <ul style="list-style-type: none"> • safety, • effectiveness, • drug utilization, etc.
Planning, conduct, evaluation	<ul style="list-style-type: none"> • Based on current scientific knowledge and practice as well as respective quality standards • Design and methods used have to be appropriate in responding to study questions • Design: epidemiological (if applicable: based on appropriate data (registries, etc.)), prospective (mostly) or retrospective, non-interventional • Representativeness to be provided and assured • Study plans: observational and analysis plan including study aim(s), investigated parameters/ questions, rationale for number of cases needed, patient collective (selection criteria), upfront identification and description of adequate analytical methods, determination of bias minimization strategies • Data management: adequate quality assurance, documentation, storing, protection, and publication
Disclosure duty	<ul style="list-style-type: none"> • EU: varies by country from full submission to simple notification • Germany (according to § 67(6) German Medicines Law): general disclosure duty (apart from studies with nonprescription products) for pharmaceutical companies regarding study site, time, objective(s), and study plan to the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung (KVB)), the national confederations of health insurance funds (Spitzenverband Bund der Krankenkassen), and the assigned higher federal authority (Bundesoberbehörde) • AEs observed during study period or follow-up to be included in PSUR

Observational study research in the context of Rx-to-OTC switches: behavioral studies – principles and proposals As discussed above (cf. Subsection 9.3.3), behavioral studies representing a subtype of observational, non-interventional study research, have become an essential means of studying outcome parameters referring to the setting of self-medication with the US pioneering this kind of study concept. Basically, as shown in Table 13 three different forms and levels of behavioral studies are to be distinguished depending on their

complexity.

Table 13: Overview of different kinds of behavioral study designs (adapted from Leonard-Segal 2009)

	Label comprehension study (LCS)	Self-selection study (SSS)	Actual Use Study (AUS)
Characteristics	<ul style="list-style-type: none"> • Development of OTC label • Readability testing • Questionnaire – based • Trial without drug intake 	<ul style="list-style-type: none"> • Determination of correct self-diagnosis and product selection by patients after reading product label based on individual medical history • Minimal assistance • Trial without drug intake (unless part of an AUS) 	<ul style="list-style-type: none"> • Simulation of OTC drug use (drug is purchased and then taken at home for intake) • Relationship between self-selection decision and purchase decision • Assessment of drug utilization, e.g., compliance/adherence • Safety documentation (tracking of adverse events) • Evaluation of effectiveness (occasionally) • Used label should have tested well in LCS • Considered as clinical trial (author’s note: at least in the US!)
Target population	<ul style="list-style-type: none"> • Representative, demographically diverse • Including subgroups of special interest • Including low literacy cohort (selected based on validated literacy test) 	<ul style="list-style-type: none"> • Representative, demographically diverse • Including subgroups of special interest • Potential users and non-users 	<ul style="list-style-type: none"> • Representative, demographically diverse • Including subgroups of special interest • Potential users and non-users
Relevance	<ul style="list-style-type: none"> • If drug is first in class in OTC setting • If targeting new OTC population • In case of a new OTC indication • In case of an extensive label change 	<ul style="list-style-type: none"> • Data mostly collected in the context of LCS or AUS 	<ul style="list-style-type: none"> • In case of a new OTC indication • In case of new directions of use • In case of new OTC warnings • In case of new OTC medical follow-up requirements or recommendations

In contrast to the US where this kind of data often is used in assessing either the approval of new OTC or Rx-to-OTC switch applications, acceptance has virtually been absent among European authorities until today with a view towards comparable approval processes. Solely a so-called “readability test of patient information leaflet (PIL)” (i.e., a kind of label comprehension study) was decided mandatory for respective authorization processes (or in cases of significant changes of the PIL) according to corresponding European guidelines (European Commission 2006b; European Commission 2009) as of November 2005.

Interestingly, when asked about their estimation of the potential relevance of such study data for the provision of data exclusivity for switch products in Europe, a large majority of experts asked voted in favor of data resulting from behavioral study research with AUS data being rated the highest, followed by LCS data (see Figure 14).

However, several issues were raised within this context. In particular, some of the concerns expressed relate to timing, practicability, quality, and legal/regulatory basis for the conduct of AUS with Rx drugs in a setting mimicking OTC conditions of use. Moreover, the lack of definitions, standards, and guidelines referring to the design and analysis aspects of such studies was also critically pointed out. Indeed, many issues and challenges have already been recognized and were discussed among expert groups in the US. For instance, in 2006 the FDA Nonprescription Drugs Advisory Committee (NDAC) already discussed essential questions in study design and data analysis, such as the definition of objectively tolerable failure and success rates that should also take into consideration associated risks and potential individual patient reasons for incorrect responses and behaviors. If limited degrees of failure to heed warnings pose a non-substantial health risk and therefore might be medically acceptable, respective rates should not be overly restrictive. The multiplicity of independent endpoints makes the construction of a data analysis plan as it is utilized in clinical trials, with primary and secondary outcomes assessing a drug’s proposed clinical benefit by predefined statistical tests, rather difficult in patient/consumer behavioral research. Traditional end points might be difficult to designate in behavioral research and performance against a comparator is usually either not available or not relevant. A prospective, iterative, hierarchical approach to endpoint definition and pre-specification of targeted correct response rates was suggested by different researchers who advocate for the need to pre-specify targets for acceptable performance and response rates in a study’s analysis plan analogous to the pre-definition of the α significance level in RCTs (Brass et al. 2009; D’Agostino 2006; Wood 2006). As generally not all messages are of equivalent clinical importance, targets might differ between endpoints resulting in a “hierarchy” or “pyramid” of endpoints (see Figure 27) (Brass et al. 2009). Beyond that, benchmarking the results of patient behavior studies, such as compliance, etc. against that of other OTC domains or prescription setting might help to put them into perspective. Available information on actual Rx or OTC usage abroad as well as use of similar OTCs or data from post-marketing surveillance should be integrated in an extrapolating analysis helping to predict OTC usage patterns (Aker 2006).



Figure 27: Hierarchy of study endpoints in terms of key messages and related patient behavior based on their clinical relevance: the pyramid bottom including the many label messages that are useful, yet normally without major clinical consequences in case of not heeding; the messages and behaviors at the upper pyramid levels to be endowed with the highest performance targets due to potential severe clinical consequences if disregarded by patients (adapted from Brass et al. 2009)

The optimal duration of actual use studies might be another aspect of discussion, as the use of many OTC drugs, in general, is at most intermittent and only limited. No “standard” recommendations are known hitherto in this regard. However, results of the expert consultation show that the relevance of these aspects (i.e., study duration and duration of follow-up (if applicable)) must not be underestimated – both were rated in the range of 1-3 on a 6-point scale (1 = extremely relevant, 6 = not relevant at all). In the author’s opinion, as these are parameters definitely depending on the individual switch scenario in terms of a drug substance’s inherent characteristics (e.g., mode and onset of action, efficacy/effectiveness, safety, etc.), the associated indication (acute, recurrent, (semi-)chronic), already existing OTC options, etc., related decisions should be taken on a case-by-case basis. In acute, self-limiting conditions, for example, a study duration at least according with the proposed period of intake (similar to that of already available therapeutic options (if any)) and an adequate period of follow-up should in either case be postulated. The length of the

follow-up phase should be decided based on elements of the label that need testing, such as recommended duration of usage, dose adjustment, requirement to consult a HCP, etc. In general, for a short-term use drug, a study period of one or two weeks longer than the labeled duration of use has been proposed as adequate “risk-window” to determine, for instance, any “carry-over safety issues” (Leonard-Segal 2006; MacDonald 2002). In (semi-)chronic conditions study duration is supposed to be longer and might be determined based on experiences from the prescription setting. Since the “naturalistic” character of an observational study might get lost at the expense of a long-term scientific follow-up, the evaluation of such trends and patterns was proposed to be shifted to OTC post-approval as one possible solution (Aker 2006).

For recurrent indications that initially need to be diagnosed by a doctor and the subsequent or anew treatment/management of which is proposed to be switched to OTC, the concept of “collaborative care” could be implemented in the corresponding behavioral study design. This scenario has come true, by way of example, for the aforementioned switch of clotrimazole (Canesten[®] GYN) for the treatment of vaginal candidiasis (cf. Chapter 5), yet no observational data had been generated or available at that time. In such cases patients could be recruited before or at medical consultations and subsequently be followed-up for continued management of the respective condition to check their ability to re-diagnose and self-medicate. Likewise, in indications where a physician’s visit becomes obligatory at a certain point in time, as it is required for the treatment of benign prostate hyperplasia in the UK (see Subsection 4.4.4), the attendance of physicians could be included in the study concept.

Another challenge within behavioral study research refers to the question of implementing a second or even more groups for the purpose of control (e.g., when a multiple-arm study should be preferred to the “classical” single-arm study most often used in patient/consumer behavioral studies). According to their questionnaire assessments experts seem to highly value “randomization” and consequently the inclusion of a “control group” as one of the main quality features used in experimental clinical trials (see Figure 15). By definition, this would ultimately imply for behavioral studies to consist of two arms, at minimum. However, due to the more or less naturalistic, non-interventional setting of behavioral studies, “randomization” in a conservative sense (i.e., double-blind treatment allocation at best) will not be feasible, as there should be as little intervention as possible. On the other hand though, this does in general not rule out multiple-arm studies including a control group. For example, educational materials and/or therapy monitoring/management devices could be provided to certain arm(s) of a behavioral study investigating an Rx-to-OTC switch candidate in its associated indication whereas it will not be provided to the control group. Subsequent analysis and comparison of results (e.g., referring to safety, effectiveness, compliance, QoL, etc.) could be essential for a positive outcome of a certain switch decision, if adjuvant measures prove to favor the respective benefit-risk profile (see also Subsection 9.3.4). In case of an indication already established OTC, a possible multiple-arm scenario could be the comparison of a potential Rx-to-OTC switch candidate with an existing OTC alternative therapy in terms of actual use, QoL, etc. – an approach which was equally voted for by the large

majority of experts interviewed (see Figure 18).

One major problem inherent to behavioral research, however, is the existence of different forms of bias, as discussed in detail in Subsection 7.2.1. Moreover, “missing data” is another huge issue in observational research with no simple handling strategies available to date. These kinds of statistical issues may often result in poor data quality and validity (Brass and Lyons 2006). Authenticity, completeness, and validity of data, as well as identification and resolution of deficiencies at an early stage should therefore be of highest interest.

Of course, every switch will be linked with its own challenges and complexities to be accounted for in the respective study design and analysis. However, different factors and strategies are available that might help contribute to an improvement in data quality and validity: first of all, basic quality criteria and recommendations for NIS listed above (see Subsection 9.3.3) should be fulfilled. Second, appropriate study design and adequate data analysis as depicted in Chapter 7 and supplemented by practical considerations below should help minimize potential confounding factors.

In spite of the non-interventional study character, observations have to be made implementing a set of operations to conduct research. The scientific challenge is to conceive of and implement these conditions in a way that the findings of the study can forecast actual OTC usage. Sampling from a not yet existing, but defined population constitutes a fundamental task in this process. There are some general principles and suggestions assisting to keep the observational study process (including recruitment and enrollment) as naturalistic as possible, even if there are set limitations such as procedures for conducting science and the protection of subjects’ rights (e.g., informed consent, data collection, etc.) (Bradford et al. 2010). For example, frequency of data collection should be minimized to reduce the potential of “patient reactivity”. With respect to the target setting, self-selection into the (comparative) trial should mimic the anticipated OTC situation – that is, subjects should obtain their drug where they normally get it and decide whether the drug is appropriate for them based on information available (equal to envisaged label and communication strategy). Data related to non-enrollers in comparison to enrollers might also be critical in order to check sample representativeness (Häcker 2010) which was considered extremely important by experts in case of a new OTC substance and indication. Depending on study complexity enhanced quality of data may be as well achieved by the use of pretested, standardized case report forms (CRFs) including source data verification⁴⁷ performed in randomly selected study centers as it is mandatory for clinical trials and was propounded for NIS in prescription setting (Theobald et al. 2009). Also, sufficiently large samples tend to be more diverse with respect to relevant factors or potential contraindications (medical history, concomitant medications, etc.) and may allow some powerful comparisons among sample subgroups (Bradford et al. 2010). In the author’s opinion, the study size should be more precisely defined by authorities (e.g., by a specific range of patients to be included, taking into consideration, of course, several influencing factors such as kind and incidence of the condition, associated risks, kind of study population, quantitative objectives, etc.). This should preferably be subclassified

⁴⁷ Source data verification refers to the evaluation of the conformity of data from CRFs with source data in order to assure reliability of data collected (Khosla et al. 2000).

by study type and serve as orientation guide for the conduct of any observational trial. With a view towards study data analysis, applied methodology, and techniques should be of current scientific standard and appropriate to encounter overt or potentially upcoming statistical issues. The so-called “propensity score technique” was presented above (cf. Chapter 7), as it displays a relatively robust method increasingly used in observational study research to balance existing known confounders and draw the right conclusions. As demonstrated by the literature available as well as the practical example at hand (cf. Subsections 7.2.2 and 7.2.3), the employment of propensity score methodology in multiple-arm studies might be one way to enhance study data validity by contributing to achieve results which are as realistic and unbiased as possible. Examples are the comparison of study groups with and without a comprehensive education and training program (q.v. Subsection 9.3.4) as well as the comparison of a switch candidate with either its counterpart in a prescription setting or therapeutic alternatives already available OTC.

As to the latter, possible approaches including essential design features were suggested by an expert group in its 2002 consensus paper (MacDonald 2002): the main focus was thereby laid on the demonstration of safety equivalence (in terms of “non-inferiority”) using the example of low-dose non-steroidal inflammatory drugs. According to this consensus paper, “a summary approach towards evaluating the safety of a new OTC drug against an appropriately chosen OTC comparator is a multinational, multicenter, pharmacy-based, randomized, double-masked, two-armed study sized to demonstrate equivalence” which should comply with GEP guidelines.

The author of the present work agrees with the proposed multinational study design in particular in case of a switch product to be marketed in several EU countries in light of differing pharmacy systems and practices as well as user populations and risk factors among various countries. However, against this background, depending on the switch candidate in question, feasibility of this approach might be rather challenging. Notwithstanding the aforementioned, if applicable, the investigation of therapeutically equivalent comparators will certainly enhance the quality of study results. With respect to randomization, in the author’s mind the most reasonable strategy would be to randomize center-wise (i.e., one pharmacy providing only one of the treatment options to be compared). A similar approach has been promoted by Kori-Lindner and Eberhardt equally suggesting the randomization of study centers but not study participants (Kori-Lindner and Eberhardt 2010). Moreover, the author holds the opinion that contrary to expert recommendations in order to retain the naturalistic character of an observational study as well as possible; blinding of study medication in theory would only make sense, if similar substances with the same mechanism and conditions of use were to be compared, but would not be feasible in practice on the basis of a non-interventional study concept.

Finally, as far as timing as well as legal and regulatory aspects of conducting such a comparative study are concerned, the expert group stated that “such a utilization study can only be done with drugs that already have an OTC license or in countries where the study drug is already OTC”. Basically, the timing will depend on the individual switch scenario. By way of example, a switch candidate representing a new therapeutic option in an already

established OTC indication might be more easily compared with existing OTC alternatives within the context of a behavioral study conducted post-switch as then both study drugs are equivalent regarding their legal status and regulatory framework.

Nevertheless, the author deems a comparison of an Rx-only switch candidate with an OTC therapy option likewise conceivable provided that a comparable supply and data collection model can be defined and implemented in the respective country of study. In Germany, for example, depending on the target indication, both Rx and OTC medications could be handed out by pharmacists together with accordant questionnaires, patient diaries, etc. for data collection. Appropriately designed data collection instruments could be used to gather data regarding safe and effective use as well as compliance, but also with respect to patient centered questions such as non-monetary determination of QoL improvement, patient satisfaction with treatment, convenience, etc.

In summary, the submission of behavioral study data referring to a certain Rx-to-OTC switch scenario is proposed as a necessary and relevant criterion regarding the possibility of data exclusivity provision based on Article 74a, Directive 2001/83/EC, as amended. Even if there is no one switch scenario like another, some basic requirements should be fulfilled, such as the consideration of current guidelines and quality recommendations, an appropriate study design (depending on substance and indication) mimicking OTC conditions at its best and including an adequate study sample as well as the application of statistical methods ensuring the highest quality and validity of data possible. Of utmost importance, however, with respect to the anticipated real-life behavior of future OTC patients is the maxim that “the more the research can stay out of the way of subject behavior, the more likely it is that the findings will reflect the way consumers will behave once the drug is made available for nonprescription use” (Bradford et al. 2010). That is, last but not least it has to be kept in mind that behavioral studies should be kept as simple as possible to preserve predictability and that it is not feasible to cover every eventuality.

Legal and regulatory strategy considerations for the conduct of a behavioral study within the context of an Rx-to-OTC switch Based on the quality requirements and recommendations mentioned above, various aspects regarding legal and regulatory basis as well as strategic aspects (timing, etc.) for the performance of an observational behavioral study for a certain Rx-to-OTC switch will be discussed below.

As mentioned above, the scientific conduct of a non-interventional behavioral study in a way that its “naturalistic character” is conserved to a maximum in order for study findings to match as much as possible with the anticipated OTC reality is a major challenge. The identification and definition of an appropriate regulatory strategy complying with the current legal framework, however, is not less intricate with respect to the fact that the aim of such a behavioral study is to investigate drug utilization under nonprescription conditions even though the drug and/or corresponding indication has the legal status “prescription-only”. Furthermore, the variety of legal settings in the different EU member states complicates this issue even further, especially in case of multinational study approaches.

Based on their definition, data from classical phase IV clinical studies or NIS - both per-

formed post-approval (i.e., in-label) in a more or less observational fashion (obligatory in case of NIS) - theoretically come closest to the data needed with a view towards prospective OTC usage. In order to gain relevant data with regards to anticipated OTC usage, the challenge thus is to create and legitimate a setting similar to the envisaged OTC environment. From a legal point of view, phase IV studies are less flexible due to constraints in terms of associated commitment to insure patients' integrity. Hence, the generation of NIS data seems to be the most promising way.

In principle, different scenarios for the conduct of an OTC-like behavioral study are conceivable mainly depending on their timing. That is, non-interventional behavioral data could theoretically either be collected in a simulated OTC setting ante-switch or in a real OTC setting after its approval as a nonprescription drug (i.e., post-switch). The legal background and potential advantages and disadvantages of both scenarios will be discussed in the following.

In both cases, the generation of OTC-like non-interventional, observational study data could and should be discussed between switch applicants and the responsible authority in the period prior to submission. For this reason the possibility of a so-called "scientific advice" is offered and highly recommended by EU regulatory bodies. In the case of a study to be completed post-switch, the approval of the proposed switch candidate would be ultimately connected with specific requirements agreed upon in the forefront of the switch decision. This approach would therefore come under the term "conditional release" or "conditional switch". If the arranged conditions were not fulfilled, the respective authority would be entitled to officially reverse its positive decision about the switch. The legal basis for such a concept can be seen in the European legal framework provided by Articles 21a (b), 22a (1a+1b) and 22b of Directive 2010/84/EC, amending Directive 2001/83/EC.

In Germany, with the 16th amendment to the German Medicines Law that came into force in October 2012, respective European provisions were implemented in § 28(3). This paragraph enables responsible authorities to mandate (e.g., further safety testing or the collection of pharmacovigilance or effectiveness data) either with approval (§ 28(3a)) or afterwards (§ 28(3b)). Importantly, the term "safety testing" has been conferred a more or less novel definition in § 4(34) saying that it adheres to any investigation regarding an approved drug conducted to determine or quantify a safety risk, confirm a drug's safety profile, or to evaluate drug associated risk management measures. On a European level, this definition traces back to Article 1(15), Directive 2001/83/EC, which defines a so-called post-authorization study (PASS) as "a pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product"⁴⁸. Correspondingly, as long as the determination of safety parameters has been appointed as a primary study objective, the definition of PASS comprises both non-interventional epidemiological observational studies and interventional clinical GCP-conform phase IV studies (Niedziolka

⁴⁸ In contrast, post-authorization efficacy studies (PAES) lack a specific official European and/or German national definition, though they can equally be required according to Articles 21a, and 22a+b, respectively, Directive 2010/84/EC as well as § 28(3a+b), German Medicines Law (Sträter 2011).

2012; VfA 2007a). Detailed information on the various study types and effective guidelines and directives is given in the current pharmacovigilance guidelines released by the European Commission (EudraLex Volume 9)⁴⁹. Of note, PASS are independent from any associated regulatory authorization strategy and therefrom can be realized within the context of every application procedure; that is, CP, MRP/DCP, and national procedure. For central applications, the legal fundament for the conducting of a post-marketing safety study can be seen in Article 10a(1a) of Regulation (EU) No 1235/2010, amending Regulation (EC) No 726/2004. As a matter of principle, non-interventional PASS can be “initiated, managed, or financed by the marketing authorization holder voluntarily or pursuant to obligations imposed by regulators” (Fitt 2011) as depicted above. In the event of new drug applications these kind of studies usually are part of a so-called “risk management plan” (RMP) (see Subsection 9.3.4) which is to be included in the drug application and/or may be required to be set up if regulatory authorities consider that there is a need for additional safety information before or after marketing.

For the purpose of ensuring quality standards and data validity, the European Medicines Agency released a “Draft template for the study protocol of a non-interventional Post-authorization safety study (PASS)” in August 2012 (EMA 2012)⁵⁰. It mainly contains study design aspects and quality control measures to be taken into account: building a synopsis of current guidelines and recommendations for NIS (see Subsection 9.3.3), which are summarized and listed in a checklist for study protocols by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

A crucial aspect definitely is depicted by the timing of the proposed behavioral study. In the case of a conditional Rx-to-OTC switch as mentioned above, the (preliminary) switch approval decision would have to be taken by authorities merely on the basis of available Rx data. However, the applying pharmaceutical company could be imposed with the generation of adequate OTC safety and utilization data over an agreed period of time post-switch, being at the basis of the respective switch proposal’s entitlement to data exclusivity provision. This approach might be of advantage for pharmaceutical manufacturers, as it could, if applicable, possibly extend the provided one-year data exclusivity period at least to the time of study duration, due to the fact that results of the committed data will be required before any generic follower will be approved. Furthermore, the responsible authority would be able to provide short-term access to a new therapeutic option in self-medication with the potential to increase public health on the basis of a well-controlled “monitored release”.

To date, the practical experience with this “conditional release” approach has been scarce, as it is limited to the example of the Rx-to-OTC switch of tamsulosin (Flomax Relief®) in the UK where a post-marketing safety study was agreed upon with the authorization of the switch (q.v. Subsection 4.4.4). Yet, as demonstrated by the new draft guideline on “How to change the legal classification of a medicine in the UK” issued by the MHRA in 2012, it

⁴⁹ cf. http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm, last accessed 2012-11-09

⁵⁰ On the contrary, instructions for interventional PASS are to be taken from EudraLex Volume 10 issued by the European Commission (q.v. <http://ec.europa.eu/health/documents/eudralex/vol-10/>, last accessed 2012-11-09)

seems to be a promising concept. The paper seizes the idea of a conditional switch stating the following: “Where post-marketing studies have been agreed, to confirm safe supply in a non-prescription setting, these may have an impact on the introduction of analogous or similar products while studies are on-going. For example, where a company has committed to undertake additional monitoring in order to validate the results of a study, there may be limited opportunity for further presentations not subject to the same controls. This is considered by the MHRA on a case by case basis” (MHRA 2012).

The model of “conditional release” was likewise suggested to expert interview partners with most of them agreeing that they could indeed imagine such a concept of post-switch data generation (cf. Figure 21).

In contrast, opponents of the approach legitimately pointed out the fact that in order to evaluate a switch candidate’s estimated benefit-risk profile in OTC at its best, data anticipating drug usage under OTC real-life conditions should be sought to be already available prior to the proposed reclassification. Potential risks might thus be minimized by the definition and implementation of appropriate risk management strategies before the official Rx-to-OTC switch approval.

Moreover, the feasibility of providing data exclusivity on the basis of notional data not yet existing was considered as an important issue within the context of conditional release. Alternatively, against this background and provided that an adequate setting will be able to be permitted and realized, the generation of OTC-mimicking data during a drug’s post-authorization phase as a prescription drug could be thought to already be implemented in a drug’s life-cycle development plan, potentially even resulting in synergy effects. Especially if neither a certain switch candidate nor its related indication have already been established OTC, the generation of appropriate data pre-switch will be valuable in getting a more precise estimation of the associated benefit-risk profile regarding both drug utilization and the ability to self-diagnose and self-manage respective conditions proposed to be reclassified OTC. The “legal infrastructure” in large parts of EU member states is yet probably seen as major hurdle to this ante-switch OTC-like data generation approach. In contrast to the US, where the conduct of actual use studies in an OTC-mimicking setting is legally possible even though the switch candidate itself has not yet been officially reclassified, similar legal provisions are not in place in European countries.

Nevertheless, the legal fundament to conducting such a behavioral study under OTC-mimicking conditions might again be the conditional performance of a post-authorization safety/efficacy study with “post” this time not referring to the point of release from prescription to nonprescription status (i.e., the Rx-to-OTC switch) but its authorization as prescription drug instead. In this case the need for accordant justification and acceptance of implementing OTC-mimicking study conditions goes without saying.

On the other hand, there are member states in the EU whose legislation inherently allows for creating a study environment fairly close to an OTC-like setting. In the UK, for example, so-called “patient group directions” (PGDs)⁵¹ anchored in UK legislation enable specially trained pharmacists to supply certain prescription drugs to a well-defined target population

⁵¹ q.v. <http://www.pharmacypgd.co.uk/>, last accessed 2012-11-15

under well-defined conditions (e.g., based on a detailed sales protocol, etc.). Although being a rather bureaucratic model not mimicking OTC conditions at its best, it may be at the basis of a non-interventional study concept and thus give an idea about a proposed switch candidate's real-life supply and utilization after being reclassified to OTC. As regards other EU countries, the identification, definition, and creation of a legally accepted comparable situation will be a major challenge for conducting an OTC-like behavioral study ante-switch. As far as Germany is concerned, a pharmacy supply model of an Rx drug provided to patients in a similar way as if it was available OTC (i.e., including patient education, hand out of questionnaires/patient diaries for data collection, etc.) possibly would come closest to the UK model.

Apart from strategic approaches mentioned above, the easiest way of conducting a behavioral study, if applicable, would presumably adhere to data collection in countries where the proposed switch drug and/or indication has already been transferred from prescription to nonprescription status. Of course, assignability of data to the respective country(/-ies) of switch application will have to be justified (e.g., by data demonstrating that the target population does not differ with regards to self-diagnosis capabilities and self-treatment practices in a specific indication, etc.). If necessary, a "bridging study" might help generate relevant data in that respect.

To summarize, a legal legitimation for a "conditional release" including the performance of a non-interventional, behavioral study under OTC-mimicking propositions can be found in the current European and national legal and regulatory frameworks (PASS/PAES) provided that the rationale behind this is a comprehensive safety/efficacy testing under real-life conditions. In the author's opinion, data generation within the context of an OTC-like observational utilization study with a view towards the potential safe and effective release of a specific Rx drug from prescription status does indeed comply with this postulation. The main reason for this assumption is the fact that next to direct safety dangers related to a certain drug's toxicity profile indirect safety parameters, such as: correct self-selection, administration of use, dosing, and therapy compliance, play a major role in a less controlled OTC setting and the envisaged target population's behavior and utilization pattern therefore needs to be thoroughly assessed. In practice, as described above, depending on the individual switch scenario such a study could be carried out as PASS during post-marketing as Rx drug (mimicking OTC conditions) or after Rx-to-OTC switch approval as nonprescription drug (real-life OTC conditions) based on § 4(34) referring to § 28(3) of the German Medicines Law. Besides, alternative study concepts of respective OTC-like data collection (e.g., in the US) were illustrated.

Against this background, according to the author's opinion, any high quality data resulting from an appropriately designed non-interventional behavioral study verified to be valid and representative for the target population in question should in all events be considered relevant and necessary for a proposed Rx-to-OTC switch and thus be eligible for the provision of data exclusivity on the basis of Article 74a, Directive 2004/27/EC.

9.3.4 Data related to risk management

In light of a constantly growing number of drug substances available on the market for the treatment or prevention of many different kinds of diseases, the European Commission has attributed increasing importance to all fields of pharmacovigilance. It therefore developed further the legal basis which was set with Regulation (EC) No 726/2004 for central and Directive 2001/83/EC for de-central, mutual recognition and national applications. Currently, the legal framework for so-called “Good Pharmacovigilance Practices” as “a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU)”⁵² is laid down in Regulation (EU) No 1235/2010 (CP) and Directive 2010/84/EC (DCP, MRP, national procedure), respectively. In Germany, respective provisions have been implemented within the context of the aforementioned 16th amendment to the German Medicines Law in § 4(36-39), § 22(5+5a), § 28(3a+b), § 62 and § 63. In short, respective legislation stipulates that a detailed so-called risk management plan describing an associated risk management system (RMS) will be required for marketing approval of new drug applications (Article 8(3), Directive 2010/84/EC and § 22(5+5a), German Medicines Law, as amended). Furthermore, it allows for responsible authorities to require either before/with or after authorization approval the implementation of proposed measures if considered necessary from a drug safety point of view (Article 21a, 22, 22a, Directive 2010/84/EC and § 28(3a+b) German Medicines Law, as amended). By definition, a RMP constitutes of “a set of pharmacovigilance activities and interventions, such as studies and reports, designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions” (Fitt 2011). A specific EU-RMP template has been provided by the EMA as of 2006⁵³.

In contrast to new drug applications, the incorporation of a detailed RMP is not (yet) mandatory for Rx-to-OTC switch applications and has not (yet) been included in the EU switch guideline. Nevertheless, such a RMP was, for example, submitted within the context of the central European switch application for orlistat (alli[®]) (EMA 2009a). Interestingly, in its draft guideline on “How to change the legal classification of a medicine in the UK”, the UK regulatory authority (MHRA) has now embedded the delivery of a detailed RMP with the reclassification application of more complex switches as a mandatory requirement. The rationale behind this is that it should outline “the important risks associated with the reclassification of the product and the proposals to manage these risks such as clear product information and in some cases other measures including any provisions for appropriate education and training for pharmacists and pharmacy staff” (MHRA 2012).

Aiming at the protection of patients and consumers from risks known from Rx-marketing (or OTC-marketing in other countries) by suitable amendments to the product information and, as necessary, the roll-out of proposed measures for safety monitoring and risk reduction, in the author’s opinion the elaboration and submission of a detailed RMP does in effect as

⁵² cf. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c, last accessed 2012-11-15

⁵³ cf. http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/\10/WC500006317.pdf, last accessed 2012-11-24

well make sense for drug products to be reclassified from a medically more or less supervised prescription setting to a commonly less controlled nonprescription setting.

Of course, risk management strategies and measures will vary depending on the nature of the individual switch scenario. For example, they should be particularly comprehensive for reclassification proposals relating to so-called “first in class” OTC switch products for the treatment of indications lacking any therapeutic experience in self-medication so far.

In practice, a detailed analysis of the actual safety and benefit-risk profile of the switch candidate should be at the basis of the proposed RMP not only factoring into experiences made during Rx marketing, but also focusing on the new target setting of self-medication. In 2011, Brass and co-workers developed a framework for the assessment of the benefit-risk profile of nonprescription drugs which was suggested by the MHRA as a useful tool to be applied within this context by Rx-to-OTC switch applicants (see Figure 28). The fundamental idea of this so-called “value-tree tool” is the assessment of common domains relevant to nonprescription drug status with regards to benefits and risks on the basis of product-specific attributes. According to the authors, “this method will help manufacturers in designing development programs by identifying the data elements that are most important to determining the magnitudes of the product-specific attributes” (i.e., associated potential benefits and risks) (Brass 2011). Moreover, the authors suggest that non-interventional consumer/patient behavior studies “can be used to address important product-specific questions in a consumer-centered [...] manner” so as to “risk-mitigation strategies can be evaluated early in the drug development process [...]”. Next, based on a comprehensive analysis of the switch candidate’s benefit-risk profile taking into account both existing Rx and, if available, OTC(-like) data, the determination and preferably evaluation of appropriate risk minimization strategies is to be seen as a crucial step in the setup of an accordant RMP.

Major issues for the setup and implementation of a risk minimization system that most notably apply to central European switches or switches in more than one EU member state, respectively, probably will be adherence to consistency and uniformity of suggested activities (e.g., communication, etc.) as best as possible. Inconsistency in healthcare professionals’ and especially pharmacists’ roles across Europe as well as the diversity of practices, cultures, perceptions and organizations of healthcare systems have to be considered as major challenge in this case.

In conclusion, based on the fact of a drug’s transfer from Rx to OTC confronting both HCPs and patients with a new situation in a less controlled setting of self-medication, appropriate and feasible risk management strategies are contemplated as crucial and relevant elements in safeguarding a switch candidate’s establishment as OTC drug intending to afford the best possible health benefit. The author thus postulates that if rigorous and valuable data referring to adequate and successful risk management/minimization measures proposed for a certain Rx-to-OTC switch will be able to yield a positive switch decision, they should also be able to qualify for an associated data exclusivity provision. In particular, if risk management measures will be integrated into the course of any non-interventional behavioral study, as discussed before, related data should, according to the author, come under the “clinical trial data” category currently mentioned in Article 74a, Directive 2004/27/EC.

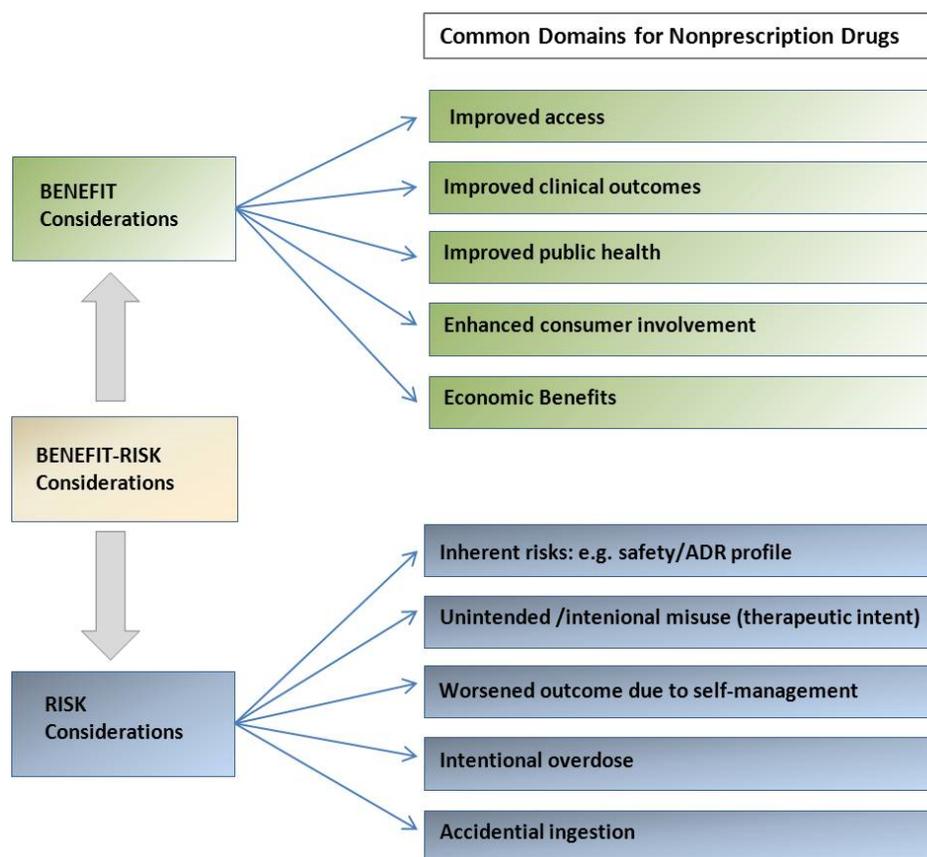


Figure 28: Value-tree framework of benefit and risk domains for nonprescription drugs (adapted from Brass 2011 and MHRA 2012, respectively)

Against this background and in allowance for the targeted setting of self-medication, activities and measures described in the following are considered as valuable and necessary elements of risk minimization provisions aiming at a safe and sustainable Rx-to-OTC reclassification process. Proposals listed below could either be a supplementation to or part of the generation of non-interventional utilization study data in an OTC-like setting as discussed above (cf. Subsection 9.3.3).

Training programs/educational material The relevance of adequate training material and educational information as integral parts of a switch and its associated benefit-risk decision is well documented throughout the corresponding literature (Bond and Hannaford 2003; Fuster and Mearns 2009; Hemwall 2010; Pawaskar 2007). Likewise, the essential role of comprehensive training concepts and educational information accompanying a drug's change of legal status was confirmed by interview partners by a major attribution to data exclusivity potential (cf. Figure 22).

Depending on the complexity of the reclassification scenario in question, HCPs with phar-

macists in particular should be provided with sufficient information regarding basic scientific characteristics (i.e., safety and efficacy) of the drug substance itself focusing on its inherent interaction profile which is of note as regards potential co-medication with OTC, but also Rx drugs, of the drug product (e.g., development of a “treatment-algorithm” for usage in the context of current OTC treatments), as well as of the targeted indication (diagnosis, potential underlying conditions, alarm signals, available diagnostic tools, etc.). In particular, if necessary, timely referral to primary physicians and/or medical specialists is an important step in pharmacists’ role as safeguarding intermediary in the self-care environment. Special pharmacy sales protocols on the basis of scientific guidelines developed in collaboration with scientific experts could assist in a switch drug’s recommendation and distribution by concurrently providing the opportunity to register crucial patient safety data that could be worthwhile to be further tracked/monitored. An appropriate legal and regulatory environment, however, including the disposability of a correspondent infrastructure would be necessary in the latter case (cf. Subsection 9.3.4). Methodological and hardware possibilities for training performances and/or the dissemination of educational material are manifold ranging from paper-based manuals and counseling kits to interactive e-learning modules that can be accessed via personal computers or special applications for mobile devices (e.g., mobile phones), to scenario based face-to-face on-site trainings. In order to ensure penetration and sustainability of contents, certified trainings including commitments to regular up-dates could be a reasonable model. By way of example, the aforementioned switch of tamsulosin (Flomax Relief[®]) in the UK has obviously, *inter alia*, been backed by an accredited pharmacist-training (OTC Bulletin 2009). Integrated training concepts involving pharmacy personnel as a team instead of separate training guides for pharmacists could be of avail in this respect (OTC Bulletin 2012). Additionally, a pharmaceutical manufacturer’s commitment to continued or regular (external) quality controls of its training concept and educational/informational materials in use is crucial in order to ensure sustainable implementation based on up-to-date information and therefore was also highly appreciated by interview respondents (cf. Figure 23).

Beyond HCP training, consumer/patient information and education are key as they may not only increase the general public’s disease awareness, but also its health and medication related knowledge (Pawaskar 2007). Educational programs focusing not only on the Rx-to-OTC switch drug product but also on accompanying favorable life-style activities are estimated to have a potential for a positive public health impact similar to the switched pharmacotherapy itself (Fuster and Mearns 2009). Accordingly, convenient symptom-based methods and/or algorithms to assist people in correct self-diagnosis were judged “very good” regarding their potential for Rx-to-OTC switch exclusivity qualification (q.v. Figure 17). Comprehensive behavioral self-help programs were offered, for instance, within the context of the release of nicotine replacement therapies, the effectiveness of which has been analyzed, evaluated, and published in the relevant literature (cf. e.g., Achanta and Rhodes 2003). Materials that are tailored to the needs of individuals (based on individuals’ demographic or behavioral characteristics) evidently tend to outperform universally standard materials (e.g., provided at the point of sale) and may provide greater penetration (Curry et al. 2003). In

case of switches aiming at the treatment of chronic risk factors consumer/patient support programs most notably lend themselves to accompany the introduction and establishment of a therapeutic option that has been released from prescription to nonprescription marketing. Informational materials that have been disseminated with effective personalized adjuncts and/or interactive elements (e.g., telephone counseling or toll-free hotlines) have consistently proven better and longer-lasting effectiveness as opposed to written standards to read-only (Curry et al. 2003; Lancaster and Stead 1999). In times of apparent growth of digital media the availability of a variety of tools has paved the way for an increasing importance of “e-health” information. Appropriately designed (personalized) websites or applications (“apps”) for mobile devices provide the possibility for implementing interactive support programs including data management and (personalized) feedback mechanisms. Above all, “flexibility in the approaches used to support consumer self-selection is important and may encompass a learned intermediary with accountability (e.g., pharmacist) or other IT solutions to product use” has been declared by Soller and colleagues as one of eight guiding principles for Rx-to-OTC switches (Soller 2012a).

In either case, three critical aspects that should be definitely taken into account are timing, consistency, and suitability of information provided. As mentioned above, research on educational programs and materials (e.g., related to the switch candidate’s labeling, etc.) might yield essential insights into its associated benefit-risk profile. If proven effective, programs might eventually drive consumers and/or patients to not only readily self-treat in case of acute, self-limiting conditions, but also to consult a health-care professional and, if applicable, shift to more comprehensive medical care or prevention strategies after identifying a more serious disease or respective risk factors (Hemwall 2010).

As to successful development of appropriate training and educational material, first of all identifying the needs of the respective target groups is of utmost importance and the benefit-risk model described above (see Figure 28) might be a helpful tool in this case. As well, development of accordant informational material and communication strategies in co-operation with those it is intended for (i.e., representatives of the various stakeholder groups) might enhance practicability and feasibility (MISG 2010). Proactive collaboration with professional bodies, organizations, etc. involved may contribute to consistency of information. Moreover, Soller and colleagues contemplate “standardization (e.g., through use of diagnostic and selection protocols, quick reference guides, patient education sheets, staff training manuals)” as “important to ensure consistency in counseling across community pharmacy practitioners and across pharmacies” (Soller 2012a).

Any training programs and educational material developed should hence be pre-tested and preferably be applied in a setting reflecting real-life conditions. Thereby manufacturers should not only prove suitability and comprehensibility of accompanying measures developed with a view to the various target groups affected, but also demonstrate that information and guidelines provided are continuously considered and applied correctly. As mentioned before (q.v. Subsection 9.3.3), within this context a multifaceted, multiple-arm behavioral study (e.g., as PASS) could be a valuable instrument to generate relevant and significant “clinical data” demonstrating the potential benefit and/or further needs of supportive ma-

terials and/or programs that are intended to facilitate the preparation, introduction, and establishment of a certain drug's release from prescription-only status.

Drug therapy monitoring According to the author's understanding in the present work, depending on its context the term "drug therapy monitoring" refers to several different situations and therefore is associated with different potential data subcategories which will be outlined below.

- HCP/Patient reporting systems

First of all, drug therapy monitoring relates to pharmacovigilance in terms of drug safety and adverse event tracking. With the establishment of specific reporting systems for (suspected) adverse drug reactions, an important pharmacovigilance system has been enacted by the EU legislative body. In pharmacoepidemiology, reporting systems commonly are used to report the occurrence of drug associated AEs. In fact, they "are particularly useful for identifying types of errors that occur too infrequently for individual health care organizations to readily detect based on their own data" (Morlock and Wu 2010). Generally, such a system not only helps keep its provider accountable for performance, but also yields information that might be crucial to improve a drug therapy's safety. In its latest renewal of the respective legal framework (i.e., Directive 2010/84/EC) the EU has thus adopted the possibility for patients to report any (suspected) ADR to a specific database provided by the responsible national authority for subsequent evaluation, a system which obviously has successfully been realized in a number of countries over a various period of time (e.g., the yellow card system in the UK as of 2008) (Mergel et al. 2012). In Germany, an accordant test phase was started as of late 2012. In addition to what was already mandatory for health care sector members before, patients now are allowed to register any suspected AE themselves. However, individual patient confidentiality (i.e., data protection issues) are still controversially debated and to be treated with caution in this matter. Likewise, the introduction of fully integrated electronic patient record systems including both an individual patient's OTC and Rx medication as well as primary and secondary care data have been proposed elsewhere, yet again would be supposed to be rather constrained or even fail due to the latter reason (Bond and Hannaford 2003).

Moreover, as respective systems are to be generally admitted and provided by superordinate institutions, in the author's opinion, associated data cannot be considered appropriate for being eligible for data exclusivity provision to a single manufacturer's Rx-to-OTC switch proposal.

- Monitoring tools supporting drug therapy self-management

Apart from the pharmacovigilance reporting systems mentioned above, specific drug monitoring tools that basically assist in the diagnosis, management, or prevention of primarily chronic risk factors and diseases on the basis of respective diagnostic parameters (e.g., blood cholesterol or sugar level) would equally come under the superordinate concept of drug therapy monitoring. The author suggests that appropriate easy-to-use

devices provided to consumers/patients within the context of an intended Rx-to-OTC switch aiming at both the prevention and treatment of (semi-)chronic diseases could largely contribute to a controlled and safe therapeutic self-management of respective risk factors (e.g., high cholesterol levels, diabetes mellitus, hypertension, etc.), as long as adequate training and education will be regularly warranted. Above all, it might be a crucial element for a specific Rx-to-OTC switch decision as it could assure the identification of the right target population, which is estimated to be a key element of an appropriate Rx-to-OTC switch model. Depending on the complexity of the switch scenario and in particular the target indication in question, self-management could be supervised by regular checks through specialized (e.g., pharmacy) personnel. In some cases, the interpretation of diagnostic findings from a nonprescription device requires professional judgment (i.e., borderline results). Suitable software technology featuring data security could enable direct data transfer from an individual patient's measurement device to the attending physician and/or pharmacist including the activation of alarming systems, if applicable, for the sake of medical feedback.

As suggested above for the development of training concepts and educational materials, the acceptability of the usage of such diagnostic measurement/monitoring devices and/or software systems (such as e-health communication tools or applications) could or rather should, respectively, as well be tested (e.g., in a non-interventional behavioral study) under OTC real-life conditions. Expert interviews showed that the investigation of special patient groups and control through specialized personnel, if applicable, might be of particular value in this regard. In case of preventive therapy switch proposals (e.g., treatment of hypercholesterolemia/hyperlipidemia, etc.) data regarding actual use should encompass compliance related to drug usage as well as acceptance of concurrent consumer support activities referring to important life-style modifications (e.g., weight loss, physical activity, etc.). Data evaluating consumer/patient diaries with respect to diagnostic drug therapy monitoring results, for instance, could be useful within this context. When asked about the kind of data they would consider particularly relevant with a view towards potential eligibility for data exclusivity, data demonstrating compliance of patients using the measurement devices/activities developed were estimated as extremely relevant by the majority of interview partners (see Figure 19).

Of note, it is important to take into account that especially in the event of asymptomatic, (semi-)chronic conditions, patients' motivation to manage existing risk factors will increase with the visibility of benefits and added value (e.g., in terms of therapeutic effect and resulting improvement of QoL, etc.) of available treatment options (see also Subsection 3.5.3). In the author's opinion, concomitantly provided, appropriate, easy-to-use self-monitoring devices and related educational measures might eventually contribute to responsible self-management of existing (semi-)chronic pre-conditions. They, therefore, add to public health in the event of corresponding prospective Rx-to-OTC switches to take place. This might eventually be demonstrated, for example, by respective non-monetary data (see below). Against this background, the author of the present work considers such data to be valuable

for potential data exclusivity provision.

9.3.5 Data related to public health value

Different types of methods and data categories assessing demonstration of public health value are available. A brief overview will be given below.

Pharmacoeconomic data By conventional definition, the term pharmacoeconomics is “the description and analysis of the costs of drug therapy to healthcare systems and society” (Bootman et al. 1996; Tsokeva et al. 2006). Depending on the method of evaluation, outcome parameters might be tangible (i.e., monetary such as direct and indirect costs) or intangible (i.e., non-monetary such as QoL, patient satisfaction, etc.). Accordingly, based on the distinct measurement of health gain various types of pharmacoeconomic analyses can be differentiated (Bodrogi and Kalo 2010). Whereas the majority of pharmacoeconomic analyses investigate cost-benefit or cost-effectiveness implications (Neumann et al. 2008), other approaches focus on analyzing cost-utility, cost-minimization (depicted in Table 14) or humanistic assessments (not shown).

Table 14: Differentiation of pharmacoeconomic evaluations based on health gain measurements (adapted from Bodrogi and Kalo 2010)

Type of evaluation	Measurement of health gain	Applicability
Cost-benefit-analysis	Monetary value	Comparison of any medical and non-medical procedures and investment options
Cost-effectiveness analysis	Natural units (traditional clinical endpoints)	Comparison of medical procedures with non-equal health gain measurable in the same health dimension
Cost-utility analysis	Quality adjusted life years (QALYs) ⁵⁴	Comparison of any medical procedures
Cost-minimization analysis	Not specified	Comparison of medical procedures with equal health gain

However, when it comes to Rx and OTC drug approval decisions, pharmacoeconomic data clearly have been affirmed to be out of regulator’s focus (Soller 2012a). This holds true not only for the US, but also for Europe. In Germany, for example, the national regulatory authority (BfArM) states in its information on the application for changing the legal status, that “the committee will be evaluating [the] application mainly on the basis of sound data concerning drug risks”⁵⁵.

⁵⁴ artificial unit integrating both quality and quantity of remaining life years (Tsokeva et al. 2006)

⁵⁵ cf. <http://www.bfarm.de/EN/vigilance/eacPrescription-only/application-changing-legal-status.html>, last accessed 2012-11-12

Nevertheless, in order to get a qualitative feedback on this issue, experts were asked for their personal opinion on the possibility of valid pharmacoeconomic data representing an eligible contribution with regard to data exclusivity provision. As indicated by questionnaire results, more than half of them could indeed imagine pharmacoeconomic data to be part of the Rx-to-OTC switch documentation eligible for data exclusivity. More specifically, the majority of these favored pharmacoeconomic analyses factoring into non-monetary assessment parameters such as (health-related) QoL improvement, accelerated and convenient therapy access, treatment satisfaction, or other so-called patient reported outcomes (PROs)⁵⁶ (cf. Figures 24 and 25).

As a result of the aforementioned (i.e., current practice in reclassification approval decision making and insights gained through qualitative expert feedback) the author holds the view that the submission of classical pharmacoeconomic data resulting in monetary values only will not be appropriate with regards to a claim on data exclusivity.

Non-monetary health-related data On the other hand, according to the author the determination of robust non-monetary patient and/or public health benefits, respectively (e.g., in the form of patient related outcomes in epidemiological studies) might indeed be an option for demonstrating a certain switch candidate's potential to increase public health value thereby positively influencing its associated benefit-risk ratio (e.g., based on the model provided by Brass and colleagues) (Brass 2011). To give an example, sound scientifically conditioned epidemiological or market research data verifying raising disease awareness and proactive treatment by patients or populations at risk (who otherwise would not seek medical consultation due to various reasons such as embarrassment, lack of time, etc.) or data comparing treatment satisfaction of therapy options available OTC with possibly more effective or convenient Rx switch candidates might be important data supporting a positive Rx-to-OTC switch decision in light of an estimated gain in public health. The author therefore promotes the acknowledgement of valuable data (e.g., epidemiological survey data, market research data, etc.) as being eligible (at least in support) for data exclusivity in case of the capability to verify an estimated public health gain, even though it might neither be classified as "pre-clinical test data" nor "clinical trial data" as indicated in the EU's current legal framework, yet, would have to be assigned to an additional data category instead (see below).

9.4 Non-clinical data as potential additional data category not reflected by Article 74a, Directive 2004/27/EC

There might be specific programs, concepts, or models that may not be able to be implemented and/or behaviorally evaluated before approval (Aker 2006). In order to be able to account for these elements all the same, the author suggests that in this case elaborated data with the potential of being eligible for or at least contributing to the grant of data

⁵⁶ In practice, PROs subsume all measures which quantify patients' state of health by analyzing outcomes reported by them. Being complementary to classical biomedical measures, PROs are increasingly used as an integral part of clinical trial and health care strategy evaluations (Refolo et al. 2012).

exclusivity without representing a direct form of “pre-clinical test data” or “clinical trial data” could possibly be subsumed under an additional data category such as, for example, “non-clinical data”. Accordant data subcategories could adhere to any educational information (e.g., theoretical, but innovative contents of training concepts, treatment algorithms, digital/printed high-quality informational materials, etc.) and/or any kind of drug therapy monitoring models (e.g., based on a specific technology/software) as well as to assessments of demographics, drug utilization characteristics, and/or non-monetary data focused on patient related outcomes and referring to public health benefit each possibly comprising corresponding epidemiological or market research (i.e., consumer/HCP survey data, etc.). Above all, a common requirement for eligibility to data exclusivity should be the fact that respective data demonstrate a potential switch candidate being first and foremost safely, but also effectively, “OTCable” for the right target population with the implementation of proposed risk management strategies thus improving the candidate’s benefit-risk profile and eventually enhancing public health. Within this context the author is convinced that a consumer-/patient-centered approach towards the development of any pre- and post-marketing risk management approaches, including accordant safety and effectiveness evaluations, will be inevitable and of utmost importance for a respective Rx-to-OTC switch decision. In fact, as can be derived from the centralized European reclassification of orlistat 60 mg (alli[®]) (see Subsection 4.4.4), such data obviously are of major interest for authorities alike as the applicant had to commit to the collection of appropriate survey data on demographics, clinical characteristics, and usage patterns for reasons of safeguarding secure and effective OTC usage.

Furthermore, the author assumes that especially in countries where reclassifications are not product-specific, yet substance-specific, there might be few or no generic followers that will be able to implement risk management measures similar to and as comprehensive as proposed by the originator company initiating a specific Rx-to-OTC switch. According to the author’s view, this is another reason why eligibility for data exclusivity should likewise admit and encompass non-clinical data, thereby reassuring a specific switch proposal’s safety and related improved benefit-risk profile, which is critical to an associated positive reclassification decision: a consistent and transparent post-approval implementation of risk management measures, such as a well-controlled and sustainable switch supply model, for instance, will thus be ensured

Against this background the author suggests that the current European legislation referring to data exclusivity provision for Rx-to-OTC switches (i.e., Article 74a, Directive 2004/27/EC) should be considered to be amended by the term “non-clinical data” as another data category option to which applicants might be able to advert to when submitting correspondent data with a claim on data exclusivity. Alternatively, replacing the term “pre-clinical test data” by “non-clinical data” actually comprising the subcategory “pre-clinical test data” could be worthy of consideration, thus offering an even broader range of data to be handed in for data exclusivity than might have been intended by the legislative body with the inclusion of “pre-clinical test data” in addition to “clinical trial data”.

However, as from experience, it might be a long and tough way until set legal provisions if

at all are about to be changed. Therefore, in the short-term, the revision and amendment of according guidelines, i.e. above all the European switch guideline in its version of 2006, might be a viable mode of widening the scope for data to be submitted with a claim on data exclusivity by introducing the acceptance of accordant non-clinical data.

9.5 Reasonable duration of the exclusivity period within the context of Rx-to-OTC switches

As already depicted before, the current EU legal framework regarding the grant of data exclusivity for Rx-to-OTC switches provides for a one-year data protection period in case of data submitted being eligible according to Article 74a, Directive 2004/27/EC⁵⁷.

As a result of the aforementioned, the author advances the view that a one-year period of data protection might not be adequate and sufficient in light of the amount and quality of data required to be generated and/or collected in addition to the data generally needed for a reclassification request in order to be able to call for a data exclusivity provision.

This opinion is supported by two aspects deserving consideration: first of all, as can be concluded from the foregoing discussion, non-interventional behavioral study data obviously seem to be the kind of data with the highest potential of being accepted with respect to data exclusivity qualification. Consequently, from the applicant's point of view, the need for conducting an appropriately sized, high-quality study possibly lasting several months to even years is a major implication of the latter. In general, without knowing the outcome of an accordant study as well as the chance of success in terms of data exclusivity, any study conducted is to be seen as a risky and resource intensive project the positive accomplishment of which should be rewarded in a way that adequately compensates the applicant's investment. Taking into account all stages of a properly conducted clinical trial as well as, if applicable, the development of any educational/informational material or technology systems eventually to be tested within the context of such a trial, the author considers one year of data exclusivity as not being adequate to enable a pharmaceutical company to recoup associated investments. Thus, at present, its role as an incentive tool for innovative concept creation and data generation aiming at improving a switch candidate's benefit-risk profile and eventually resulting in a benefit to public health might not be of adequate relevance.

Secondly, what is of even greater importance especially from a public health perspective, depending on the complexity of the switch in question the introduction and establishment of a new therapeutic option in a nonprescription setting including reasonable HCP and patient/consumer education will take a considerable period of time. This was precisely addressed on the occasion of a discussion about widening access to medicines via reclassification during the 6th UK "Ministerial Industry Strategy Group (MISG) New Technologies Forum" in 2010 by participants pointing out that "[...] exclusivity is not just about recouping costs

⁵⁷ The original wording is as follows: "Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised."

but about providing the time for consumer and health care professionals' engagement in the switch and for the market to develop" (MISG 2010).

To give an example, in Germany it is said that in the case of ibuprofen as prominent representative of the category of NSAIDs for symptomatic self-treatment of acute, mild to moderate pain and fever, a period of almost up to ten years had passed after its reclassification from prescription status until it reached sufficient acknowledgement and acceptance by both HCPs and patients/consumers as a safe and effective therapeutic option in the face of existing OTC alternatives. As noted before, transparency and in particular consistency of information provided is to be seen as a crucial step within the process of a sustainable introduction and implementation of a specific Rx-to-OTC switch model. Within this context, the reclassification of the PPI omeprazole (q.v. Subsection 3.5.1) for the treatment of heartburn and acid regurgitation in 2009 in Germany is indicative of a rather less commendable environment when transferring a drug from prescription to nonprescription status. In particular, due to the absence of data exclusivity (which had not been applied for) apart from the company having initiated the Rx-to-OTC switch (originator), a rash of generics took the chance to simultaneously enter the market partly supported by none, partly by informational/educational and training material often differing from that provided by the originator in preparation of the switch. Consequently, associated precariousness and reservation experienced by both HCPs and patients/consumers might have resulted in OTC-PPIs being an existent safe and effective though apparently not (yet) commonly accepted therapeutic alternative in the self-treatment of heartburn and acid regurgitation.

Of note, the author's view obviously is shared by the majority of experts interviewed who judged the one-year period as being "too short" ($n = 6$), whereas two of them considered it as "just appropriate" and only one as being "too long" (see Figure 8). When asked about an alternative time period of protection that would be more appropriate within the context of Rx-to-OTC switches according to their view, three years were largely suggested as a minimum and five years as maximum to be provided.

As described earlier (see Subsection 4.4.1), in the US, if eligible, Rx-to-OTC switches will be granted a three-year marketing exclusivity period on a similar basis as found in the current EU legislation, i.e., in case of "significant" data judged essential by FDA assessors on a case-by-case basis due to the fact that as in the EU no specific guidelines are in place. From the author's point of view, a three-year exclusivity period seems a lot more reasonable and appropriate, even more so when considering that an adequate education and training of HCPs assigned with supply and recommendation of the product as well as the accomplishment of disease awareness campaigns, etc. means that an important part of the exclusive marketing phase would have elapsed before the reclassified product could be successfully marketed. The reason behind this is that from a legal perspective applicants in general will not be able to officially start to prepare the market for a product-related switch before authorization. Moreover, a three-year period of data exclusivity would arrange for comparable conditions within Europe and the United States and thus could eventually close the gap with respect to the value of exclusivity provision as an incentive tool in place for Rx-to-OTC switches

potentially resulting in an overall EU switch climate that is as vital as in the US⁵⁸. Furthermore, the complexity of an individual Rx-to-OTC switch case and the extent to which a certain switch model including all accompanying measures has to be elaborated and implemented are important factors to be taken into account. Therefore, a kind of “sliding” or “proportional” scale of exclusivity duration was suggested by one of the interview partners, implicating a gradual period of data exclusivity to be granted depending on efforts made and resources invested as well as on the respective public health gain associated with the realization of a specific Rx-to-OTC switch model. In the author’s mind this proposal seems to be an interesting approach, yet unless there will be well-defined prerequisites linked to the granting of a distinct length of data exclusivity, the seemingly less transparent and arbitrary provision of different phases of data exclusivity will be a crucial issue for further discussion. Altogether, based on the data categories and criteria proposed in the work at hand with respect to eligibility for data exclusivity provision and in light of the reasons mentioned above, the author regards a data exclusivity period of not less than three years as essential and reasonable.

⁵⁸ However, whereas in the US the three-year exclusivity period refers to market exclusivity hence allowing competitors to immediately enter the market after its expiration, in Europe generic abridged applications according to current law would only be processed at the end of the three-year (data) exclusivity period. This procedure implicates an effective prolongation of the latter, unless a marketing authorization will already be able to be processed and granted before with the obligation to only enter the market after the data exclusivity period would have expired.

10 Conclusions and recommendations

The present work displays an attempt of substantiating the legal definitions referring to the data exclusivity provision for Rx-to-OTC switches within Europe by suggesting different data categories, outcome parameters, and criteria of varying relevance to be considered when data intended for a claim on exclusivity are submitted.

It has been shown that along with recent sociocultural, sociopolitical, and socioeconomic evolutions there is a trend in Rx-to-OTC switch movement aiming at the reclassification of prevention or treatment options for increasingly complex diseases compared to previous targets of acute, minor, and self-limiting ailments. If taken on successfully, this trend will eventually contribute to the enhancement of public health value not only by raising disease awareness and encouraging individuals to responsibly manage their own health/disease status, but also from an increasingly burdened health care systems' perspective. However, at the same time requirements associated with the planning, realization, and sustainably safe and effective implementation of a certain Rx-to-OTC switch will, on the other hand, continuously be rising. In conclusion, a supportive political, legal, and regulatory framework is crucial in order that accordant switch projects be initiated and adequately prepared in the future.

Within this context the provision of data protection for Rx-to-OTC switches anchored in the European legislation is basically considered as a reasonable tool: in general, an Rx-to-OTC switch changes the situation within self-medication by extending the availability of therapeutic alternatives in a specific category or by even creating a completely new therapeutic area. Consequently, both HCPs and patients are confronted with a new situation regarding OTC treatment options and/or indications. In order for pharmacy personnel, patients, and other stakeholders to be equipped well in time for a certain Rx-to-OTC switch to take place, manufacturers should start preparations (data review/generation, risk management planning, etc.) in due time before the official authorization approval – a more or less risky and costly investment when considering the uncertainty of a switch approval and even more so the possibility of data exclusivity receipt. Only the latter though will help ensure a consistent and transparent implementation of communication, education, and risk management measures developed by the company originally initiating a certain switch as a result of related pre-switch data generation by exclusively consigning this company with the adequate introduction and establishment as well as monitoring of a respective switch candidate in self-medication. Concurrently, responsible authorities would be able to accompany and control the switch process as a whole, e.g., by imposing, if applicable, appropriate conditions and requirements (“conditional release”).

As to the entrepreneurial risk generally inherent in drug development efforts, maximum predictability is an essential objective for promoting and facilitating the development pro-

cess aiding companies in forecasting development costs and potential return on investment (Soller 2012a). In order to work as such, incentive tools for pharmaceutical drug manufacturers aiming at fostering innovative drug development for the benefit of public health value should therefore be associated with clear guidance and instructions regarding requirements that need to be fulfilled.

However, the present work has demonstrated the actual European legal framework regarding data exclusivity provisions for Rx-to-OTC switches (i.e., Article 74, Directive 2004/27/EC) to be rather indefinite. Correspondingly, “pre-clinical test data” and “clinical trial data” are judged eligible for the grant of data exclusivity if considered “significant” for the reclassification requested. Yet, as long as the aforementioned terms are not further specified and/or are interpreted in a conservative way, the practical applicability of data exclusivity is limited, as the possibilities to generate novel data in addition to drug-specific Rx data generally extensively available for any potential switch candidate are quite restricted. Against this background existent data categories provided by the current legislation have been discussed as well as specified and amended considering aspects relevant to a change of classification from Rx to OTC taking into account the view of representatives of all stakeholder groups involved in such a process. The different proposals elaborated are summarized in Table 15 below.

Whereas the basic Rx-to-OTC reclassification process according to current EU switch criteria as listed in the EU switch guideline mainly focuses on a drug substance’s inherent safety and efficacy profile, usually derived from data collected prior to or during Rx marketing, drug utilization in the targeted OTC setting - indicative of (if at all) very little medical guidance and a broad and usually heterogeneous patient population - often can only be anticipated (no OTC data at all or only from other countries/populations). Accordingly, potential safety hazards emanating from OTC usage might be missed and adequate risk management measures will thus not be readily in place. Therefore, the generation of OTC-like, non-interventional study data is contemplated as crucial and a most valuable additional element in either supporting or preventing a certain Rx-to-OTC switch decision by pointing out indispensable risk management activities eventually to be implemented in order to enable secure and effective self-medication. Furthermore, any kind of newly compiled or generated data favoring and/or aiming at both safe and effective drug utilization in the targeted indication and patient population within self-medication will complement a drug substance’s existing Rx data largely rounding off its associated benefit-risk profile. By fulfilling the legal requirement of Article 74a (i.e., being “significant” in the sense of necessary and relevant, as well as being decisive for a certain switch proposal) the author concludes and stipulates such data in principle to be valued as eligible for the provision of data exclusivity.

The items proposed in Table 15 have been rated based on the author’s estimation of their potential eligibility for Rx-to-OTC data exclusivity provision. Of note, in order to embrace data that typically is neither of pre-clinical nor clinical nature, yet is still able to provide more or less valuable insight into a switch candidate’s envisaged OTC usage pattern, the author puts forward to adapt the relevant legal framework including corresponding guidelines to the introduction of “non-clinical data” as an additional superordinate data category.

Such data could, for example, encompass any data (model) related to risk management or any kind of epidemiological or market research/consumer survey data indicating a benefit to public health (e.g., by an increase in disease awareness, QoL improvement, etc.).

Having taken the aforementioned into consideration, the author postulates that the existent EU data exclusivity period of one year's time should be challenged aiming at a reasonable and justifiable prolongation (e.g., to three years as in the US or a varying elongation depending on an individual switch's complexity). A suitably extended data exclusivity period would not only be able to adequately allow for entrepreneurial switch efforts to be accounted for, but also confer enough time for a certain switch candidate's safe and successful settlement in the self-medication sector on the basis of consistent and transparent information and education as well as continuous monitoring and control (if applicable). Finally, the author is aware of the fact that any change in respective legal settings, if at all, will only be achieved in the long-term. However, given the ongoing sociocultural, sociopolitical, and socioeconomic developments and trends, the author deems it crucial to have initiated the debate on the appropriateness of respective legal provisions and their interpretations by challenging the status quo and elaborating proposals for adaptation most of which could more or less be implemented in the short-term by modification and specification of corresponding switch guidelines. Moreover, stakeholders most notably effected by suggestions made and recommendations given in the present work are advised to be adequately prepared and well-equipped in due time in order to be capable to cope with accordant future tasks and requirements.

In practice, pharmaceutical manufacturers are appealed to consider the potential of prospective OTC usage and correspondent possibilities of data generation early in a drug's life-cycle development. Thereby, accurately timed seeking of regulatory advice regarding an individual switch proposal and its potential for obtaining data exclusivity as well as early stakeholder support are judged to be of major importance. In principle, data submitted in support of exclusivity applications should be explicitly designated and come up with the need of being "novel" (i.e., not derivable from "basic" and often already published data provided with the general switch application). Last but not least, it is deemed to be of utmost importance that any data based on an exclusivity request will have to reflect intended OTC conditions at their best (e.g., targeted indication, dosage, duration, patient population, etc.).

Besides, regulatory authorities will, on the other hand, need to provide and build up, respectively, special expertise with a view towards the assessment of OTC relevant data particularly from a quality perspective (e.g., statistics, data reliability/validity, study design, methodological and analysis aspects, etc.).

To summarize, the author is positive about further innovative and complex switches with a probable public health gain to come on the grounds of the availability and above all applicability of appropriate incentive tools. Within this context data exclusivity provision is regarded as a valuable approach. However, existent legal prerequisites and guidelines will have to be revised and specified in order to be able to acknowledge efforts undertaken to generate high quality data reliably demonstrating and safeguarding consumers' and patients'

safe and effective self-management practices in disease prevention and treatment. In any case, Rx-to-OTC switch decisions should be based on a profound and transparent scientific assessment of data relevant for the envisaged legal classification status and best possibly beware of multiple influences due to different interests and opinions often affecting individual Rx-to-OTC reclassification processes.

Table 15: Overview of existing and proposed Rx-to-OTC switch criteria, data categories, and their estimated relevance for data exclusivity (DE) provision according to Article 74a, Directive 2004/27/EC; 1 = low, 2 = medium, 3 = high; (*) depending on outcome parameters; (**) possibly not appropriate/applicable for OTC (cf. Section 8.1); (***) depending on switch scenario

Rx-to-OTC switch data categories	Pre-clinical test data	Relevance for DE	Clinical trial data	Relevance for DE	Non-clinical data	Relevance for DE
Major outcome parameters	<ul style="list-style-type: none"> • Safety: -toxicity -interaction profile -carcinogenic potential 	<p>1</p> <p>2</p> <p>1</p>	<ul style="list-style-type: none"> • Safety: -direct dangers (detection/tracking of AEs) -indirect dangers (e.g., masking of serious underlying diseases, resistance) • Utilization/Actual use (daily-life): -self-diagnosis -self-selection -label comprehension -compliance -ab-/misuse -assessment of risk management measures 	<p>3</p> <p>3</p> <p>3</p> <p>3</p> <p>3</p> <p>3</p> <p>3</p> <p>3</p>	<ul style="list-style-type: none"> • Risk management measures/plan: -package labeling/restriction -HCP/Patient education and training -supply model -(diagnostic) drug therapy monitoring tools 	<p>3</p> <p>3</p> <p>2-3^{***}</p> <p>2-3^{***}</p>

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Table 15 – Continued

Rx-to-OTC switch data categories	Pre-clinical test data	Relevance for DE	Clinical trial data	Relevance for DE	Non-clinical data	Relevance for DE
	<ul style="list-style-type: none"> • Efficacy: <ul style="list-style-type: none"> -dose-response relationship 1 -bioequivalence, etc. (if applicable, e.g., new pharmaceutical form) 2 		<ul style="list-style-type: none"> • Effectiveness: <ul style="list-style-type: none"> -treatment effect of medication in relevant dose range under daily life conditions in target population 3 -comparison with existing therapeutic alternatives 2-3 -QoL improvement, patient satisfaction with treatment (if applicable) 2-3 		<ul style="list-style-type: none"> • Patient/Public health benefit: <ul style="list-style-type: none"> -disease awareness 2-3 -access to medicine 2 -HCP contacts, etc. 2-3 -non-monetary values/PROs: QoL improvement, patient satisfaction with treatment, convenience, e.g., also compared with existing therapy options 2-3 	
Kind of data	<ul style="list-style-type: none"> • Re-analysis of existing Rx data under OTC relevant aspects 1 • <i>In vitro</i> testing 1-2* • Animal model testing 1-2* • Diagnostic tool testing 2 		<ul style="list-style-type: none"> • Re-analysis of existing Rx data under OTC relevant aspects 1 • Classical clinical trials as RCTs (e.g., phase III or IV studies) 3** • NIS (e.g., as PASS or PAES) 3 • AUS, LCS, SSS 3 • Bridging study using data from abroad (if applicable) 2-3 		<ul style="list-style-type: none"> • Epidemiological data 2 • Market research data 2 • Consumer survey data (demographics, clinical characteristics, usage patterns, etc.) 2 • Embedded in clinical data generation (e.g., NIS, if applicable) 3 	

Continued on next page...

Table 15 – Continued

Rx-to-OTC switch data categories	Pre-clinical test data	Relevance for DE	Clinical trial data	Relevance for DE	Non-clinical data	Relevance for DE
Important criteria/quality aspects	• Data generation/evaluation:		• Data generation/evaluation:		• Data generation/evaluation:	
	-under OTC relevant aspects (dosage regimen, target population, etc.)	3	-under OTC relevant aspects (dosage regimen, target population, etc.)	3	-under OTC relevant aspects (dosage regimen, target population, etc.)	3
	-according to current scientific knowledge and standards	3	-according to current scientific knowledge and standards	3	-according to current scientific knowledge and standards	3
			• Adequate kind and size of study population	3	• Feasibility check (risk management measures, etc.)	2-3
		• Bias reduction (appropriate study design and statistical techniques such as propensity scores, etc.)	3			
		• Control group (if applicable)	2-3			

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A Appendix

A.1 List of databases used for literature research

- Biomedical Core Database, Bayer HealthCare AG: meta-database consisting of six different databases (cf. Table 16 below)

Table 16: Databases included in the Biomedical Core Database, Bayer HealthCare AG (based on information from Bayer HealthCare AG)

Database	Provider	Discipline, Focus	Coverage	Update Rhythm
BIOSIS Previews	Thomson Reuters	Biology, biomedicine, pre-clinical research	1947 – present	Weekly
Current Contents	Thomson Reuters	Life science, clinical medicine	1991 – present	Weekly
Derwent Drug File	Thomson Reuters	Drug-related publications, enhanced abstracts used for drug literature	1963 – present	Weekly
EMBASE	Elsevier	Drug research and pharmacology	1947 – present	Daily
MEDLINE	US National Library of Medicine	Biomedicine and clinical medicine	1950 – present	Daily
Product Literature Information (PLI)	Bayer HealthCare Global R&D Information	Publications dealing with Bayer HealthCare development and marketed drugs	1963 – present	Daily

- Additional databases as depicted in the following Table 17:

Table 17: Additional databases used for literature research

Database	Provider	Discipline, Focus	Coverage	Update Rhythm
Google Scholar	Google	Multidisciplinary	N/A - present	N/A
PubMed	National Institutes of Health, US National Library of Medicine	Biomedical	Late 1940s – present ⁵⁹	Daily ⁶⁰
SpringerLink ⁶¹	Springer	Multidisciplinary	1996 – present	Weekly
WorldCat ⁶²	Online Computer Library Center	Multidisciplinary	Before 1000 BC – present	Daily

A.2 Expert questionnaire regarding the issue of data exclusivity for Rx-to-OTC switches (German and English version)

The questionnaire developed for qualitative interviews with selected national (i.e., German) and international experts regarding the issue of data exclusivity provision for Rx-to-OTC switches within Europe is depicted below in both the German and English version.

⁵⁹ http://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.PubMed_Coverage, last accessed 2013-02-27
⁶⁰ (Falagas et al. 2008)
⁶¹ <http://www.irelibrary.ie/resource.aspx?id=39>, last accessed 2013-02-27
⁶² <http://www.oclc.org/support/documentation/firstsearch/databases/dbdetails/details/worldcat.htm>, last accessed 2013-02-27

A.2.1 Questionnaire German version

Fragebogen zum Thema „Datenexklusivität bei der Entlassung von Arzneimitteln aus der Verschreibungspflicht“

PRÄAMBEL

Aufgrund einer i.d.R. langjährigen und kostenintensiven Entwicklungsphase spielt das Thema „Datenschutz“ bei der Entwicklung von Arzneimitteln eine große Rolle und diesem wird im Rahmen des Patentschutzes größtenteils Rechnung getragen. Doch nicht alle Szenarien, die einen solchen Schutz verdienen, sind dadurch abgedeckt. Dementsprechend hat sich im Laufe der Jahre neben dem Patentrecht auch die Vergabe von Datenexklusivität als ein Instrument zum Schutz von geistigem Eigentum in der Gesetzgebung etabliert.

So besteht z.B. bei der Entlassung von Arzneimitteln aus der Verschreibungspflicht in die Selbstmedikation (sog. Rx-to-OTC Switch) laut Art. 74a¹ der EU-Richtlinie 2004/27/EC unter bestimmten Voraussetzungen die Möglichkeit zu einer einjährigen Datenexklusivität. Eine kurze Interpretation des Art. 74a findet sich in der aktuellen EU-Switchguideline (s. Anhang). Die Tatsache, dass diese Möglichkeit des Datenschutzes bei Rx-to-OTC Switchen bislang in Europa bis auf eine Ausnahme keine Anwendung gefunden hat, wirft an dieser Stelle nicht nur die Frage nach der Bedeutung von Datenexklusivität für einen Rx-to-OTC Switch auf, sondern auch danach, wie realistisch eine solche Vergabe unter den aktuellen Rahmenbedingungen ist.

Die in den letzten Jahren zunehmende Zahl an Entlassungen aus der Verschreibungspflicht ist im Wesentlichen zwei Entwicklungen geschuldet – dem wachsenden Gesundheitsbewusstsein der Patienten inklusive deren Wunsch nach mehr Eigenverantwortung bei der eigenen Gesundheitsversorgung sowie steigenden Kosten der Gesundheitssysteme. Um diesem Trend bei immer größeren Anforderungen hinsichtlich der im Rahmen der Selbstmedikation zu etablierenden Therapieoptionen gerecht zu werden, bedarf es neben einer Konsensus basierten Kooperation aller beteiligten Interessengruppen auch adäquaten Anreizsystemen für Forschungsunternehmen.

Vor diesem Hintergrund bietet die Möglichkeit der Datenexklusivität einerseits eine Motivationsgrundlage für Forschungsunternehmen bzw. Switchantragsteller, die den Switchanforderungen und –anstrengungen Tribut zollen soll. Damit eng verbunden ist andererseits jedoch auch der grundlegende Gedanke, dass den Bemühungen um Datenexklusivität entsprechende für den Switch relevante „therapeutische Konzepte“ zugrunde liegen, die letztlich dem Wohle und Schutz der Patienten dienen und eine optimale Gesundheitsversorgung gewährleisten sollen. Daraus resultiert nicht zuletzt die Forderung nach klaren und transparenten Exklusivitätskriterien, die das Instrument „Datenexklusivität“ für Rx-to-OTC Switches entsprechend nutzbar werden lassen.

¹ “Where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.”

Im folgenden Fragebogen interessiert neben Ihrer generellen Haltung gegenüber „Datenexklusivität bei Rx-to-OTC Switchen“ insbesondere Ihre Meinung bezüglich möglicher Voraussetzungen bzw. Anforderungen an die Datengenerierung für die Vergabe einer solchen Datenexklusivität.

Selbstverständlich werden alle Daten anonymisiert behandelt.

Herzlichen Dank dafür, dass Sie sich die Zeit nehmen, den Fragebogen möglichst vollständig auszufüllen!

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Der Fragebogen befasst sich inhaltlich mit dem Thema „Vergabe von Datenexklusivität bei der Entlassung von Arzneimitteln aus der Verschreibungspflicht“. Die nachfolgend dargestellten Szenarien bezüglich der Entlassung aus der Verschreibungspflicht (Rx-to-OTC Switchszenarien) sollen Ihnen bei der Beantwortung der Fragen als Orientierungshilfe dienen.

Im Hinblick auf die Entlassung eines Wirkstoffes bzw. Indikation aus der Verschreibungspflicht sind verschiedenen Szenarien theoretisch denkbar und auch teilweise praktisch schon erfolgt:

- A: Neuer OTC-Wirkstoff, bekannte OTC-Indikation:
Prominentes Beispiel hierfür ist die Entlassung von Protonenpumpeninhibitoren (PPI) aus der Verschreibungspflicht zur Behandlung von Sodbrennen und saurem Aufstoßen.
 - B: Neuer OTC-Wirkstoff, neue OTC-Indikation:
Als Beispiel wäre hier die potentielle Entlassung von Arzneimitteln zur Blutdrucksenkung (z.B. Sartane) anzuführen.
 - C: Bekannter OTC-Wirkstoff, neue OTC-Indikation:
Hier wäre z.B. die Selbstmedikation der Arthrose mit bereits OTC-fähigen Wirkstoffen wie beispielsweise Naproxen theoretisch denkbar.
-

Artikel 74 a, Direktive 2004/27/EC:

“Where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.”

1 Allgemeines

- 1.1 Wie beurteilen Sie die rechtlichen Vorgaben² zur Vergabe von Datenexklusivität unter dem Gesichtspunkt „Anforderungen bzw. Kriterien für die Datengenerierung im Falle von Exklusivitätsanspruch“?

Bitte treffen Sie Ihre Bewertung anhand der nachfolgenden Skala (1 = sehr gut, 6 = sehr schlecht)

	1	2	3	4	5	6	Keine Meinung
verständlich	<input type="radio"/>						
präzise	<input type="radio"/>						
relevant	<input type="radio"/>						

- 1.2 Wie bewerten Sie die Dauer der innerhalb der EU für Rx-to-OTC Switches zu vergebenden Exklusivitätsperiode von einem Jahr?
- Zu kurz Genau richtig Zu lang

2 Präklinische Testdaten als Basis für die Vergabe von Datenexklusivität bei Rx-to-OTC Switchen

Im Rahmen einer Rx-Zulassung werden in der Regel umfangreiche präklinische Testdaten generiert.

- 2.1 Wie schätzen Sie grundsätzlich die Eignung präklinischer Daten als Basis für die Vergabe von Datenexklusivität beim Rx-to-OTC Switch einer bestimmten Substanz ein?
- Halte ich im Hinblick auf das Sicherheitsprofil der Substanz für notwendig
- Halte ich im Hinblick auf das Sicherheitsprofil der Substanz für geeignet
- Halte ich im Hinblick auf die für die Rx-Zulassung der Substanz generierten Daten nicht für notwendig
- Halte ich im Hinblick auf die für die Rx-Zulassung der Substanz generierten Daten nicht für geeignet

² Art. 74a, Direktive 2004/27/EC bzw. Guideline on changing the classification for the supply of a medicinal product for human use (EU-Switchguideline, 2006)

- 2.2 Könnte Ihrer Meinung nach auch eine Re-Analyse präklinischer Daten unter OTC relevanten Aspekten, die bereits im Rahmen der Rx-Zulassung generiert wurden, relevant sein?

Ja Nein (-> weiter mit 3.1) Keine Meinung

- 2.2.1 Bitte nennen Sie die Aspekte, die Sie vor diesem Hintergrund für besonders OTC relevant halten. Als Beispiel seien hier Interaktionsstudien mit neuen Wirkstoffen genannt.

3 Klinische Studiendaten als Basis für die Vergabe von Datenexklusivität bei Rx-to-OTC Switchen

Ebenfalls in großem Umfang werden für die Rx-Zulassung eines Medikaments klinische Studien durchgeführt und ausgewertet. Hinzu kommen je nach Dauer der Zulassung im Rx-Markt zahlreiche Daten aus der Postmarketing-Überwachung.

- 3.1 Könnte hier prinzipiell auch eine Aufarbeitung bereits existenter klinischer Rx-Daten im Sinne einer Re-Analyse bzw. –Strukturierung bzw. Extrapolation unter OTC-relevanten Aspekten zur Antizipation einer Anwendung in der Selbstmedikation vor dem Hintergrund eines Anspruches auf Datenexklusivität von Bedeutung sein?

Ja Nein (-> weiter mit 3.3) Keine Meinung

- 3.2 Wie würden Sie die Bedeutung folgender Ziel- bzw. Auswertungsparameter bei einer derartigen Re-Analyse in Bezug auf ihre Bedeutung für die Selbstmedikation einschätzen?

Bitte treffen Sie Ihre Bewertung anhand der nachfolgenden Skala (1 = sehr wichtig, 6 = überhaupt nicht wichtig)

	1	2	3	4	5	6	Keine Meinung
Größe der Studienpopulation	<input type="radio"/>						
Art der Studienpopulation	<input type="radio"/>						
Spezielle Patientengruppen ³	<input type="radio"/>						
Anzahl ausgewerteter Studien	<input type="radio"/>						
Qualität ausgewerteter Studien	<input type="radio"/>						
Monitoring (Art, Umfang)	<input type="radio"/>						
Studiendauer	<input type="radio"/>						
Sicherheit/Pharmakovigilanz	<input type="radio"/>						
Wirksamkeit	<input type="radio"/>						
Compliance	<input type="radio"/>						

³ z.B. Ältere, Multimorbide, Schwangere etc.

Spezielle Patientengruppen	A: <input type="radio"/> B: <input type="radio"/> C: <input type="radio"/>						
Studiendauer	A: <input type="radio"/> B: <input type="radio"/> C: <input type="radio"/>						
Monitoring	A: <input type="radio"/> B: <input type="radio"/> C: <input type="radio"/>						
Follow-Up	A: <input type="radio"/> B: <input type="radio"/> C: <input type="radio"/>						

3.5.1 Welche der genannten Parameter sind Ihnen dabei besonders wichtig (Top 3)?

1.
2.
3.

Die folgenden Fragen beziehen sich auf die Generierung von Datenexklusivität bei der potentiellen Entlassung von Indikationen im Rahmen der Prävention bzw. Therapie von oftmals (semi-) chronischen Erkrankungsbildern, die initial eine ärztliche Diagnose erfordern und deren Re-Diagnose, Monitoring bzw. Management in der Folge durch den Patienten selbst unter ärztlicher Kontrolle erfolgt. Beispiele hierfür sind die bereits OTC-fähige Indikation der Vaginalmykose oder auch die Behandlung von Bluthochdruck mit z.B. noch ausschließlich verschreibungspflichtigen Sartanen.

- 3.6 Könnten sich Ihrer Meinung nach Daten, die die Fähigkeit zur Eigendiagnose bzw. zum selbständigen Therapiemanagement einer betroffenen Patientenpopulation (nach einer ärztlichen Initialdiagnose) zeigen, generell für die Vergabe von Datenexklusivität im Rahmen eines angestrebten Rx-to-OTC Switches qualifizieren?
- Ja Nein (-> weiter mit 3.8) Keine Meinung
- 3.7 Verantwortungsbewusstes Therapiemanagement und –monitoring durch den Patienten spielt in der Selbstmedikation eine große Rolle, insbesondere im Falle von (semi-) chronischen Erkrankungsbildern bzw. Präventionstherapien wie z.B. Bluthochdruck, Hyperlipidämie, Hypercholesterinämie, Diabetes mellitus u.a..
- Bitte beurteilen Sie vor diesem Hintergrund die folgenden Punkte im Hinblick auf ihre Eignung für Datenexklusivität bei einem entsprechenden Szenario eines Rx-to-OTC Switches:

- 3.9 Wie würden Sie die Bedeutung folgender Ziel- und Auswertungsparameter bei einer solchen Vergleichsstudie einschätzen?

	1	2	3	4	5	6	Keine Meinung
Größe der Studienpopulation	<input type="radio"/>						
Art der Studienpopulation	<input type="radio"/>						
Spezielle Patientengruppen	<input type="radio"/>						
Sicherheit/Pharmakovigilanz	<input type="radio"/>						
Wirksamkeit	<input type="radio"/>						
Compliance	<input type="radio"/>						
Überlegenheit	<input type="radio"/>						
Nicht-Unterlegenheit	<input type="radio"/>						

- 3.9.1 Welche der genannten Parameter sind Ihnen dabei besonders wichtig (Top 3)?

1.

2.

3.

- 3.10 Könnte in Ihren Augen eine mit den entsprechenden Entscheidungsgremien abgestimmte nicht- interventionelle Studie im Sinne einer klassischen Anwendungsbeobachtung nach Entlassung aus der Verschreibungspflicht, die neue Erkenntnisse bezüglich Wirksamkeit, Sicherheit, Einnahmeverhalten und Patientenzufriedenheit unter Alltagsbedingungen liefert, Grundlage für die Vergabe von Datenexklusivität im Rahmen von Rx-to-OTC Switches sein?

Ja Nein Keine Meinung

4 Informations- und Edukationsmaßnahmen

Hier interessiert Ihre Meinung bezüglich umfangreicher und detaillierter fach- bzw. patientenspezifischer Informations- und Schulungsprogramme im Hinblick auf die Qualifizierung von Daten für Exklusivität im Rahmen eines Rx-to-OTC Switches.

- 4.1 Könnten Sie sich generell umfangreiche und neuartige Informations- und Schulungsmaßnahmen sowohl für Patienten als auch für Fachkräfte als Voraussetzung für die Vergabe von Datenexklusivität vorstellen?

Ja Nein (-> weiter mit 5.1) Keine Meinung

- 4.2 Falls „Ja“, welche der genannten Punkte könnten Ihrer Ansicht nach in einem solchen Fall als Basis für Datenexklusivität dienen⁴? (Mehrfachauswahl möglich)

⁴ auch wenn gemäß Wortlaut Art. 74a („präklinische oder klinische Studien“) nicht definiert

Schulungskonzept	<input type="checkbox"/>
Informations- und Schulungsmaterialien	<input type="checkbox"/>
Testergebnisse von Materialien/Konzepten an Zielgruppe mit Fokus auf... - Lesbarkeit - Verständnis - Verhaltensänderung	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Daten/Maßnahmen, die eine entsprechende Nutzung der entwickelten Maßnahmen zeigen bzw. sicherstellen	<input type="checkbox"/>
Commitment zu regelmäßigen Qualitätskontrollen	<input type="checkbox"/>
Keine Meinung	<input type="checkbox"/>

4.2.1 Welche der genannten Punkte erachten Sie dabei als besonders relevant (Top 3)?

1.
2.
3.

5 Pharmakoökonomische Aspekte

Klinische Studien allein können den Wert einer bestimmten Therapie für die „öffentliche Gesundheit“ oft nicht quantifizieren, weshalb diese häufig durch sog. Kosten-Nutzen-Analysen komplementiert werden.

5.1 Könnten Sie sich derartige Analysen/Studien im Hinblick auf Rx-to-OTC Switches prinzipiell für die Vergabe von Datenexklusivität vorstellen?

- Ja Nein (-> Ende der Befragung) Keine Meinung

5.1.1 Falls „Ja“, welche Art von Analysen würden sich Ihrer Meinung nach am besten dafür eignen?

- Kosten- Nutzen-Analysen (monetär)
 Kosten-Nutzwert-Analysen (nicht monetär, z.B. Verbesserung der Lebensqualität etc.)
 Sonstige:

Vielen Dank für Ihre Unterstützung!

Bitte senden Sie den ausgefüllten Fragebogen per Mail oder per Post zurück an:

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A.2.2 Questionnaire English version

Questionnaire with respect to the issue of „data exclusivity provision for the transfer of pharmaceuticals from prescription to non-prescription status“

PREAMBEL

Due to a generally long-lasting and cost-intensive development phase the issue of „data protection“ plays an important role for which allowance is made for mainly within the context of patent protection. However, not all scenarios deserving such a protection are thereby covered. Correspondingly, the provision of data exclusivity has been established in legislation over the years as an instrument for protection of intellectual property apart from patent law.

In the case of the transfer of pharmaceuticals from prescription status to self-medication (so-called Rx-to-OTC switch), for example, there is under certain preconditions the opportunity of a one-year data exclusivity according to Art. 74a¹ of EU-Directive 2004/27/EC (see attachment). The fact, that this option has not yet been exercised in Europe apart from one exceptional case, at this point raises the question not only regarding the relevance of data exclusivity for an Rx-to-OTC switch, but also regarding the extent of how realistic such a provision actually is under the current framework.

The increasing number of transfers from prescription to non-prescription status over the last years is mainly owing to two movements – the growing health consciousness of patients including their demand for more personal responsibility as well as rising costs within healthcare systems. To come up with this trend while facing ever growing requirements as regards the therapeutic options to be established within self-medication, there is a need for both a consensus based cooperation of all stakeholders involved and adequate incentive systems for research companies.

Against this background the opportunity of data exclusivity on the one hand would provide a motivational fundament for research companies or switch applicants, respectively, in order to recognize the switch requirements and the efforts involved. On the other hand this comes ultimately along with the basic idea, that the efforts for data exclusivity are based on corresponding “therapeutic concepts” relevant for the switch and basically aiming at the well-being and protection of patients and the guarantee of an optimal healthcare provision. Last but not least this should aim at the postulation of clear and transparent exclusivity criteria in order to enable to make use of the instrument of „data exclusivity“ within the context of Rx-to-OTC switches.

¹ “Where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.”

In the following questionnaire your opinion regarding potential preconditions and requirements for data generation targeting at the provision of such a data exclusivity are of particular interest apart from your general attitude towards „data exclusivity for Rx-to-OTC switches“.

As a matter of course all data is treated anonymously.

Thank you very much for taking your time to complete this questionnaire!

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As regards content the questionnaire deals with the issue of „data exclusivity provision within the context of transfer of pharmaceuticals from prescription to non-prescription status“. The scenarios depicted in the following relating to the transfer from prescription status (Rx-to-OTC switch scenarios) are intended to serve as guidance when answering the questions.

Different scenarios with respect to the transfer of an active substance or an indication from prescription to non-prescription status are theoretically thinkable or have in parts occurred yet in practice:

A: New OTC substance, known OTC indication:

A prominent example here is the transfer of proton pump inhibitors (PPI) from prescription to non-prescription status for the treatment of heartburn and acid regurgitation (initial OTC indication in Germany).

B: New OTC substance, new OTC indication:

The potential transfer of pharmaceuticals for the reduction of high blood pressure (e.g. sartanes) would be such an option.

C: Known OTC substance, new OTC indication:

Self-treatment of osteoarthritis with active substances already OTC-compatible such as naproxen is theoretically thinkable here.

Article 74 a, Directive 2004/27/EC:

“Where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.”

1 Preface

- 1.1 How do you judge the legal specifications² regarding the provision of data exclusivity from the viewpoint of “requirements or criteria, respectively, for the generation of data in the case of exclusivity demand”?

Please judge with the help of the following scale (1 = very good, 6 = poor)

	1	2	3	4	5	6	No opinion
Comprehensible	<input type="radio"/>						
Precise	<input type="radio"/>						
Relevant	<input type="radio"/>						

- 1.2 How do you assess the one-year duration of exclusivity periods to be awarded for Rx-to-OTC switches within the EU?
- Too short Just appropriate Too long

2 Preclinical test data as basis for the provision of data exclusivity for Rx-to-OTC switches

As a general rule, comprehensive preclinical test data are generated within the context of an Rx-registration approval process.

- 2.1 In principle, how do you estimate the eligibility of preclinical data as a basis for the provision of data exclusivity for the Rx-to-OTC switch of a certain substance?
- I consider it necessary with respect to the safety profile of the substance
- I consider it appropriate with respect to the safety profile of the substance
- I do not consider it necessary with respect to the safety profile of the substance
- I do not consider it appropriate with respect to the safety profile of the substance
- 2.2 In your opinion, could a re-analysis of preclinical data that have already been generated within the context of the Rx-authorization under OTC pertinent aspects be relevant?
- Yes No (-> continue with 3.1) No opinion

² Art. 74a, Direktive 2004/27/EC bzw. Guideline on changing the classification for the supply of a medicinal product for human use (EU-Switchguideline, 2006)

- 2.2.1 Against this background please mention all aspects that you assess particular relevant for OTC. Interaction studies with new active substances are cited here as an example.

3 Clinical study data as a basis for the provision of data exclusivity for Rx-to-OTC switches

Likewise, clinical trials are conducted and evaluated to a large extent for a pharmaceutical's Rx authorization. Additionally, depending on the duration of the Rx-registration in the market, much data from post-marketing surveillance accrues.

- 3.1 As a matter of principle, could a recycling of already existing clinical Rx-data in the sense of a re-analysis, re-structuring or extrapolation, respectively, under OTC pertinent aspects in order to anticipate self-medication practice be of relevance against the background of data exclusivity?
- Yes No (-> continue with 3.3) No opinion

- 3.2 How would you assess the significance of the following outcome measures within such a re-analysis regarding their relevance for self-medication?

Please judge with the help of the following scale (1 = very important, 6 = not important at all)

	1	2	3	4	5	6	No opinion
Size of study population	<input type="radio"/>						
Sort of study population	<input type="radio"/>						
Special patient groups ³	<input type="radio"/>						
Number of studies evaluated	<input type="radio"/>						
Quality of studies evaluated	<input type="radio"/>						
Monitoring (kind, amount)	<input type="radio"/>						
Study duration	<input type="radio"/>						
Safety/Pharmacovigilance	<input type="radio"/>						
Efficacy	<input type="radio"/>						
Compliance	<input type="radio"/>						

- 3.2.1 Which of the parameters mentioned do you think are particularly important in this respect (top 3)?

1.

2.

3.

³ e.g. elderly, multimorbid patients, pregnant women etc.

3.7.1 Within this context, how do you assess the following possibilities of data generation?

Please judge with the help of the following scale (1= extremely relevant, 6= not relevant at all)

	1	2	3	4	5	6	No opinion
Data from surveys with patients from the target group	<input type="radio"/>						
Data from actual use studies with patients from the target group (without control through specialized personnel)	<input type="radio"/>						
Data from actual use studies with patients from the target group (with control through specialized personnel)	<input type="radio"/>						
Data from actual use studies with special patient groups (with control through specialized personnel)	<input type="radio"/>						
Data demonstrating increased compliance of patients using the measurement devices/activities developed	<input type="radio"/>						
Data to be regularly generated on the basis of quality controls of corresponding measurement devices/activities	<input type="radio"/>						

Below it is about the comparison of a substance potentially to be removed from prescription status with already existing therapeutic alternatives in a specific indication within self-medication (to give an example the transfer of certain proton pump inhibitors from prescription to non-prescription status in Germany for the treatment of heartburn and acid regurgitation might be quoted here).

3.8 From your perspective, is the comparison of a potential Rx-to-OTC switch candidate with already available OTC-alternatives by means of a clinical study or the like (e.g. phase IV study) of relevance in reference to a potential claim of data exclusivity?

Yes No (-> continue with 3.10) No opinion

3.9 How would you estimate the importance of the following outcome measures within the context of such a comparative study?

	1	2	3	4	5	6	No opinion
Size of study population	<input type="radio"/>						
Kind of study population	<input type="radio"/>						
Special patient groups	<input type="radio"/>						
Safety/Pharmacovigilance	<input type="radio"/>						
Efficacy	<input type="radio"/>						
Compliance	<input type="radio"/>						
Superiority	<input type="radio"/>						
Non-inferiority	<input type="radio"/>						

3.9.1 Which of the parameters mentioned do you think are particularly important in this respect (top 3)?

1.
2.
3.

- 3.10 From your point of view, could the provision of data exclusivity for Rx-to-OTC switches be based on a non-interventional study in the sense of a classical actual use study after transfer from prescription to non-prescription status? Agreed upon with the accordant decision-making bodies, such a study could provide new insights concerning efficacy, safety, intake and patient satisfaction under daily-life conditions.

Yes No No opinion

4 Informational and educational measures

Your opinion regarding comprehensive and detailed subject- and patient specific informational or training programs, respectively, is of interest here with reference to the qualification of data for exclusivity within the context of an Rx-to-OTC switch.

- 4.1 In principal, could you imagine novel comprehensive informational and educational activities both for patients and health care professionals as a requirement for the provision of data exclusivity?

Yes No (-> continue with 5.1) No opinion

- 4.2 If „yes“, which of the items listed below could provide the bases for data exclusivity from your point of view⁴? (Multiple selection possible)

Training concept	<input type="checkbox"/>
Informational and educational material	<input type="checkbox"/>
Results from tests with target group regarding materials/concepts focusing on...	
- readability	<input type="checkbox"/>
- comprehension	<input type="checkbox"/>
- behavioral change	<input type="checkbox"/>
Data/measures demonstrating or ensuring, respectively, adequate utilization of the activities developed	<input type="checkbox"/>
Commitment to regular quality checks	<input type="checkbox"/>
No opinion	<input type="checkbox"/>

- 4.2.1 Which of the parameters mentioned do you think are particularly important here (top 3)?

1.
2.
3.

5 Pharmacoeconomic aspects

Clinical studies on their own often are not able to quantify the value of a certain therapy for the “public health” and therefore often are complemented by so-called cost-benefit analyses.

⁴ even if not defined according to the wording of Art. 74a („preclinical or clinical studies“)

5.1 Could you imagine such analyses/studies with regard to Rx-to-OTC switches for the sake of the provision of data exclusivity?

- Yes No (-> end of survey) No opinion

5.1.1 If „yes“, according to you, what sort of analysis would suit best for it?

- Cost-benefit-analyses (monetary)
 Cost-effectiveness/utility-analyses (non-monetary, e.g. improvement of quality of life etc.)
 Others

Thank you very much for your support!

Please send back the completed questionnaire by e-mail or airmail to:

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Danksagung

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Erklärung

Ich versichere, dass ich meine Promotion

„Rx-to-OTC switch and the provision of data exclusivity in Europe – specification and elaboration of eligibility criteria based on a status quo analysis“

selbständig ohne unerlaubte Hilfe angefertigt und mich dabei keiner anderen als der von mir ausdrücklich bezeichneten Quellen bedient habe. Die Dissertation wurde in der jetzigen oder einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungszwecken gedient.

Marburg, den _____

Carolin Stäbler

Curriculum Vitae

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