Anti-Counterfeiting in Global Pharmacovigilance

A Question of Patient Safety

Dissertation

zur

Erlangung des Doktorgrades (Dr. rer. nat.)

der

Mathematisch-Naturwissenschaftlichen Fakultät

der

Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Jessica Krüger

aus Potsdam

Bonn 2015

Die vorliegende Arbeit wurde in der Zeit vom März 2011 bis Februar 2015 unter der Leitung von Prof. Dr. Harald G. Schweim am Lehrstuhl für Drug Regulatory Affairs des Pharmazeutischen Instituts der Rheinischen Friedrich-Wilhelms-Universität Bonn angefertigt.

Mit Unterstützung der Bayer Pharma AG unter Mitbetreuung von Dr. Ilona-Maria Weltrowski; Abteilung Global Pharmacovigilance – Product Technical Complaint & Device Vigilance

Angefertigt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn

Promotionskommission:

Erstgutachter:	Prof. Dr. Harald G. Schweim
Zweitgutachter:	Priv.-Doz. Dr. Harald Enzmann
Fachnahes Mitglied:	Prof. Dr. Karl Wagner
Fachangrenzendes Mitglied:	Prof. Dr. Andreas Schieber

Tag der Promotion: 26.06.2015

Erscheinungsjahr: 2015

Hiermit versichere ich, dass ich diese Arbeit selbstständig und ohne jede unerlaubte Hilfe angefertigt habe und dass diese oder eine ähnliche Arbeit noch keiner anderen Stelle zur Prüfung vorgelegt wurde.

Jessica Krüger

ACKNOWLEDGEMENTS

I would like to thank Prof. Dr. Harald G. Schweim for supervising me during the dissertation and for all his advice, thoughts and feedback. I also thank the second referee and the two further examiners for taking the time to review the dissertation and for volunteering to attend the examining board.

My special thanks are directed to my company-internal supervisor, Dr. Ilona-Maria Weltrowski who supported me from the beginning onwards with my thesis and with the projects I conducted in connection with it. Our detailed discussions and her constructive criticism helped to enhance the structure and the significance of my work.

I am very grateful to the company's Counterfeit Protection Manager Dr. Stephan Schwarze for the supportive exchange of ideas and for his advice and support during the projects in relation to the dissertation.

Furthermore, I like to thank all employees of the company who participated in the projects, the survey, the interviews and the preparation of the monitoring concept, in particular Dr. Tina Müller for her statistical evaluation tips. It would not have been possible to create this dissertation without their meaningful contribution.

Special thanks are also directed to the proofreaders Christina Dickson and Clare Moloney-Wahl who helped me with respect to all my questions regarding the English wording, to Dr. Susanne Ladewig who also reviewed multiple paragraphs and provided me with great advice and to Dr. Christiane Noeske-Jungblut who took her time to read my dissertation with regard to the legal aspect.

Last but not least, I would like to say a big thank you to my family, in particular my boyfriend and my mother, for their emotional support. They had the patience to indulge my bad moods when I was in despair and encouraged me when I reached the limits of my strength.

TABLE OF CONTENTS

ABBREVIATIONS

2D	2-dimensional
3D	3-dimensional
ABDA	Federal Union of German Associations of Pharmacists (Germany)
ACF	Anti-counterfeiting
ADR	Adverse drug reaction
AE	Adverse event
AIFA	Italian Medicines Agency
AMG	Medicinal Products Act (Germany)
API	Active pharmaceutical ingredient
ApoG	Pharmacies Act (Germany)
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
BMG	Federal Ministry of Health (Germany)
BKA	Federal Criminal Police Office (Germany)
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CDH	Country Division Head
CDSCO	Central Drugs Standard Control Organization (India)
CF	Counterfeit(s)
CFDA	China Food and Drug Administration (former SFDA)
CMD	Country Medical Director
CPM	Counts per million
DIMDI	German Institute of Medical Documentation and Information
EAASM	European Alliance for Access to Safe Medicines
EAEPC	European Association of Euro-Pharmaceutical Companies
ED	Erectile dysfunction

EEA	European Economic Area
EEC	European Economic Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMVS	European Medicines Verification System
ESM	European Stakeholder Model
EU	European Union
FDA	Food and Drug Administration
FTIR	Fourier transform infrared
GIRP	European Association of Pharmaceutical Full-line Wholesalers
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
GSL	Global Safety Leader
HCC	Hepatocellular carcinoma
HCP	Healthcare professional
HIV	Human immuno-deficiency virus
HLGT	High level group term
HLT	High level term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
INTERPOL	International Criminal Police Organization
IP	Intellectual property
IR	Infrared
LACM	Local Anti-Counterfeiting Manager
LLT	Low level term

LODE	Lack of drug effect
LODE TOE	LODE type of event(s)
LQR	Local Quality Representative
MAH	Marketing authorization holder
MEA	Middle East & Africa
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare (Japanese Health Authority)
MI	Medical Information
MSSO	Maintenance and Support Services Organization
NAFDAC	Nigerian National Agency for Food and Drug Control
NTIN	National Trade Item Number
OC	Oral contraceptive
OSCS	Oversulfated chondroitin sulfate
OTC	Over the counter (non-prescription medicine)
PAP / PSP	Patient assistant program / Patient support program
PBRER	Periodic benefit-risk evaluation report
PEI	Paul-Ehrlich-Institute, Federal Institute for Vaccines and Biomedicines (Germany)
PGEU	Pharmaceutical Group of the European Union
PIICC	Pharmaceutical Industry Initiative to Combat Crime
PIL	Patient information leaflet
POM	Prescription-only medicine
PPN	Pharmacy Product Number
PSI	Pharmaceutical Security Institute
PSUR	Periodic safety update report
PT	Preferred term
PV	Pharmacovigilance

PVCH	Pharmacovigilance Country Head
QPPV	Qualified person for pharmacovigilance
RCC	Renal cell carcinoma
RFID	Radio Frequency Identification
SFDA	State Food and Drug Administration (China)
SFFC	Spurious / falsely-labeled / falsified / counterfeit
SOC	System organ class
TC	Telephone conference
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UNODC	United Nations Office on Drugs and Crime
UK	United Kingdom
US	United States
US FDA	United States Food and Drug Administration
UMC	Uppsala Monitoring Center
WHO	World health organization
WTO	World Trade Organization
ZL	Central Laboratory of German Pharmacists

ABSTRACT

Health is a basic and fundamental requirement of all societies. Medicinal products have the purpose to serve this requirement by "*treating or preventing disease*", enabling "*a medical diagnosis*" or by "*restoring, correcting or modifying physiological functions*". [1][1] Over the last century, healthcare systems have rapidly evolved with respect to advanced medical treatment. Moreover, the scope of today's healthcare systems is not limited to medicinal products only, but it also includes medical devices, diagnostics and diagnostic technologies. The healthcare systems shall guarantee the sustenance of the population with medicinal products of highest standard, quality and safety, as needed. In contrast, medicinal products which do not uphold the quality measures, set forth by health authorities worldwide, present a serious risk to patients. This includes counterfeit medicinal products, in particular. Criminals try to make a profit out of putting other people's health at risk by manufacturing products of bad quality or even toxic nature and selling them under the pretense of being authorized medicinal products.

One of the first modern medicines regulations, addressing the problem of counterfeit medicines, is the Federal Food and Drugs Act of 1906 in the United States (US) that prohibited interstate transportation of adulterated and misbranded food and drugs. [2][2] Before the passage of drug regulations regarding the accurate labeling of medicinal products, especially proprietary medicinal products[3], it may have been easier to market unauthorized medicines without raising any suspicion or doubts regarding their quality, effectiveness and safety. In contrast, with respect to present drug regulations, the most effective way to put unauthorized medicinal products on the (white) market is to offer them under the name of an approved medicinal product of a licensed pharmaceutical company. Unfortunately, the number of counterfeit medicinal products on the market has dramatically increased over the past 10 years. [3][4] The internet is considered as one of the major sources for counterfeit

[1] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].

[2] "The 1906 Food and Drugs Act and Its Enforcement," [Online]. Available: http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054819.htm. [Accessed 11 November 2013].

[3] *Proprietary medicinal product:* any ready-prepared medicinal product placed on the market under a special name and in a special pack. [88] "Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products," (OJ L 22, 9.2.1965, p. 369). [Online]. Available: http://www.echamp.eu/fileadmin/user_upload/Regulation/Directive_65-65-EEC__-__Consolidated_Version.pdf. [Accessed 11 November 2013].

[4] "PSI - Counterfeits - Trend Data," [Online]. Available: http://www.psi-inc.org/incidentTrends.cfm. [Accessed 31 January 2015].

drugs, especially in the developed countries. [4][5] Counterfeit medicines can cause serious injuries, resistances and even death [5][6] and thus, pose a serious threat to patient safety and welfare.

In this dissertation the current regulatory framework and recent changes of the legislation regarding counterfeit medicines are presented, with specific focus on the situation in the European Union. Examples of international initiatives and actions that have already been done to combat the counterfeiting of medicines are outlined, as well.

Moreover, the purpose and the development of pharmacovigilance (PV) and its regulatory framework are explained and the respective obligations of a marketing authorization holder (MAH) are outlined. A marketing authorization holder is held responsible for the standard of its pharmaceutical products. It is the MAH's obligation to prove the quality, safety and efficacy of its medicinal products by means of conducting clinical studies before receipt of the marketing authorization and thus, the market release of the respective medicinal product. [1][7] Additionally, all authorized medicines have to be monitored after their market release using an appropriate pharmacovigilance system. The process includes the collection and evaluation of all relevant information for the surveillance of medicinal products, with particular reference to adverse reactions and information on misuse or abuse of medicinal products to continuously evaluate the benefit-risk profile of the pharmaceutical products [1][8] and to identify product-related safety signals, posing a risk to the patient. Hence, required changes with respect to e.g. the product's label and information leaflet or, if necessary, safety restrictions regarding the respective product can be initiated.

However, it is not sufficient for the pharmaceutical industry to accept responsibility for its own original products, only. The pharmaceutical industry holds also responsibility to protect its patients against the health risk that is caused by counterfeits of its genuine medicinal products. As mentioned above, such counterfeit medicines can pose a serious threat to patient safety. Some examples with respect to the consequences caused by counterfeit medicines are given in the dissertation to illustrate the health risk which counterfeit drugs

[5] IMPACT, "Counterfeit Drugs Kill!," May 2008. [Online]. Available: http://www.who.int/impact/FinalBrochureWHA2008a.pdf. [Accessed 7 November 2013].
[6] "WHO Fact sheet N° 275," May 2012. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs275/en/index.html. [Accessed 29 October 2013].
[7] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].
[8] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].

pose. In addition, the large amounts of seized counterfeit medicinal products e.g. at border controls and exposed manufacturing places of counterfeiters also hint at an expanding presence of counterfeit medicines on the market and therefore, to a growing threat to patients. Thus, it is the pharmaceutical industry's obligation to adopt respective anti-counterfeiting (ACF) measures to fight against the counterfeit problem and thereby, to protect its patients' welfare. There are several approaches with respect to the protection against counterfeiting of medicines that should be considered by the pharmaceutical industry with the objective to establish effective anti-counterfeiting strategies. Therefore, a variety of options for the pharmaceutical industry to adopt anti-counterfeiting measures is outlined in the dissertation, including data monitoring and evaluation, collaboration with authorities, investigative, legal and technological measures, measures with the purpose to raise awareness of the counterfeit problem and measures to examine company-internal procedures regarding the counterfeit topic. The options and their limitations, which have to be put into consideration, are explained and discussed, giving examples. In this context, measures with the purpose to monitor and evaluate data, to raise awareness of the counterfeit issue and to review company-internal procedures are in special focus. Hence, these measures are outlined in more detail using practical examples.

It is a marketing authorization holder's obligation to collect, to document and to evaluate all information, potentially related to its products, which is brought to its attention. This includes reports related to adverse events, as well as suspected counterfeit incidents. Based on the fact that many counterfeit drugs are visually very close to the originals they mimic, they are hard to distinguish. The high quantities of counterfeit medicinal products on the market and the comparatively low amounts of suspected counterfeit incidents, reported by patients and healthcare professionals (HCP), give reason to presume that the majority of counterfeit medicines is consumed without questioning their authenticity. This leads to the assumption that marketing authorization holders receive adverse event reports concerning their original products that are actually not related to the genuine products, but to their counterfeits. As all received adverse event-related data has to be included in the evaluation of the benefit-risk profiles of the respective medicinal products, it can be assumed that counterfeit medicines influence the benefit-risk profile of the genuine medicinal products which they mimic. In this context, one purpose of this dissertation is to analyze data from the company's global pharmacovigilance database and the company's global technical complaint database to examine if a correlation between adverse event data and counterfeit incident data can be identified. The data analysis and evaluation are described and the outcomes discussed in the dissertation.

The data basis for monitoring and evaluation activities depends a lot on the behavior in which e.g. authorities, healthcare professionals or patients report relevant information to the MAH. The reporting behavior can be influenced by several factors, which are discussed in the thesis. For example, one means to influence the reporting behavior of the public regarding suspected counterfeit incidents in a positive way is to adopt measures with the purpose to raise awareness of the counterfeit medicines problem, e.g. the conduct of a public anti-counterfeiting education campaign. Two options with regard to the setup of an anti-counterfeiting education campaign are outlined in detail in the dissertation and their advantages and disadvantages are discussed. One option is to conduct a general (product-unspecific) education campaign in one or multiple countries to warn the public against the threat that counterfeit drugs pose to their health and to educate them about what they should be aware of in order to protect themselves, and whom to contact in case a suspicious product is detected. To implement such a campaign successfully, several information regarding present knowledge and awareness among the public, often-used and seen-as-reliable media regarding health issues, and reporting and purchasing behavior has to be gained beforehand the planning of the campaign and the selection of its contents. An applicable means to collect the required information is to survey a representative population of the public of the country or countries in scope. Another option is to conduct a product-specific education campaign in one country. The implementation of such a campaign would be conducted as a pilot project and would serve as an orientation for the implementation of further campaigns concerning the same or other products in other countries. In the dissertation both possible approaches are outlined and compared for their advantages, limitations and opportunities. In addition, a product-specific education campaign was conducted and its preparation, organization (including the approval process), contents and developed materials are described, including an assessment of its effectiveness.

The third and last anti-counterfeiting measure, examined in detail and based on practical examples, is the review of (company-internal) procedures with regard to the counterfeit medicines topic. The correct internal handling of counterfeit incident data and the cross-functional collaboration within one country and across countries is essential for an effective anti-counterfeiting concept of a global pharmaceutical company. Such a company has affiliates in multiple countries all over the world and has to ensure to implement its anti-counterfeiting concept consistently in all its affiliates. With regard to required adaptations to local circumstances, the implementation can be quite a challenge. For that reason, an analysis of the current state of company-internal procedures and measures with regard to anti-counterfeiting was done. A company-wide internal affiliate survey has been conducted to gain the relevant information. The preparation and the conduct of the global company-

internal affiliate survey is described, its results presented and conclusions regarding the current state and further desirable actions outlined. In order to further and in more detail explore the country-specific framework (e.g. regulatory or cultural circumstances), gained experiences in anti-counterfeiting activities and local needs with regard to the global ACF concept interviews have been carried out with a selection of countries which participated in the affiliate survey and showed high interest in the counterfeit topic. The selected countries are representative for all regions of the world (Asia Pacific, Latin America, Northern America, Europe and Africa/Middle East). Again, the preparation and the conduct of the interviews are outlined in the dissertation and the outcomes and possible response actions discussed.

All results from the data analysis, the education campaign pilot project, the affiliate survey and the interviews are summed up in the thesis. The drawn conclusions regarding the results of the examined anti-counterfeiting measures and the outlined points to be considered implementing such measures shall serve as an orientation on the variety of ACF measures that the pharmaceutical industry should take into consideration in order to establish effective anti-counterfeiting concepts. The gained information and experiences, outlined in this dissertation, reflect the importance of adopting anti-counterfeiting measures. Thereby, more pharmaceutical companies shall be encouraged to take action in the fight against counterfeit drugs.

CHAPTER ONE - INTRODUCTION

1.1 Framework of counterfeit medicines

1.1.1 Definition of counterfeit medicines

It is difficult to find a globally harmonized definition on counterfeit drugs, since each country has its own understanding what counterfeit drugs may be [6][9] with regard to the broad spectrum of types of counterfeiting of medicinal products, e.g. patent infringement, fraudulent generics, diversion of genuine products, as well as tampering of original product's packaging materials up to the complete imitation of licensed branded or generic pharmaceutical products. For these various types the potential risk on patient safety and the stakeholders' interest in anti-counterfeiting activities may differ significantly. The World Health Organization (WHO) developed the following definition for counterfeit medicines:

> *"A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."* [6][10]

This definition equals the definition of spurious / falsely-labeled / falsified / counterfeit (SFFC) medicines which is a more comprehensive term for counterfeit medicines [5][11], as it tries to cover various types of counterfeit medicinal products.

1.1.2 Classification and definitions of counterfeit incidents

The following overview, given in figure 1, represents the suggestion of a possible classification of the types of counterfeit medicines. The respective definitions are provided below.

[9] "WHO - Counterfeit medicines: General information," [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/. [Accessed 25 October 2013].
[10] "WHO - Counterfeit medicines: General information," [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/. [Accessed 25 October 2013].
[11] "WHO Fact sheet N° 275," May 2012. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs275/en/index.html. [Accessed 29 October 2013].

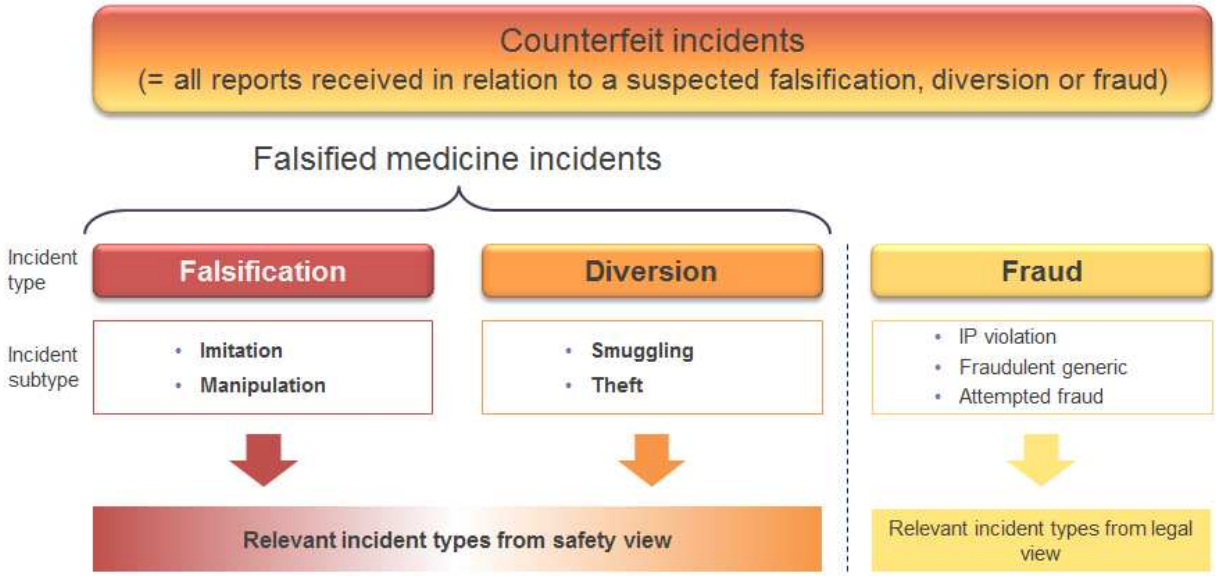

Figure 1: Classification overview of counterfeit incidents

The counterfeit-relevant types are condensed under the term "counterfeit incidents". The definitions used for the different counterfeit incidents are based on the Pharmaceutical Security Institute's (PSI) definitions of "counterfeit medicines", "illegal diversion", "pharmaceutical theft", and "incident".

An "incident" is defined by the PSI as follows:

> *"An incident is a discrete event triggered by the discovery of counterfeit, illegally diverted or stolen pharmaceuticals. PSI considers an incident to be a unique occurrence. It must have adequate factual information such as a particular date, time, place and type of pharmaceutical product involved in order for it to be considered a unique incident."* [7][12]

Hence, all occurrences related to suspected counterfeit drugs are denoted as "counterfeit incidents". As indicated above, an incident must be related to factual information. Depending on the specific characteristics of each incident, the counterfeit incidents are assigned to one of the three incident types "falsification", "diversion" or "fraud", which are defined below.

1.1.2.1 Falsification

The incident type "falsification" is defined based on the WHO's definition of counterfeit medicines as mentioned above which the PSI also refers to:

[12] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].

"Counterfeit medicines are products deliberately and fraudulently produced and/or mislabeled with respect to identity and/or source to make it appear to be a genuine product. This definition applies to both branded and generic products." [7][13]

The term "falsification" is used in accordance to the "Falsified Medicines Directive" (Directive 2011/62/EU), which refers to the term to distinguish the products in scope from products that are related to intellectual property violations. [8][14] Incidents related to intellectual property violations are assigned to the incident type "fraud" (see paragraph 1.1.2.4).

The incident type "falsification" comprises the incident subtypes "imitation" and "manipulation". According to the PSI definition of "counterfeit medicines" two main types are mentioned.

"Counterfeit products appear with a wide range of deficiencies. For example, counterfeit medicines have been found to contain less than or more than the required amount of active pharmaceutical ingredients (API) used in the authentic version or even contain the correct amount of API but have been manufactured in unsanitary, unsafe conditions." [7][15]

This description meets the incident subtype "imitation". The key point is that the dosage form, e.g. tablets, capsules or solution, itself, is not genuine i.e. it was not manufactured by the declared marketing authorization holder or one of its licensed manufacturers. In this case, the packaging materials, too, can be counterfeited, imitating the visual characteristics of the genuine packaging materials, or can be genuine, e.g. stolen or illicitly recycled.

The other incident subtype of the incident type "falsification" is the "manipulation", which meets the PSI description:

"Genuine medicines can also be counterfeited. For example, cases have been discovered where genuine medicines have been placed in counterfeited packaging to extend the expiry date or to commit a fraud against various government programs." [7][16]

In this case, the dosage form, itself, is genuine, e.g. stolen or illicitly recycled. However, the packaging materials are either manufactured by a third party without authorization, imitating

[13] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].
[14] "European Commission - Medicinal Products for Human Use," [Online]. Available: http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm. [Accessed 5 November 2013].
[15] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].
[16] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].

the genuine packaging materials, or they are genuine but adulterated, including the change (reprinting) of the variable data and / or the product name, the insertion of a genuine primary packaging, containing the genuine dosage form, in a genuine but non-matching secondary packaging, and the erasing of labels e.g. “medical sample – not for sale”.

1.1.2.2 Diversion

The incident type “diversion” comprises the incident subtypes “smuggling” and “theft”, which are based on the PSI definitions of “illegal diversion” and “pharmaceutical theft”.

“Illegal diversion occurs when a genuine pharmaceutical product is approved and intended for sale in one country, but is then illegally intercepted and sold in another country. […] At times, drug regulators in the second country have not approved the use of the diverted drug. Illegal diversion may also occur within the same geographic area, within the same country or city. This type involves diverting discounted medicines from one intended group of consumers to another group buying medicines in an unregulated open market.” [7][17]

“Pharmaceutical theft is defined as an illegal taking of medicines. Thefts include burglary, robbery, or an embezzlement of goods. The responsible individuals may be insiders such as employees, or outsiders such as professional thieves. The theft may occur anywhere in the distribution chain such as at the site of manufacture, freight forwarder, distribution centers, warehouses, pharmacies, or hospitals.” [7][18].

1.1.2.3 Falsified medicine incidents

Falsifications and diversions are aggregated to “falsified medicine incidents” as these incidents potentially have a major safety relevance. Wrong, potentially allergenic or toxic ingredients, the wrong amount of active pharmaceutical ingredients (API), impurities of the API or any other ingredients can cause adverse drug reactions and thereby harm the patient. Counterfeit medicines without any API, at all, can also put the health of patients at risk e.g. with respect to life-saving drugs. The quality of manipulated, smuggled or stolen genuine medicinal products can be reduced e.g. because of improper storage conditions. Depending on the characteristics of the respective product, e.g. regarding the drug formulation or the stability of the API, improper storage conditions can have a major effect on the quality of the medicinal product e.g. on solutions for parenteral administration or tablets with a temperature-sensitive, hygroscopic or instable active pharmaceutical ingredient. Such

[17] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].
[18] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].

products are no longer guaranteed to meet their standard of quality, effectiveness and safety. Expired genuine medicinal products can be substandard, too, e.g. due to a reduced amount of the API. Furthermore, the patient is endangered if the medicinal products' labeling and their patient information leaflets (PIL) are in a foreign language (e.g. in case of smuggled pharmaceutical goods). The patient or the treating healthcare professional would not be able to read the PIL and thus, to attend to the safety instructions. The occurrence of medication errors or handling errors would be a possible consequence.

1.1.2.4 Fraud

The third incident type is "fraud" and comprises the types of counterfeit incidents that do not classify for the incident types "falsification" and "diversion". According to the Oxford Dictionary the word fraud is described as a:

"*Wrongful or criminal deception intended to result in financial or personal gain*" [9][19].

Counterfeit incidents classified as "fraud" mainly have legal relevance rather than safety relevance. Such incidents comprise cases of intellectual property (IP) violation e.g. the unauthorized use of another MAH's brand name or trademark, patent-protected product or API by a third, probably licensed, pharmaceutical company. In these cases, the medicinal products may be of high quality (meeting all specifications), which means there is no risk for the patient. However, IP rights have been infringed, which makes the respective medicinal product a counterfeit medicine.

Incidents referring to pharmaceutical products, manufactured by a non-licensed third party, which do not refer to a licensed MAH, a brand name or a trademark but to a registered active pharmaceutical ingredient, that is not or no more patent-protected, are also classified under the incident type "fraud". Such products do not contain the declared API or the correct amount of the declared API. Therefore, they are mislabeled with respect to their content, not with respect to their identity or source. Such products are denoted as fraudulent generics.

In the majority of cases a genuine medicinal product tampered with is intended to deceive the stakeholders of the supply chain and, in the end, the patient. However, it also occurs that the patient tampers with the medicinal product in order to claim reimbursement or compensatory from the marketing authorization holder. If the investigation of the respective incident confirms a product manipulation done by the patient, the incident is also classified as "fraud". Such incidents are denoted as "attempted fraud".

[19] "Oxford Dictionaries - Fraud," [Online]. Available: http://www.oxforddictionaries.com/definition/american_english/fraud. [Accessed 5 November 2013].

1.1.3 Development over previous years and impact on patient safety

1.1.3.1 Extent of the problem

The necessity to combat the problem of counterfeit medicines becomes more obvious regarding the upstream of incidents on the market during the last 29 years[20], and with it, the increasing threat to patient safety and health.

The globalization and the explosion of free trade, as well as the ascending availability of medicines via the internet, call for a widening of the scope of market surveillance. New hazards to public health emerged in connection with the changing situation regarding the drug market. Some examples for these alarming developments are increasing self-medication practices, illegal sale of medicines over the internet, including drugs of abuse and prescription-only medicines without prescription, and, especially in the focus of this thesis, widespread manufacture and sale of counterfeit medicines. [10][21] The Pharmaceutical Security Institute collects data on confirmed incidents related to counterfeit medicines, illegal diversion of medicinal products and pharmaceutical theft, worldwide. The collected information comes from various sources, including open media reports, PSI member company submissions and public-private sector partnerships. [7][22] The following figure shows the total number of confirmed incidents by year over the last decade, published by the PSI.

[20] The appearance of counterfeit medicines in international commerce was first mentioned as a problem at the WHO Conference of Experts on Rational Drug Use in Nairobi, Kenya, in 1985. [6] "WHO - Counterfeit medicines: General information," [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/. [Accessed 25 October 2013].

[21] "The Importance of Pharmacovigilance - Safety Monitoring of medicinal products, WHO 2002," [Online]. Available: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. [Accessed 29 October 2013].

[22] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].

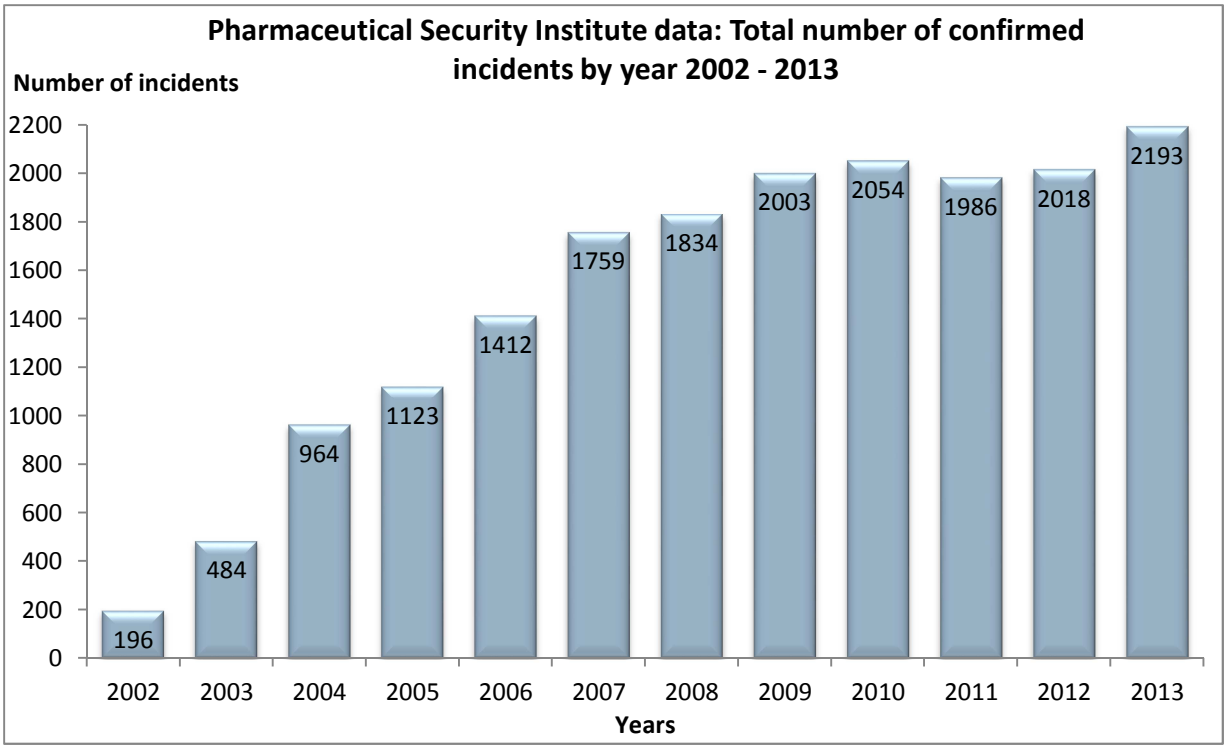

Figure 2: Pharmaceutical Security Institute data: Total number of confirmed incidents by year 2002 – 2013 [3][23]

As the figures show, the number of confirmed incidents distinctly increased since 2002 presenting only a minor decrease in the years of 2011 and 2012. As the PSI data are dependent on the data brought to the attention of the PSI sources, e.g. the PSI member companies, the figures do not represent the total extent of the counterfeit problem but can provide a tendency. Data provided by the European Commission Taxation and Customs Union show clearly that the problem of counterfeit medicines is still increasing. While the category of medicinal products made “only” 3% of the total amount of confiscated articles at European borders in 2010, the percentage increased dramatically to 24% of the total number of confiscated articles in 2011. [11][24] [12][25] According to the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), launched by the WHO in February 2006, the extent of the problem of counterfeit medicines is impossible to quantify. [4][26] Nevertheless, the

[23] "PSI - Counterfeits - Trend Data," [Online]. Available: http://www.psi-inc.org/incidentTrends.cfm. [Accessed 31 January 2015].
[24] "Report on EU customs enforcment of intellectual property rights - Results at the EU borders - 2010," 2011. [Online]. Available: http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/statistics_2010.pdf. [Accessed 13 November 2013].
[25] "Report on EU customs enforcment of intellectual property rights - Results at the EU borders - 2011," 2012. [Online]. Available: http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/2012_ipr_statistics_en.pdf. [Accessed 13 November 2013].
[26] IMPACT, "Counterfeit Drugs Kill!," May 2008. [Online]. Available: http://www.who.int/impact/FinalBrochureWHA2008a.pdf. [Accessed 7 November 2013].

IMPACT estimates the proportion of counterfeit medicines at less than 1% of the market value in most of the industrialized countries, having established effective regulatory systems and market control (e.g. USA, most of the EU, Australia, Canada, Japan, New Zealand), at above 20% in many countries of the former Soviet Union and at around 30% in many countries of Africa and parts of Asia and Latin America. [4][27] However, there are countries where even 90% of the medicines on sale are considered to be counterfeit. [13][28] Although the incidence of counterfeit drugs in the legal supply chain in the industrialized countries is less than 1% of market value [5][29], it is estimated to reach an extent of around 50% in the illegal supply chain. [13][30] These percentages demonstrate the magnitude of the illegal trade of counterfeit drugs with an estimated turnover of 75 billion dollars [14][31] to 200 billion dollars a year [15][32].

1.1.3.2 Impact on patient safety

The extent of the problem and its impact on public health becomes apparent, looking at examples of past incidents related to counterfeit medicines. In 1990, more than 100 children died in Nigeria because of a cough mixture that was diluted with a poisonous solvent. [16][33] In 2002, the Nigerian National Agency for Food and Drug Control (NAFDAC) asserted that 60% of their medicines are falsified, substandard or with exhausted expiry date. [16][34] However, counterfeit drugs are not only a problem of the developing countries, anymore. The developed countries are concerned as well. [6][35] In 2003, there was a recall of almost 20 million doses of Lipitor®, a cholesterol-lowering medication, in the USA. Again, concerning

[27] IMPACT, "Counterfeit Drugs Kill!," May 2008. [Online]. Available: http://www.who.int/impact/FinalBrochureWHA2008a.pdf. [Accessed 7 November 2013].
[28] H. G. Schweim, "Arzneimittelkauf im Ausland - das kann gefährlich sein!," *Deutsche Apotheker Zeitung,* no. 21, pp. 48-51, 2010.
[29] "WHO Fact sheet N° 275," May 2012. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs275/en/index.html. [Accessed 29 October 2013].
[30] H. G. Schweim, "Arzneimittelkauf im Ausland - das kann gefährlich sein!," *Deutsche Apotheker Zeitung,* no. 21, pp. 48-51, 2010.
[31] B. Moran, "Cracking Down on Counterfeit Drugs," 20 August 2013. [Online]. Available: http://www.pbs.org/wgbh/nova/next/body/uncovering-counterfeit-medicines/. [Accessed 19 November 2013].
[32] S. Kannan, "BBC News: Counterfeit drugs targeted by technology in India," 11 October 2011. [Online]. Available: http://www.bbc.co.uk/news/business-15208595. [Accessed 19 November 2013].
[33] "GPHF homepage," [Online]. Available: http://www.gphf.org/web/en/minilab/hintergrund_arzneimittelfaelschungen.htm. [Accessed 29 October 2013].
[34] "GPHF homepage," [Online]. Available: http://www.gphf.org/web/en/minilab/hintergrund_arzneimittelfaelschungen.htm. [Accessed 29 October 2013].
[35] "WHO - Counterfeit medicines: General information," [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/. [Accessed 25 October 2013].

counterfeit Lipitor® a whole batch had to be recalled in the UK in 2005. [17][36] Likewise in 2005, some illegal trading of counterfeit lifestyle drugs via the internet, including the anti-obesity medicines Reductil® and Xenical®, the smoking cessation drug Zyban®, the hair restorer Propecia® and the erectile dysfunction medicines Cialis® and Viagra®, was uncovered and the main responsible person identified. [18][37] Patients may be lucky if the dosage form itself is not falsified, but only the packaging. However, the impact on the product quality of the tampered product remains uncertain, and thus, poses potential risk to the patient. One example for such a criminal activity is the illegal selling of HIV-medicines on the German market, revealed in 2009. The genuine HIV-medicines, intended to be sold on the African market and therefore less priced by the pharmaceutical manufacturer, were repackaged and brought back to Germany illegally. It is said that this is about more than 10,000 packages of the HIV drugs valued at about 6 Million Euro or more. [19][38] The danger to health becomes even more obvious considering the following two incidents which are related to counterfeit life-saving medicines. In 2011, antimalarial drugs, which contained the analgesic agent acetaminophen and the Viagra® API sildenafil instead of the declared active ingredient, were found in 11 African countries. [20][39] In 2012, the United States Food and Drug Administration (US FDA) advised the public against counterfeit Avastin®, an angiogenesis inhibitor for the treatment of various types of cancers. The counterfeit product did not contain the declared active ingredient. [21][40] Another case of counterfeit cancer drugs was discovered in 2013. US Homeland Security agents investigated confiscated batches of Sutent® and found them to be completely without any active ingredient. [22][41]

The presented examples show that the problem of counterfeit drugs is not limited to certain product groups, life style drugs for instance, but can be found across a broad range of therapeutic categories. Reports about counterfeit drugs, received by the WHO, relate to the medicinal drug categories antibiotics, hormones, analgesics, steroids and antihistamines.

[36] K. Monson and A. Schoenstadt, "MedTV homepage - Lipitor Recall," 6 January 2009. [Online]. Available: http://cholesterol.emedtv.com/lipitor/lipitor-recall.html. [Accessed 29 October 2013].
[37] H. G. Schweim, "DAZ Online Arzneimittelfälschungen global und in," 11 August 2005. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/daz-ausgabe/artikel/articlesingle/2005/32/14414.html. [Accessed 29 October 2013].
[38] H. Korzilius, "Deutsches Ärzteblatt Gefälschte HIV-Medikamente: Schäbiges Geschäft," 4 March 2011. [Online]. Available: http://www.aerzteblatt.de/archiv/81141. [Accessed 29 October 2013].
[39] K. Bachmann, "Vorsicht, Fälschung!," *GEO,* no. 11, pp. 56-64, 2012.
[40] "FDA sends letters to 19 medical practices about counterfeit product and other unapproved cancer medicines," 14 February 2012. [Online]. Available: http://www.fda.gov/drugs/drugsafety/ucm291960.htm. [Accessed 21 November 2013].
[41] "SafeMedicines.org - Counterfeit Cancer Drugs Are A Big Money Maker for Fake Drug Criminals," [Online]. Available: http://www.safemedicines.org/counterfeit-cancer-drugs-are-a-big-money-maker-for-fake-drug-criminals.html. [Accessed 6 January 2015].

[6][42] Regarding therapeutic categories the PSI specifies medicinal products in the genitourinary, anti-infective and central nervous system therapeutic categories as mostly in the scope of counterfeiters. Furthermore, the PSI data show an increase in the percentage of incidents with respect to six therapeutic categories on a year to year basis. [23][43]

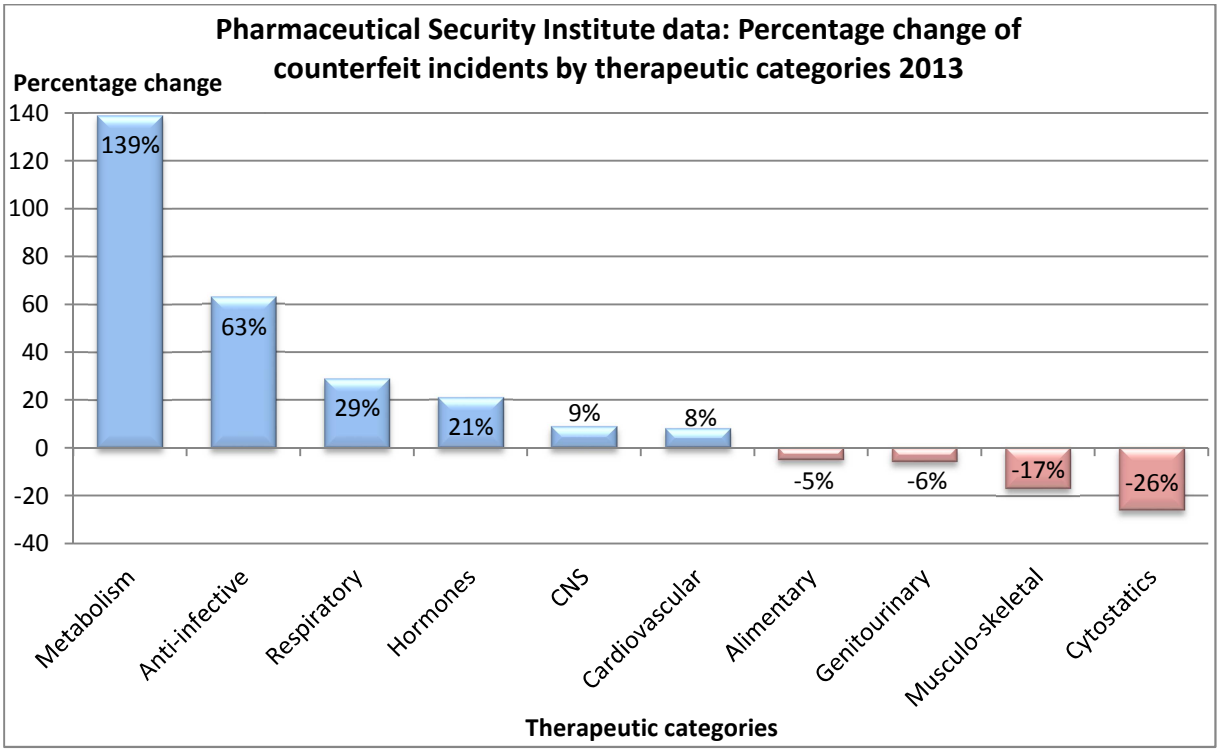

Figure 3: Pharmaceutical Security Institute data: Percentage change of counterfeit incidents by therapeutic categories 2013 [23][44]

Different types of counterfeit medicines were found in the context of anti-counterfeiting activities e.g. the international anti-counterfeiting initiative called PANGEA which is coordinated by the International Criminal Police Organization (INTERPOL) (see paragraph 1.2 for more detailed information). The majority of the detected counterfeit drugs contained no active ingredients, at all. Some products contained false ingredients or the wrong amount of the correct active ingredients as the following figure shows.

[42] "WHO - Counterfeit medicines: General information," [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/. [Accessed 25 October 2013].
[43] "PSI - Counterfeits - Therapeutic Categories," [Online]. Available: http://www.psi-inc.org/therapeuticCategories.cfm. [Accessed 31 January 2015].
[44] "PSI - Counterfeits - Therapeutic Categories," [Online]. Available: http://www.psi-inc.org/therapeuticCategories.cfm. [Accessed 31 January 2015].

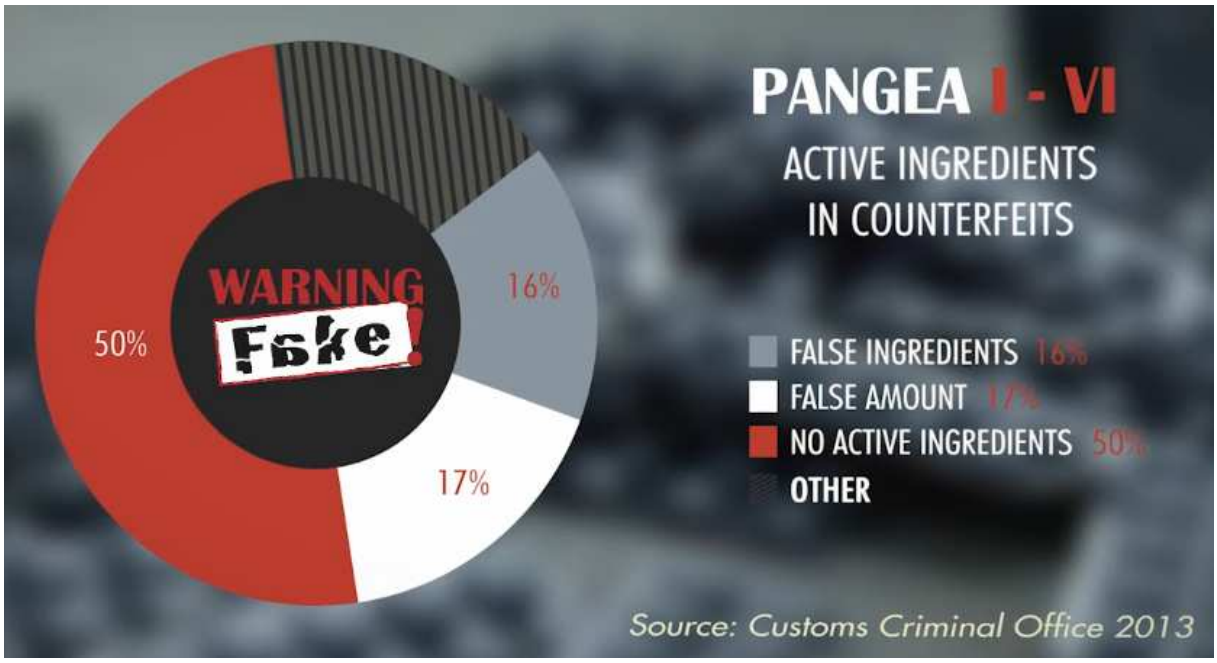

Figure 4: What exactly is in counterfeit medicines? [24][45]

Depending on the therapeutic category counterfeit drugs can have various effects. A counterfeit medicinal product without the correct active ingredient will lead very likely to a failure of the therapeutic effect. With regard to lifestyle drugs the failure of the therapeutic effect may be annoying but not life-threatening. In contrast, counterfeit life-saving medicines, e.g. of the therapeutic categories cardiovascular, cytostatic or anti-infective, which do not contain the correct API can cause serious injuries, relapse or exacerbation of the respective disease with hospitalization or death as possible consequences. [25][46] Also the false amount of ingredients in counterfeit medicinal products can lead to a failure of the therapeutic effect. With respect to anti-infective medicines counterfeit drugs containing too little active ingredient can cause the development of resistant organisms against the respective API. This would consequently even affect patients being treated with a genuine product due to the decreased effect of the API on the resistant bacteria strain. [25][47] Too high amounts of active ingredients can cause an increase in adverse drug reactions (ADR) of the respective medicinal product, e.g. hormones. Counterfeit medicinal products containing wrong ingredients may cause allergic reactions as false active ingredients are not declared and thus, cannot be avoided by allergy sufferers. Wrong ingredients with toxic potential can lead to intoxications that can be

[45] ABDA, Pfizer and Bayer, "03 Warning Fake – What exactly is in counterfeit medicines? EN," 2013. [Online]. Available: http://vimeo.com/74366006. [Accessed 19 November 2013].
[46] World Health Organization, "General information on counterfeit medicines: Factors encouraging counterfeiting of drugs," 2014. [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/index1.html. [Accessed 29 October 2013].
[47] World Health Organization, "General information on counterfeit medicines: Factors encouraging counterfeiting of drugs," 2014. [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/index1.html. [Accessed 29 October 2013].

lethal, in the worst case. Even if counterfeit medicinal products contain the correct API in the correct amount the products can still fail the desired therapeutic effect or cause adverse drug reaction as the efficacy of drugs also depends on further aspects, including the formulation of the dosage form or the modification of the API. Regarding the safety of medicinal products aspects, including particle size and sterility, have to be considered and ensured. For that reason, the manufacturing of medicinal products has to comply with the GMP (Good Manufacturing Practice) guidelines, which counterfeiters do not follow. Therefore, the risk of counterfeit medicines causing harm to public health is huge.

1.1.3.3 Encouraging factors for counterfeiting medicines

There is a variety of factors encouraging counterfeiters to infiltrate the medicine market. The demand for medicines is infinite. The expenses for the production of counterfeit medicines are low, since one can use cheap substitutes or no active ingredient, at all. Furthermore, expenses for the manufacture are low when the production takes place in e.g. some kind of a dirty backyard or a small cottage industry. Since counterfeiters do not maintain cost-intensive systems for quality assurance and Good Manufacturing Practices, their expenses are reduced additionally. All in all, considering the low costs for the manufacture of counterfeit medicines in comparison to their high value on the market, the profit to be made is huge. [25][48] According to United Nations Office on Drugs and Crime (UNODC) "*drug trafficking is the most lucrative form of business for criminals*". [26][49] And while the profit in illegal trade of counterfeit medicines is extremely high, the risk to be apprehended and prosecuted is rather low. Moreover, the penalties are not of such scale to deter counterfeiters. [25][50]

If there is a competent national drug regulatory authority established in a country to control the manufacture, importation, distribution and sale of medicines, it is more difficult for counterfeiters to infiltrate the national distribution channels. However, at present, this is the case in only about 20% of the WHO member states. The remaining member states have a less developed drug regulation or none at all. For that reason, the amount of illegal or

[48] World Health Organization, "General information on counterfeit medicines: Factors encouraging counterfeiting of drugs," 2014. [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/index1.html. [Accessed 29 October 2013].
[49] United Nations Office on Drugs and Crime, "New UNODC campaign highlights transnational organized crime as a US$870 billion a year business," 16 July 2012. [Online]. Available: http://www.unodc.org/unodc/en/frontpage/2012/July/new-unodc-campaign-highlights-transnational-organized-crime-as-an-us-870-billion-a-year-business.html. [Accessed 9 March 2014].
[50] World Health Organization, "General information on counterfeit medicines: Factors encouraging counterfeiting of drugs," 2014. [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/index1.html. [Accessed 29 October 2013].

counterfeit medicinal products on the market is higher in these countries. [25][51] Other reasons for a greater amount of counterfeit medicines on the market, especially in the developing countries, are a huge demand of medicines that already exceeds the available genuine product supply or the fact that many people are not able to afford expensive medicines and thus, use any option to purchase less expensive drugs. In the developed countries the reason for purchasing medicines from dubious sources may rather be driven by a lack of knowledge and awareness or by the intention to bypass prescription. [25][52] Any purchase behavior which does not question the reliability of the sources of medicinal products is welcomed by the counterfeiters.

1.1.4 Distribution of medicinal products and access points for counterfeiters

1.1.4.1 Legal and illegal supply chain

Unfortunately, the presence of counterfeit medicinal products is not limited to illegitimate distribution ways. Even the legal supply chain is affected in both developing and developed countries. In Germany, for example, the Federal Criminal Police Office (BKA) documented 49 cases of counterfeit drugs in the legal supply chain. [27][53] For reasons, including the globalization of the supply chains, the high number of participants and the great variety of rules in different countries, the complexity and with it the vulnerability of the legal supply chain increased. [28][54] The access points for counterfeiters are not limited to the distribution chain after the finished medicinal products were manufactured but during the steps of manufacturing, as well, as Figure 5 illustrates. The pharmaceutical products' ingredients, active or inactive, or the raw materials needed to produce the active pharmaceutical ingredients can be falsified as incidents like the deaths in Panama caused by toxic cough syrup or the heparin scandal show.

In late 2007 and the beginning of 2008, US health authorities documented an increase in adverse event reports, which were found to be related to the widely used blood thinner heparin made by Baxter International Inc. Analysis results revealed that the medicinal

[51] World Health Organization, "General information on counterfeit medicines: Factors encouraging counterfeiting of drugs," 2014. [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/index1.html. [Accessed 29 October 2013].
[52] World Health Organization, "General information on counterfeit medicines: Factors encouraging counterfeiting of drugs," 2014. [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/index1.html. [Accessed 29 October 2013].
[53] ABDA, "Factsheet Counterfeit Medicines," October 2013. [Online]. Available: http://www.abda.de/fileadmin/assets/Faktenblaetter/Faktenblatt_Arzneimittelfaelschungen_Oktober_2013_final.pdf. [Accessed 20 November 2013].
[54] C. Jung and J. McCue, "Protecting Patients from Counterfeit and Other Substandard Drugs/Supply Chain Threats; FDA 2nd Annual Health Professional Organizations Conference," 4 October 2012. [Online]. Available: http://www.fda.gov/downloads/ForHealthProfessionals/UCM330640.pdf. [Accessed 20 November 2013].

product was adulterated with oversulfated chondroitin sulfate (OSCS) that could not be detected by the standard assays the pharmaceutical company used to check the raw materials. The exact source of the adulteration could not be identified but OSCS was also detected in the basic heparin material (heparin crude) that was produced in China. As the synthetic material OSCS is almost 100 times less cost-intensive to produce, it is assumed that the heparin crude was diluted with OSCS to cut costs. [29][55]

According to official numbers, 78 people died because of a toxic cough medicine distributed to patients in Panama in 2006. The toxic ingredient, diethylene glycol, was falsely labeled and sold as glycerin by a Chinese factory. The counterfeit product reached Panama after passing through brokers in China and Spain. The Panamanian government unknowingly purchased the falsified inactive ingredient to use it for the manufacture of cough medicines. [29][56]

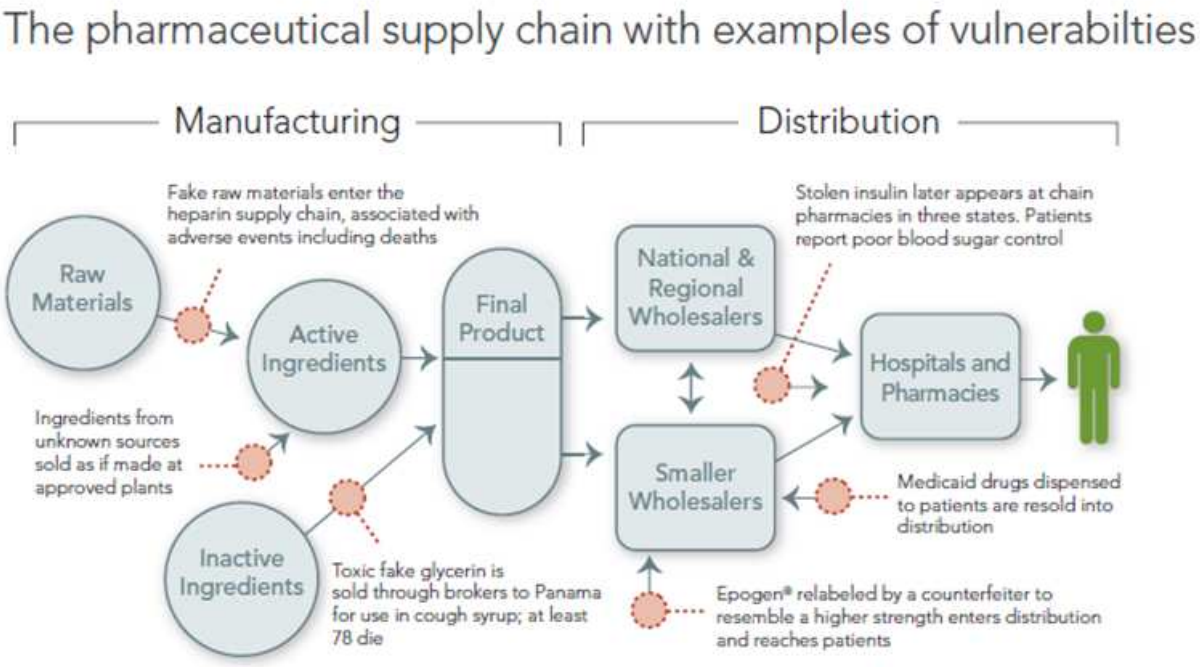

Figure 5: The pharmaceutical supply chain with examples of vulnerabilities [29][57]

[55] P. H. Group, "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," 12 July 2011. [Online]. Available: http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Reports/Health/Pew_Heparin_Final_HR.pdf. [Accessed 20 November 2013].

[56] P. H. Group, "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," 12 July 2011. [Online]. Available: http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Reports/Health/Pew_Heparin_Final_HR.pdf. [Accessed 20 November 2013].

[57] P. H. Group, "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," 12 July 2011. [Online]. Available: http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Reports/Health/Pew_Heparin_Final_HR.pdf. [Accessed 20 November 2013].

To prevent the entry of falsified or substandard active ingredients into the legal supply chain the European Union, for instance, demands by law that active substances for medicinal products for human use shall only be imported into the EU from third countries if they are accompanied by a “written confirmation”, provided by the competent authority of the respective exporting third country. [30][58] (See paragraph 1.3 for more detailed information.)

Counterfeiters more often use access points in the legal supply chain which are located subsequent to the manufacturing steps as the high amounts of counterfeit medicines, confiscated by customs or seized during police raids, show. Mainly the products are packaged according to the original products or at least the finalized bulk products. As the following figure displays, the complex legal supply chain presents multiple access points for counterfeiters besides the illegitimate supply chain, which is considered as the possible main flow for counterfeit medicinal products.

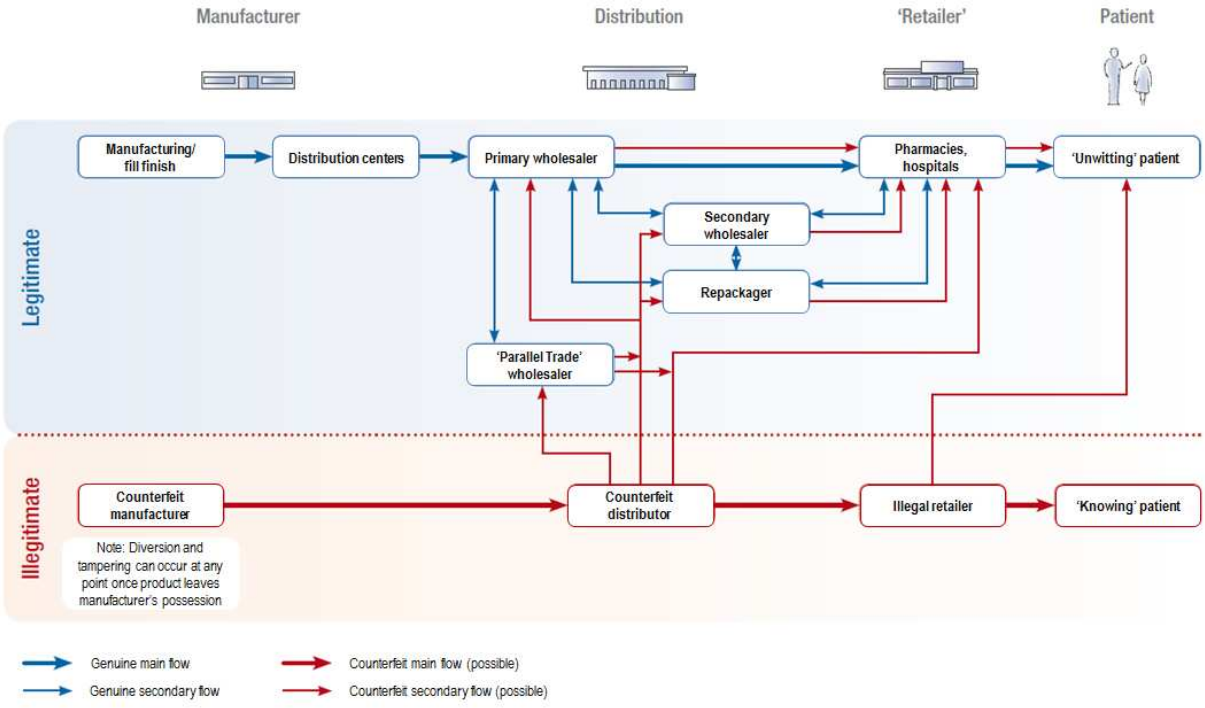

Figure 6: Possible inflow of counterfeits to the legitimate distribution channel [31][59] [32][60]

[58] European Commission, "Quality of medicines and Good Manufacturing Practices," 31 January 2015. [Online]. Available: http://ec.europa.eu/health/human-use/quality/index_en.htm. [Accessed 31 January 2015].
[59] European Alliance for Access to Safe Medicines, "Packaging Patient Protection - Recommendations for new legislation to combat counterfeit medicines," 2009. [Online]. Available: http://www.eaasm.eu/cache/downloads/5dhbepyu124ggkoc4kgsw48os/PPP%20to%20print%20FINAL.pdf. [Accessed 28 November 2013].
[60] C. J. Shaw, "Combating Pharmaceutical Counterfeiting; Second Global Congress for Combating Counterfeiting, Lyon, France," 14-15 November 2005. [Online]. Available: http://www.ccapcongress.net/archives/Lyon/files/CJShaw.pdf. [Accessed 20 November 2013].

1.1.4.2 Pharmaceutical parallel trade

One aspect of the distribution chain with respect to medicinal products which is seen very critical with regard to safety issues is the concept of pharmaceutical parallel trade. Pharmaceutical parallel imports are defined as "*products marketed by the patent owner (or trademark- or copyright-owner, etc.) or with the patent owner's permission in one country and imported into another country without the approval of the patent owner.*" by the World Trade Organization (WTO). [33][61] The basis for pharmaceutical parallel trade is provided by differences in regulatory practices across countries and resulting price differences of medicinal products. [34][62] One purpose of pharmaceutical parallel trade is to enhance the affordability and availability of medicinal products. Due to the consequent price competition patent holders are withheld to charge excessively high prices in a particular market. [35][63] The concept of parallel importation of medicinal products is compatible with the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS) as it is one of the provisions, known as TRIPS public health safeguards, with the purpose to enhance the affordability and availability of medicines. [36][64]

In the European Union, for instance, the concept of parallel trade of medicines is legitimate. The principle of parallel importation applies to medicinal products which are authorized to be marketed in EU countries, based on national or decentralized, national approvals. Parallel importers are allowed to import such medicines in parallel in the respective EU countries if they have a respective authorization. For each medicinal product an application for approval has to be submitted to the competent authority of the respective country where the product shall be distributed. [37][65] [38][66] Receiving approval for marketing the parallel importer becomes the marketing authorization holder of the respective imported medicinal product, including all obligations and responsibilities. With respect to medicinal products for which a centralized marketing authorization was approved by the EMA the principle of parallel distribution applies. A national authorization for the importer is not required. Instead, the

[61] "WTO Fact sheet: TRIPS and PHarmaceutical Patents," September 2006. [Online]. Available: http://www.wto.org/english/tratop_e/trips_e/factsheet_pharm02_e.htm. [Accessed 25 November 2013].
[62] P. Kanavos, J. Costa-i-Font, S. Merkur and M. Gemmill, "The Economic Impact of Pharmaceutical Parallel Trade in European Union Member States: A Stakeholder Analysis," January 2004. [Online]. Available: http://archives.who.int/prioritymeds/report/append/829paper.pdf. [Accessed 21 November 2013].
[63] "WHO - Access to medicines," [Online]. Available: http://www.who.int/trade/glossary/story002/en/index.html. [Accessed 25 November 2013].
[64] "WHO - Trade-related aspects of intellectual property rights (TRIPS)," [Online]. Available: http://www.who.int/trade/glossary/story091/en/index.html. [Accessed 25 November 2013].
[65] BfArM, "Parallelimport von Arzneimitteln," 2013. [Online]. Available: http://www.bfarm.de/DE/Arzneimittel/zul/zulassungsverfahren/parimp/_node.html. [Accessed 15 January 2015].
[66] "PZ online Bedenken bei Parallel- und Importware?," 2011. [Online]. Available: http://www.pharmazeutische-zeitung.de/index.php?id=39580. [Accessed 15 January 2015].

requirements of the European Medicines Agency notification procedure for parallel distribution have to be followed. [39][67]

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has concerns about potential safety risks related to pharmaceutical parallel trade. According to the EFPIA the rise in parallel importing within the EU has led to increased difficulty in tracking medicines. Therefore, the supply chain of parallel traders presents a potential access point to traders of medicinal products from dubious sources or counterfeit medicines. The required re-packaging procedures in terms of parallel importation of medicinal products are also considered as a risk factor promoting the introduction of substandard or counterfeit medicines into the legal supply chain. [40][68] Pharmaceutical parallel trade as a potential access point is displayed in Figure 6, as well.

The risk of counterfeit medicines being introduced into the legal supply chain through parallel trade is demonstrated by cases like the theft of multiple pharmaceutical products in Italy and their illegal diversion to other European countries, discovered in 2014. [41][69] According to the Italian Medicines Agency (AIFA) more than 80 medicinal products of Italian origin are affected. Via bogus operators in Eastern Europe the stolen medicines were sold to authorized wholesalers in Italy. [42][70] In this way they entered the legal supply chain and were distributed to multiple European countries, mainly Germany. [43][71] The AIFA published lists of the bogus operators, involved authorized operators as well as the affected medicinal products and recommends the recall of all packages affected by the illegitimate trade. [42][72] In July 2014, the Italian police stated to have arrested the most important suspects and have

[67] European Medicines Agency, "Parallel distribution," 2015. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000067.jsp&mid=WC0b01ac0580024594. [Accessed 15 January 2015].
[68] EFPIA Position Paper, "International Exaustion of Trade Mark Rights - Protecting Patients - The Importance of Trade Mark Rights for Medicines," April 2001. [Online]. Available: http://efpia.org/Objects/1/Files/protecpatients.pdf. [Accessed 25 November 2013].
[69] K. Sucker-Sket, "DAZ Online Spektrum Gefälschte Import-Ware landet vor allem in Deutschland," 28 August 2014. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/spektrum/news/2014/08/28/gefaelschte-import-ware-landet-vor-allem-in-deutschland/13680.html. [Accessed 15 January 2015].
[70] Italian Medicines Agency, "Rapid Alert - August 8, 2014," 11 August 2014. [Online]. Available: http://www.agenziafarmaco.gov.it/en/content/rapid-alert-august-8-2014. [Accessed 15 January 2015].
[71] J. Pradel, "apotheke adhoc BMG lässt Parallelhandel überprüfen," 2 October 2014. [Online]. Available: http://www.apotheke-adhoc.de/nachrichten/nachricht-detail/arzneimittelfaelschungen-bundesgesundheitsministerium-eu-kommission-soll-rechtsrahmen-fuer-parallelh/. [Accessed 15 January 2015].
[72] Italian Medicines Agency, "Rapid Alert - August 8, 2014," 11 August 2014. [Online]. Available: http://www.agenziafarmaco.gov.it/en/content/rapid-alert-august-8-2014. [Accessed 15 January 2015].

identified two of them as persons responsible. [41][73] As a consequence of this illegal diversion which affected the legal supply chain through parallel distribution ways, the German Federal Ministry of Health (BMG) issued a request to the European Commission to reconsider the legal framework on pharmaceutical parallel trade in the EU. Since effectively all medicinal products, affected by the illegal diversion, have a centralized authorization, the request especially relates to the notification procedure for parallel distribution and the required documentation regarding the distribution. [43][74]

1.1.4.3 The internet and online sale of medicines

The internet has become the criminal pusher's best friend with respect to counterfeit medicines. In over 50% of cases, medicines purchased over the internet from illicit online pharmacies that conceal their physical address have been found to be counterfeit. [5][75] Moreover, they are available to everyone, even to teenagers and children, since these illegal websites have no mechanisms to block children to access or purchase prescription drugs as the CASA-Study "You've Got Drugs!" on the diversion and abuse of prescription drugs revealed. Even when the identification of the patient's age is required to access the website, it is just as easy to key in a fake age to the form. [44][76] Facts like that make it much more complicated, e.g. for parents, to comply to the warning "keep out of the reach of children", let alone the potential adverse effects in children or adult patients caused by illegally sold and likely counterfeit medicines.

According to the OpSec Security, Inc. study "Risk Assessment: Counterfeit Pharmaceuticals in the Online Marketplace" of 2010, the percentage of illegitimate online pharmacies offering prescription-only medicines without demanding a prescription increased significantly from 51% in 2007 to 89% in 2010. [45][77] The results of the "The Counterfeiting Superhighway" research, conducted by the European Alliance for Access to Safe Medicines (EAASM) and

[73] K. Sucker-Sket, "DAZ Online Spektrum Gefälschte Import-Ware landet vor allem in Deutschland," 28 August 2014. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/spektrum/news/2014/08/28/gefaelschte-import-ware-landet-vor-allem-in-deutschland/13680.html. [Accessed 15 January 2015].

[74] J. Pradel, "apotheke adhoc BMG lässt Parallelhandel überprüfen," 2 October 2014. [Online]. Available: http://www.apotheke-adhoc.de/nachrichten/nachricht-detail/arzneimittelfaelschungen-bundesgesundheitsministerium-eu-kommission-soll-rechtsrahmen-fuer-parallelh/. [Accessed 15 January 2015].

[75] "WHO Fact sheet N° 275," May 2012. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs275/en/index.html. [Accessed 29 October 2013].

[76] The National Center on Addiction and Substance Abuse at Colombia University , "You've Got Drugs! V: Prescription Drug Pushers on the Internet," July 2008. [Online]. Available: http://www.casacolumbia.org/articlefiles/531-2008%20You%27ve%20Got%20Drugs%20V.pdf. [Accessed 29 October 2013].

[77] OpSec Security, Inc., "Risk Assessment: Counterfeit Pharmaceuticals in the Online Marketplace," 15 November 2010. [Online]. Available: http://info.opsecsecurity.com/assessing-the-risk-of-counterfeit-pharmaceuticals-in-the-online-marketplace. [Accessed 25 November 2013].

published in 2008, revealed similar disturbing data. It was found that 62% of the medicines purchased online were falsified or substandard, 96% of the examined internet pharmacies were operating illegally and 90% of the researched online pharmacies offered prescription-only medicines without demanding a prescription. [46][78] And the results of Pfizer's "Cracking Counterfeits" survey, involving 14,000 respondents in 14 European countries revealed that 21% of the Europeans at least once purchased prescription-only medicine without having a prescription. Furthermore, less than 50% of the respondents have concerns about the authenticity of the medicinal products purchased via the internet. The survey also shows that some people are not even aware which medicines are prescription-only medicines to be able to question online pharmacies offering the respective pharmaceutical products without demanding a prescription. For example, 32% of the respondents thought Viagra® was a medicine which does not require a prescription. In fact, 14% of the surveyed Europeans stated that even if they knew that the purchased drugs may be counterfeits, they still would order prescription-only medicines without having a prescription via the internet. [47][79]

Low prices, convenience and the anonymity given in the internet keep many people stick to internet pharmacies to save money or to avoid the physician's consultation on sensitive topics such as erectile dysfunction or incontinence, etc. Other reasons may be to reach out to drugs for misuse or abuse, e.g. anabolic drugs or narcotics. In these cases most of the patients most likely will not report the occurrence of an adverse effect or a lack of drug effect after using the medicines. [48][80] Due to the minor reporting of adverse events related to suspected counterfeits thorough signal detection is hardly possible. Altogether, patients are not sufficiently aware of the risk to receive counterfeit drugs when purchasing medicines over the internet. Thus, the majority would not raise suspicions against the authenticity of the medicines they purchased, which could be reported. Hence, the slight amount of data on the presence of counterfeit medicines makes it harder to implement appropriate actions, e.g. to warn other patients, in a timely manner. For that reason, it is indispensable to raise people's

[78] European Alliance for Access to Safe Medicines, "The Counterfeiting Superhighway," June 2008. [Online]. Available: http://www.eaasm.eu/cache/downloads/dqqt3sge9hwssgcgcos440g40/455_EAASM_counterfeiting%20report_020608%281%29.pdf. [Accessed 29 November 2013].

[79] Pfizer, "Cracking Counterfeit Europe," February 2010. [Online]. Available: http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=6&ved=0CF4QFjAF&url=http%3A%2F%2Fwww.ots.at%2Fanhang%2FOTS_20100218_OTS0066.pdf&ei=gGyTUparI8f2ygOAr4Bo&usg=AFQjCNGZ642DdFk0dPLC0Z3MeLn0C2KMxQ&bvm=bv.56988011,d.bGQ. [Accessed 25 November 2013].

[80] "Gesundheitsrisiko Arzneimittelfälschungen - Zwischen Kavaliersdelikt und Lebensgefahr," *Deutsche Apotheker Zeitung,* no. 11, pp. 30-32, 2011.

awareness of the hazard counterfeit medicines pose to patients' welfare and public health and of the risks of purchasing medicinal products from dubious or illegal sources. [49][81]

For example, in Germany the online sale of medicinal products was legalized in 2004 in accordance to the 12th amendment of the German Medicinal Products Act (AMG). In the course of this, the occurrence of counterfeit medicinal products in Germany increased swiftly. [50][82] The German customs seized 500,000 falsified tablets and capsules in 2005 and with about 5 million counterfeit drugs in 2009, already the tenfold. [48][83] The EU-Committee reports an amount of more than 11 million falsified medicinal products seized in the EU, in 2009. [50][84] Furthermore, it has to be considered that the estimated number of unknown cases is huge. The internet is the main source of supply with regard to counterfeit medicinal products. [48][85] Round about 95 percent of all online pharmacies are illegal as the German Federal Institute for Drugs and Medical Devices (BfArM) reports. [49][86] Today, it is no longer difficult to create your own website, therefore persons or organizations with sufficient criminal incentive can easily set up a website undermining security features, and thus, pretending to be an authorized online pharmacy. [51][87] Unfortunately, when the online sale of medicines was legalized, the German Government did not implement a specialized competent authority which constantly observes internet pharmacies and checks their legality. [52][88] At present, institutions such as the German Institute of Medical Documentation and Information (DIMDI), the BKA and the Central Laboratory of German Pharmacists (ZL) are involved in observing and checking online pharmacies [48][89] but such efforts remain limited whereby the risk for patients to purchase counterfeit medicinal products from non-authorized internet pharmacies maintains rather high. Mystery shopping, as the German ZL performs, shows that patients can purchase any prescription drugs via the internet without having a prescription, but none of the delivered products were genuine or with authorization for Germany. 50 to 60 percent of

[81] S. Schersch, "Arzneimittelfälschungen - Aufklärung als höchstes Ziel," *Pharmazeutische Zeitung,* no. 9, pp. 10-11, 2010.
[82] H. G. Schweim and J. Fuchs, "Arzneimittelfälschungen und Scheinsicherheit - Wie effektiv ist das Sicherheitslogo für Versandapotheken?," *Deutsche Apotheker Zeitung,* no. 10, pp. 52-55, 2011.
[83] "Gesundheitsrisiko Arzneimittelfälschungen - Zwischen Kavaliersdelikt und Lebensgefahr," *Deutsche Apotheker Zeitung,* no. 11, pp. 30-32, 2011.
[84] H. G. Schweim and J. Fuchs, "Arzneimittelfälschungen und Scheinsicherheit - Wie effektiv ist das Sicherheitslogo für Versandapotheken?," *Deutsche Apotheker Zeitung,* no. 10, pp. 52-55, 2011.
[85] "Gesundheitsrisiko Arzneimittelfälschungen - Zwischen Kavaliersdelikt und Lebensgefahr," *Deutsche Apotheker Zeitung,* no. 11, pp. 30-32, 2011.
[86] S. Schersch, "Arzneimittelfälschungen - Aufklärung als höchstes Ziel," *Pharmazeutische Zeitung,* no. 9, pp. 10-11, 2010.
[87] H. G. Schweim, "DAZ Online Arzneimittel im Internet-Versandhandel - sicher!?," 2007, 27. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/daz-ausgabe/artikel/articlesingle/2007/27/24083.html. [Accessed 30 October 2013].
[88] "Der Kardinalfehler," *Deutsche Apotheker Zeitung,* no. 27, p. 3, 2007.
[89] "Gesundheitsrisiko Arzneimittelfälschungen - Zwischen Kavaliersdelikt und Lebensgefahr," *Deutsche Apotheker Zeitung,* no. 11, pp. 30-32, 2011.

the lifestyle drugs were falsified or substandard. [48][90] On top of this, many patients are not aware enough of the risk concerning counterfeit medicines.

The AMG § 43 [53][91], combined with the German Pharmacies Act (ApoG) § 11a [54][92], stipulates that only community pharmacies, holding permission of the competent authority, are allowed to run an internet pharmacy which has to be reported to the DIMDI that lists all authorized online pharmacies in Germany. Such an authorized pharmacy can implement a security symbol, licensed by the DIMDI, which identifies it as legal. Unfortunately, most of the population just knows that licensed internet pharmacies have a security symbol to be identified as licensed, but they often do not know how it looks like. Thus, a fake symbol can easily be used to deceive patients and to make them feel safe about the authenticity of the – in this case – non-authorized internet pharmacy. [50][93]

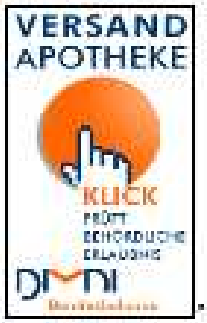

Figure 7: DIMDI security symbol, Copyright 1995-2013 DIMDI [55][94]

There is a similar verification system for online pharmacies used in the US. The Verified Internet Pharmacy Practice Sites (VIPPS) program was initiated by the National Association of Boards of Pharmacy (NABP), in 1999. Pharmacies have to meet several criteria, e.g. compliance with licensing and inspection requirements, to be VIPPS accredited. Then they are allowed to display the VIPPS hyperlink seal on their website. [56][95]

[90] "Gesundheitsrisiko Arzneimittelfälschungen - Zwischen Kavaliersdelikt und Lebensgefahr," *Deutsche Apotheker Zeitung,* no. 11, pp. 30-32, 2011.
[91] "German Medicinal Products Act; Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG)," as announced on 12 December 2005 (Federal Law Gazette I p. 3394); last amended on 10 October 2013 (Federal Law Gazette I p. 3813). [Online]. Available: http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf. [Accessed 26 November 2013].
[92] "German Pharmacies Act; Gesetz über das Apothekenwesen (Apothekengesetz - ApoG)," as announced on 15 October 1980 (Federal Law Gazette I p. 1993); last ammended on 15 July 2013. [Online]. Available: http://www.gesetze-im-internet.de/bundesrecht/apog/gesamt.pdf. [Accessed 26 November 2013].
[93] H. G. Schweim and J. Fuchs, "Arzneimittelfälschungen und Scheinsicherheit - Wie effektiv ist das Sicherheitslogo für Versandapotheken?," *Deutsche Apotheker Zeitung,* no. 10, pp. 52-55, 2011.
[94] "DIMDI - Licensed Online Pharmacies," 23 September 2013. [Online]. Available: http://www.dimdi.de/static/de/amg/var/index.htm. [Accessed 27 November 2013].
[95] National Association of Boards of Pharmacy, "VIPPS information and verification site," 13 January 2011. [Online]. Available: http://vipps.nabp.net/. [Accessed 27 November 2013].

Figure 8: VIPPS security symbol, Copyright 2013 NABP [57][96]

A comparable security symbol is also planned to be implemented in the European Union. In the Directive 2011/62/EU the symbol is referred to as the "common logo" and shall be displayed on the websites of legally-operating online pharmacies. It is intended that the common logo contains a hyperlink to a list of all national legally-operating online pharmacies and retailers of the respective Member State, where they are established. It is the obligation of each Member State to provide such a list by means of a dedicated website. Each entry of the list shall be connected to the website of the respective online pharmacy or retailer using a hyperlink. A concept paper on the implementing act of the common logo was submitted for public consultation, in 2012. Among others, it comprises two different options with regard to the design of the logo. Moreover, it was under discussion if the design options should, in the end, include a national element and text or not. [58][97] On June 24, 2014 the European Commission adopted the Implementing Regulation 699/2014 and with it the common logo. The Member States have a timeframe of one year from this date to accomplish the provisions with respect to the common logo. [59][98] The following figure shows a model of the common logo of the selected design (design option 2 including a national element and text). In the displayed model a white rectangle replaces the national flag of the respective Member State. [60][99] Further information on the EU rules concerning the common logo and the online sale of medicinal products are presented in paragraph 1.3.

[96] "NABP - VIPPS," 2013. [Online]. Available: http://www.nabp.net/programs/accreditation/vipps. [Accessed 27 November 2013].
[97] European Commission, "Concept paper for public consultation on the implementing act on a common logo for legally-operating online pharmacies/retailers offering medicinal products for human use for sale at a distance to the public," 17 October 2012. [Online]. Available: http://ec.europa.eu/health/files/falsified_medicines/commonlogo_consult.pdf. [Accessed 5 January 2015].
[98] European Commission, "EU logo for online sale of medicines," 27 June 2014. [Online]. Available: http://ec.europa.eu/health/human-use/eu-logo/index_en.htm. [Accessed 6 January 2015].
[99] European Commission, "Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014," (OJ L 184, 25.06.2014, p. 5). [Online]. Available: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_184_R_0004&from=EN. [Accessed 6 January 2015].

Figure 9: Common logo, Copyright 2012 European Commission [60][100]

The problem of patients not being able to differentiate authorized internet pharmacies from non-authorized internet pharmacies remains unless the drug regulatory authorities, with the aid of physicians and pharmacists, will not enhance people's knowledge and awareness with respect to this issue. The hazard to patients' welfare is not to be underestimated.

In this context, a campaign, mainly targeted to demonstrate how easy it can be to setup a fake online pharmacy and attract customers and to educate patients and consumers about the dangers of purchasing medicines from dubious internet pharmacies, was conducted by the European Alliance for Access to Safe Medicines (EAASM) in Germany, in 2011. The campaign is called "Counterfeiting the Counterfeiter". During the project the EAASM collaborated with the DIMDI, several pharmaceutical companies, patients groups, health information providers, internet search engines and credit card processors. The core tool of the campaign was an online pharmacy website, setup by the initiators of the project, with the purpose to appeal like a legitimate internet pharmacy, but actually being illicit, and therefore attract potential purchasers of counterfeit medicinal products, particularly prescription-only medicines. The visitors of this particular website were not provided with fake medicines but with helpful information about and warnings against the threat of counterfeit medicinal products to patients' health and the risks of purchasing such via the internet. This was done by linking the EAASM's fake online pharmacy landing page to websites which contained the mentioned warnings and information, to the DIMDI website providing information about legitimate online and offline pharmacies, and to websites of further organizations and associations e.g. the WHO or pan-European patient groups which also provide topic-specific

[100] European Commission, "Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014," (OJ L 184, 25.06.2014, p. 5). [Online]. Available: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_184_R_0004&from=EN. [Accessed 6 January 2015].

information. All in all, the website was online and heavily promoted in Germany for 9 weeks in 2011 and therewith attracted over 182,000 individual visitors, from which over 142,000 viewed the warning messages and over 12,000 accessed the DIMDI website about the legitimate online pharmacies. [61][101] Hence, the EAASM's education campaign "Counterfeiting the Counterfeiter" was a very successful contribution to one of the basic requirements in the fight against counterfeit medicines, which is to raise awareness among patients and consumers.

1.2 International anti-counterfeiting initiatives

The WHO reacted to the enhancing hazard caused by counterfeit medicines by launching the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), in 2006, which is a partnership, including international organizations, drug regulatory authorities and pharmaceutical manufacturer associations. It is the IMPACT's aim to combat the production and distribution of counterfeit medicinal products by building coordinated global networks between countries. [62][102] Together with INTERPOL and the WHO, the IMPACT was involved in the, at present, seven international operations against the illegal trade of medicines over the internet, called Pangea I - VII. Each Pangea operation is about a week of international collaboration of customs, health regulators, national police and the private sector actively combatting the online sale of counterfeit and illicit medicines. [63][103] Each time, the participants worked together to inspect internet pharmacies and their websites, internet service providers and mail services. A huge amount of illegally distributed and falsified medicinal products could be seized, many non-authorized internet pharmacies identified and many websites closed down. The Pangea operations additionally serve the purpose to sensitize the public to the problem of counterfeit medicines and the extensive risk to patients' health that they constitute. [64][104] [65][105] The first operation, carried out in 2008, counted 10 countries that took part. The number of participating countries continuously

[101] European Alliance for Access to Safe Medicines, "Counterfeiting the Counterfeiter," 2012. [Online]. Available: http://www.eaasm.eu/cache/downloads/av3r9l87z4wg4ocs8w84gogs0/CtC%20report%202012.pdf. [Accessed 29 November 2013].

[102] "IMPACT homepage," [Online]. Available: http://www.who.int/impact/about/en/. [Accessed 30 October 2013].

[103] "INTERPOL - Operation Pangea," 2015. [Online]. Available: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea. [Accessed 2 January 2015].

[104] K. Sucker-Sket, "DAZ Online Spektrum Operation Pangea II - Weltweite Razzia gegen illegale Internet-"Apotheken"," 20 November 2009. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/spektrum/news/2009/11/20/weltweite-razzia-gegen-illegale-internet-apotheken.html. [Accessed 30 October 2013].

[105] K. Sucker-Sket, "DAZ Online Spektrum Operation Pangea III - Aktion gegen illegale Internet-Anbieter von Arzneimitteln," 14 October 2010. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/spektrum/news/2010/10/14/aktion-gegen-illegale-internet-anbieter-von-arzneimitteln.html. [Accessed 30 October 2013].

increased with every operation and reached a number of more than 100 participating countries during the week of Pangea VII, in 2014. Pangea VII counted 113 participating countries joining the combat against counterfeiting and the illegal trade of medicines. [63][106] In total, an amount of more than 27 million illicit and counterfeit pills were confiscated, of an estimated worth of more than 91 million US dollars. As a consequence of the Pangea operations about 57,450 illegitimate websites offering medicinal products were shut down. [63][107]

A new global initiative, coordinated by INTERPOL, was announced on March 12th, 2013. It is called Pharmaceutical Industry Initiative to Combat Crime (PIICC). 29 global pharmaceutical companies will collaborate to combat the growing threat of counterfeit medicinal products and thereby protect patient safety. The initiative's scope covers the fight against pharmaceutical crime with respect to both branded and generic medicines. It is the aim to support investigative activities to identify and expose organized crime networks involved in illegal activities regarding medicinal products, to intensify enforcement operations and to raise awareness of the risks related to counterfeit medicines among the public. [66][108] [67][109]

In the EU an international project with the objective to guaranty the reliability of the legal supply chain of medicinal products has been started. [68][110] Based on the provision of the "Falsified Medicines Directive" (Directive 2011/62/EU) that a safety feature shall be applied to medicinal products for human use to enable their identification and a verification of their authenticity [69][111], an EU-wide coding and serialization system was set up (see paragraph 1.3 for details on the legislative framework regarding the safety feature). The project, called European Stakeholder Model (ESM), is supported by several stakeholders, including EFPIA, EAEPC (European Association of Euro-Pharmaceutical Companies), GIRP (European Association of Pharmaceutical Full-line Wholesalers) and PGEU (Pharmaceutical Group of

[106] "INTERPOL - Operation Pangea," 2015. [Online]. Available: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea. [Accessed 2 January 2015].
[107] "INTERPOL - Operation Pangea," 2015. [Online]. Available: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea. [Accessed 2 January 2015].
[108] European Federation of Pharmaceutical Industries and Associations, "INTERPOL and pharmaceutical industry join forces in new global initiative to protect patients from counterfeit medicines," 12 March 2013. [Online]. Available: http://www.efpia.eu/mediaroom/13/85/INTERPOL-and-pharmaceutical-industry-join-forces-in-new-global-initiative-to-protect-patients-from-counterfeit-medicines. [Accessed 27 November 2013].
[109] INTERPOL, "Pharmaceutical Industry Initiative to Combat Crime," 2015. [Online]. Available: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Pharmaceutical-Industry-Initiative-to-Combat-Crime. [Accessed 8 January 2015].
[110] European Federation of Pharmaceutical Industries and Associations, "Stamping out Falsified Medicines," 2015. [Online]. Available: http://www.efpia.eu/topics/industry-economy/falsified-medicines. [Accessed 8 January 2015].
[111] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

the European Union), representing Europe's research-based manufacturers, the pan-EU licensed parallel distribution companies, wholesalers and pharmacists. It is their aim to create and to implement the European Medicines Verification System (EMVS). This system shall enable the authenticity check of individual packs of medicines before they are dispensed to the patient in order to ensure that the patient receives a genuine product. This authenticity check is performed by using individual pack level serial numbers to be applied to the packs and to be saved in national data repositories. In the years of 2009 to 2010, the technical approach of the verification system was tested in Sweden, where a successful pilot project was performed. The EMVS will be also interoperable between various countries to ensure that principles like the parallel trade of medicines and multi-country pack management stay feasible. This is achieved through the European Hub, which is connected to the national data repositories. In order to promote the EMVS implementation the ESM partners signed a contract with an IT service provider, in April 2013. In addition, the EFPIA has developed guidelines to support the EMVS's implementation and to ease its implementation for affected stakeholders. The ESM partners' work continues on the national interface with the securPharm project, performed in Germany. [68][112] The interface of securPharm's German system to ESM's European Hub shall demonstrate for the first time how European and national components of the EMVS can be linked. It was scheduled to be performed in July 2014. [70][113]

The securPharm initiative was launched on January 1, 2013. [71][114] The seven members of the securPharm initiative represent all stakeholders of the distribution chain of medicinal products in Germany. [72][115] The initiative should serve the purpose of the development, implementation and testing of a system that meets the requirements regarding the verification of medicinal products laid down in the Directive 2011/62/EU. The securPharm project is performed under real-life conditions of the German pharmaceutical market. The verification of single packs is based on the principle of serialization and the use of a carrier of the relevant serial number to be applied to the packs. A machine-readable data matrix code is used as the carrier, containing four data elements which are the product number

[112] European Federation of Pharmaceutical Industries and Associations, "Stamping out Falsified Medicines," 2015. [Online]. Available: http://www.efpia.eu/topics/industry-economy/falsified-medicines. [Accessed 8 January 2015].
[113] European Federation of Pharmaceutical Industries and Associations, "Progress towards a European Medicines Verification System: the European Stakeholder Model and securPharm link-up," 4 March 2014. [Online]. Available: http://www.efpia.eu/mediaroom/147/21/Progress-towards-a-European-Medicines-Verification-System-the-European-Stakeholder-Model-and-securPharm-link-up. [Accessed 8 January 2015].
[114] "securPharm – the German shield against counterfeit medicines," 2015. [Online]. Available: http://www.securpharm.de/international-sites/english.html. [Accessed 8 January 2015].
[115] "securPharm - Mitglieder der Initiative," 2015. [Online]. Available: http://www.securpharm.de/securpharm-initiative/mitglieder.html. [Accessed 13 January 2015].

(Pharmacy Product Number (PPN) or National Trade Item Number (NTIN)), the lot number, the expiration date and the serial number. To ensure that the data matrix code is used in a standardized way by all stakeholders of the initiative securPharm has generated a guidance document on the coding rules and the labeling on pharmaceutical packaging. During the production process the data matrix code containing all relevant information is printed on the package. In addition, the respective information, provided by the marketing authorization holder, is retained in the manufacturers' central database. The authenticity check of the individual package is performed by the pharmacy staff scanning the data matrix code before dispensing the medicinal product to the patient. The scanned information is checked against the central database. If the data is correct and was not requested before, the package can be dispensed, consequently changing the package's status to "dispensed". If the data is not correct or the status of the respective pack is "dispensed", the system causes an alert. [73][116] The following figure displays the procedure of the securPharm control system.

[116] "securPharm - Status Report 1. 2014," 18 March 2014. [Online]. Available: http://www.securpharm.de/fileadmin/pdf/englisch/Statusbericht_Druckbogen_engl._1.2014_final.pdf. [Accessed 13 January 2015].

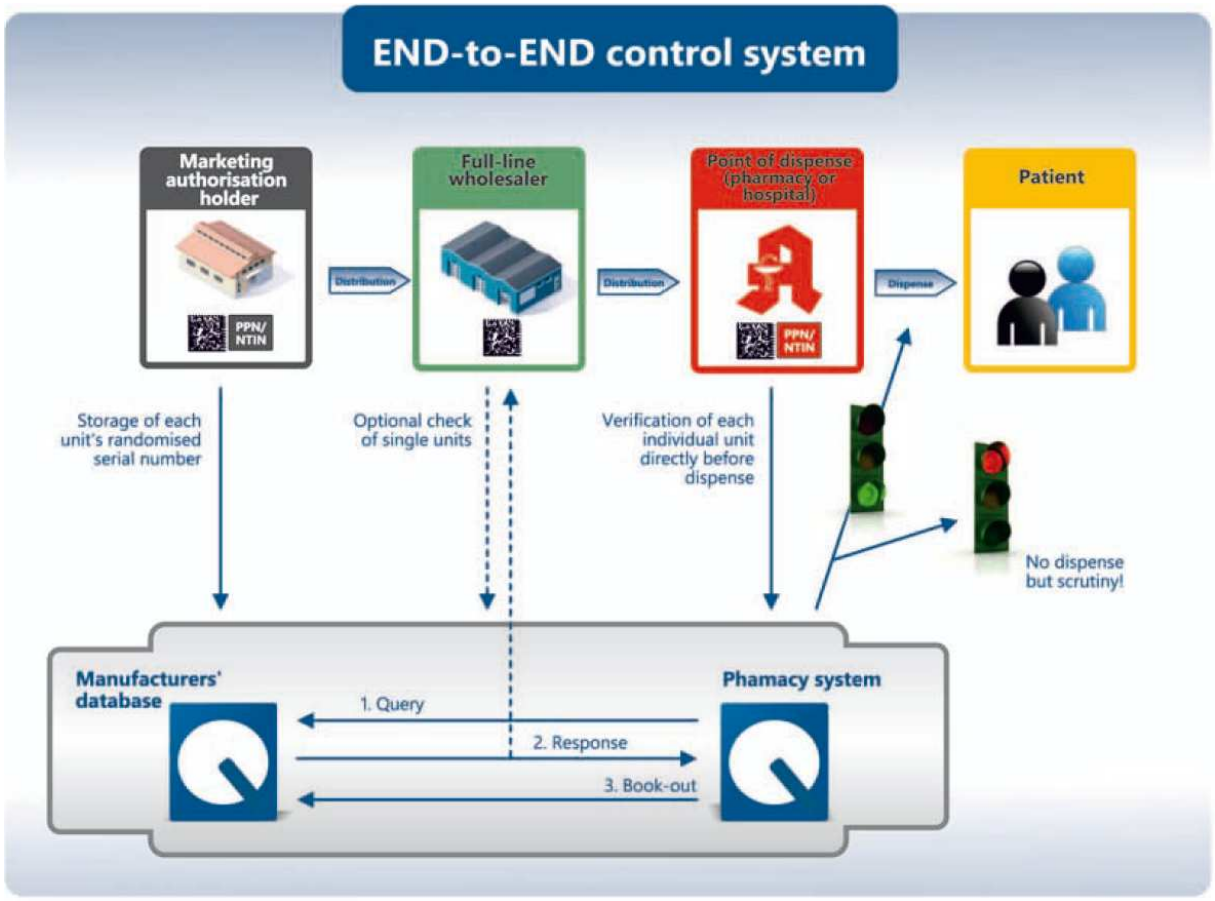

Figure 10: securPharm end-to-end control system [73][117]

As of the beginning of 2013, 24 pharmaceutical companies and around 400 community pharmacies are participating in the securPharm project. Furthermore, the participants include parallel importers, generics companies, a wholesaler, including all of its German offices, an IT systems integrator and five pharmacy software providers. As of the end of 2013, 110 medicinal products had been coded, comprising more than 7.5 million serialized packages on the German market. The project revealed highly satisfactory results regarding the system's usability, resilience, performance and availability. securPharm is considered a success and represents the German component for the security network of the European Stakeholder Model for the protection against falsified medicines. [73][118]

1.3 Regulatory framework in the EU

Because of the increasing numbers with respect to counterfeit drugs, among other things, the EU initiated changes in the drug legislation and issued the so called "Pharmaceutical

[117] "securPharm - Status Report 1. 2014," 18 March 2014. [Online]. Available: http://www.securpharm.de/fileadmin/pdf/englisch/Statusbericht_Druckbogen_engl._1.2014_final.pdf. [Accessed 13 January 2015].
[118] "securPharm - Status Report 1. 2014," 18 March 2014. [Online]. Available: http://www.securpharm.de/fileadmin/pdf/englisch/Statusbericht_Druckbogen_engl._1.2014_final.pdf. [Accessed 13 January 2015].

Package" containing three legislative proposals, adopted by the European Commission (EC) on December 10th, 2008. The first proposal aims to "*ensure that EU citizens have access to reliable information on medicines*". For this purpose, harmonized rules with regard to information about prescription-only medicines provided by pharmaceutical companies shall be established. [74][119]

The second proposal of the Pharmaceutical Package focuses on "*strengthening the EU's system for the safety monitoring of medicines (pharmacovigilance)".* It is the aim to consolidate and to simplify the complex pharmacovigilance system of the European Union. [74][120] The EU's international pharmacovigilance database "EudraVigilance", managed by the European Medicines Agency (EMA) was launched in December 2001. It serves as a data processing network and management system for reporting and evaluating suspected adverse reactions regarding medicinal products authorized in the European Economic Area (EEA). [75][121] Hence, an international surveillance and exchange of information about suspected adverse drug reactions is available. In 2012, the EMA launched a website which provides public access to the information on reports related to suspected adverse events, collected in the EudraVigilance database. [76][122]

The third and last proposal specifically addresses the issue of counterfeit medicinal products. Its purpose is to "*protect the legal distribution chain from the infiltration of fake medicines*". [74][123] In December of 2010 the European Parliament agreed on a draft according to the amendments of the EU Directive 2001/83/EC which were adopted on February 16, 2011. These amendments had to be transferred into national law within two years. [77][124] On June 8, 2011, the EU Directive 2011/62/EU, also known as the "Falsified Medicines Directive" came into effect. [69][125]

[119] "European Commission - Pharmaceutical package," 2013. [Online]. Available: http://ec.europa.eu/health/human-use/package_en.htm. [Accessed 29 November 2013].
[120] "European Commission - Pharmaceutical package," 2013. [Online]. Available: http://ec.europa.eu/health/human-use/package_en.htm. [Accessed 29 November 2013].
[121] European Medicines Agency, "EudraVigilance homepage," 9 April 2013. [Online]. Available: https://eudravigilance.ema.europa.eu/human/index.asp. [Accessed 3 December 2013].
[122] European Medicines Agency, "EudraVigilance - Background," 2013. [Online]. Available: http://www.adrreports.eu/EN/background.html. [Accessed 3 December 2013].
[123] "European Commission - Pharmaceutical package," 2013. [Online]. Available: http://ec.europa.eu/health/human-use/package_en.htm. [Accessed 29 November 2013].
[124] R. Eicher, "European Compliance Acadamy - GMP News," 16 February 2011. [Online]. Available: http://www.gmp-compliance.org/eca_news_2439_6748,6737,6762,6892.html. [Accessed 31 October 2013].
[125] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

The directive contains statutory provisions based on the proposals comprised in the Pharmaceutical Package. It includes the criteria of a falsified medicinal product and thereby gives a definition of such. Furthermore, it stipulates enhanced controls of the legal distribution chain including the verification of manufacturers, distributors, wholesalers, importers and brokers of medicinal products, active ingredients or excipients to comply with the guidelines of good manufacturing practice (GMP) and good distribution practice (GDP), each as applicable. The verification is to be done by the means of audits, e.g. by the marketing authorization holder in the case of a contract manufacturer or by the competent authorities of the Member States. Manufacturers, distributors, wholesalers, importers and brokers have to be registered with the competent authority of the Member State in which they are established. The Member States have to enter the information received in relation to the registration in a Union database to be managed by the EMA. [69][126] The respective database is the EudraGMDP database that was first launched in April 2007 and is available as a public version since 2011. The database comprises all EU-relevant information on manufacturing, import and wholesale-distribution authorizations, and good manufacturing practice and good distribution practice certificates. [78][127] In addition, EU-wide rules for the importation of active substances for medicinal products for human use from third countries have been introduced. [30][128] Since July 02, 2013 [79][129] active substances shall only be imported if they are accompanied by a “written confirmation” according to Article 46b(2) of Directive 2001/83/EC. The “written confirmation” has to be given by the competent authority of the exporting third country. In doing so the competent authority confirms that the site manufacturing the exported active substance is in compliance with EU GMP for active substances and that the control of the manufacturer is equivalent to the standards in the EU. [80][130] If a third country’s regulatory framework applicable to active substances exported to the EU, as well as respective control and enforcement measures safeguard a level of protection of public health that is equivalent to that of the EU, the country can export active substances to the EU

[126] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

[127] European Medicines Agency, "EudraGDMP database," 2013. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000159.jsp. [Accessed 3 December 2013].

[128] European Commission, "Quality of medicines and Good Manufacturing Practices," 31 January 2015. [Online]. Available: http://ec.europa.eu/health/human-use/quality/index_en.htm. [Accessed 31 January 2015].

[129] GMP Navigator, "EU-Kommission veröffentlicht erweitertes Frage-Antwort Dokument zur Written Confirmation," 4 February 2013. [Online]. Available: http://www.gmp-navigator.com/nav_news_3547_7675,7817.html. [Accessed 3 January 2015].

[130] European Commission, "Template for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC Version 2.0," 28 January 2013. [Online]. Available: http://ec.europa.eu/health/files/gmp/2013_01_28_template.pdf. [Accessed 3 January 2015].

without enclosing a “written confirmation”. [81][131] All third countries for which this rule applies are recorded in the European Commission’s “Listing of third countries” after their application, to be submitted to the EC, was checked and approved. Several documents regarding the national legislation have to be enclosed to the application, for example the English translation of all national legislation relevant to the manufacture of APIs and documents on good manufacturing practices for APIs applicable in the respective country. At present, the applications of Switzerland, Australia, Japan and the USA were approved. Concerning API manufacturing sites which are found to be non-compliant with EU GMP for active substances, a statement of non-compliance is issued and publicly available in the Union database EudraGMDP. The regulation regarding the “written confirmation” supports the purpose of preventing falsified medicinal products to enter the legal distribution chain. [30][132] About 80% of all active substances which are used for the manufacture of medicinal products in the EU are imported from third countries, such as India, China, Japan and the USA. As mentioned above the applications of the USA and Japan to be added to the “Listing of third countries” already are approved. However, it is a debatable point whether the competent authorities of the other exporting countries are able to fulfill the provisions imposed to them by the European Union. The two most important exporting countries, China and India, are of special interest in this regard. It is doubted that India and China can provide the required organizational conditions. As a first step the Indian Central Drugs Standard Control Organization (CDSCO) published a list of “written confirmations” already given to national manufacturers on its website. European authorities and importers can use this list for orientation. With respect to China, for instance, it is doubted that the China Food and Drug Administration (CFDA) is able to check and evaluate the conformity with European GMP standards of all required manufacturers, i.e. manufacturers which are not already under supervision of European authorities. The present capacities and resources, as well as the limited knowledge and experience with regard to European GMP standards are considered to be the reasons. The fact that there is no distinction between manufacturers of active substances and chemicals in China represents an additional problem regarding the inspection and control of the manufacturers’ GMP conformity. Meanwhile, it is uncertain to which extent European importers can purchase the required active substances from manufacturers which are already controlled through routine audits by European authorities.

[131] "Commission Implementing Decision of 23 January 2013," (OJ L 21, 24.01.2013, p. 36). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dec_2013_51/dec_2013_51_en.pdf. [Accessed 7 January 2015].

[132] European Commission, "Quality of medicines and Good Manufacturing Practices," 31 January 2015. [Online]. Available: http://ec.europa.eu/health/human-use/quality/index_en.htm. [Accessed 31 January 2015].

[82][133] In order to minimize the risk of drug shortages the EC relies on the collaboration between the pharmaceutical industry and the competent authorities. The pharmaceutical industry is asked to immediately inform all relevant authorities on problems concerning the lack of active substances. [83][134]

Another measure for the protection against counterfeit medicines is the extension of the opportunities to retrace medicinal products by the provision to affix safety features on the packaging. The safety features have the purpose to enable the verification of authenticity and the identification of medicinal products, even individual packs, and to provide evidence of tampering of medicinal products. These safety features shall not be removed or covered. The exception concerning re-packaging processes requires the manufacturing authorization holder to verify the respective medicinal product's authenticity and that the product has not been tampered with, prior to removing or covering the safety features. The manufacturing authorization holder is further obliged to conduct the re-packaging process without opening the immediate packaging and to apply equivalent safety features and tamper-evident features to the medicinal product. [69][135] The detailed rules for the unique identifier, to be applied to medicinal products for human use, and its verification will be laid down in a respective delegated act issued by the European Commission. After its publication the Member States have a timeframe of three years for implementation. In November 2011, the EC submitted a concept paper for public consultation on the respective delegated act. It stipulates that a randomized serialization number shall be applied to the medicinal products to ensure the uniquely identification of individual packs. With respect to the technical characteristics of the serialization number carrier the concept paper refers to three options, namely linear barcode, 2D barcode and radio-frequency identification. [84][136] Most certainly the 2D barcode will be used to display the serialization number on the packs. [85][137] The

[133] E. Podpetschnig-Fopp, "Wirkstoffimport aus Drittländern - Notfallplan der MHRA zur Sicherstellung der Arzneimittelversorgung," Pharm. Ind. 75, no. 7, pp. 1188-1190, 2013. [Online]. Available: http://www.ecv.de/download/download/Zeitschriften//pharmind/volltext/PI-2013-07-1188_PI7507_0579_podpetschnig-fopp_umbr2-web.pdf. [Accessed 16 January 2015].

[134] G. Macdonald, "EC Wants Info on API Import Law-Related Shortages," 1 July 2013. [Online]. Available: http://www.in-pharmatechnologist.com/Regulatory-Safety/EC-Wants-Info-on-API-Import-Law-Related-Shortages. [Accessed 16 January 2015].

[135] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

[136] European Commission, "Concept paper for public consultation on the delegated act on the detailed rules for the unique identifier for medicinal products for human use and its verification," 18 November 2011. [Online]. Available: http://ec.europa.eu/health/files/counterf_par_trade/safety_2011-11.pdf. [Accessed 7 January 2015].

[137] G. Jones, "The Pharmaceutical Journal - The Falsified Medicines Directive: time to get is right," 16 October 2014. [Online]. Available: http://www.pharmaceutical-journal.com/opinion/comment/the-falsified-medicines-directive-time-to-get-it-right/20066783.article. [Accessed 7 January 2015].

concept of using a 2D barcode (data matrix) allows a unique serialization of each single pack. The code can be read by a scanner so that the encrypted information about e.g. the serial number, pharmaceutical manufacturer product code, batch number and expiry date, i.e. the authenticity of the product, can be verified. The scanned barcode data is compared automatically to the registered codes in a database so that any unregistered, double or adulterated package would be identified by causing an alert. [86][138] To adhere to the cost-benefit ratio the unique identifier will not be applied to all medicines. Only prescription medicines, with a few exceptions, and some non-prescription medicines, assessed to be at risk of falsification, will be provided with this safety feature. [69][139] The prescription medicines that shall not bear the unique identifier will be listed on the so-called “white list”. The “black list” will comprise all non-prescription medicines the unique identifier shall be applied to. [85][140] The general distinction of the medicinal products to which the safety feature shall be applied is based on their classification being a subject to medical prescription or not. The Directive 2001/83/EC includes aspects to be considered regarding the classification of medicinal products into prescription medicines and non-prescription medicines. However, the final decision resides with the competent authorities of the Member States leading to differences regarding the prescription classification across the Member States. [1][141] This fact differentiates the medicines’ classification with respect to the “black list” and “white list”. All members of the distribution chain are obliged to inform the respective competent authority immediately when a falsified medicinal product or a product, suspected to be falsified, has been found. All Member States are constrained to have a system in place to collect and handle all notifications of suspected counterfeit medicines as well as suspected quality defects to prevent potentially dangerous medicinal products from reaching the patient. The information about medicines under suspicion to present a serious risk to public health must be transmitted from the Member State of occurrence to all other Member States without any delay. [69][142]

[138] "European Stakeholder Model," 2012. [Online]. Available: http://www.esm-system.eu/about-us/what-we-do.html. [Accessed 3 December 2013].
[139] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].
[140] G. Jones, "The Pharmaceutical Journal - The Falsified Medicines Directive: time to get is right," 16 October 2014. [Online]. Available: http://www.pharmaceutical-journal.com/opinion/comment/the-falsified-medicines-directive-time-to-get-it-right/20066783.article. [Accessed 7 January 2015].
[141] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].
[142] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

Concerning natural or legal persons offering medicinal products for sale at a distance the directive comprises new regulations, as well. All suppliers, intending to offer medicines for sale at a distance, need to have an authorization according to national legislation of the Member State where the supplier is established. The supplier has to inform the Member State about certain data, including name and address of the place of activity, address of the website and the starting date of activity. All medicinal products to be offered for sale at a distance must comply with the national legislation of the Member State of destination. The websites of the suppliers have to contain certain information, including the contact details of the respective competent authority and a hyperlink to the respective Member State's website, mentioned below. Moreover, every licensed website has to contain the common logo that shall be recognizable throughout the EU. [69][143] It was introduced by the European Commission adopting the Implementing Regulation 699/2014, on June 24, 2014. [59][144] Each Member State is obliged to set up a website including information on the national legislation regarding the sale at a distance of medicines, the purpose of the common logo, a national list of legally-operating online pharmacies and retailers, the risks with regard to illegally supplied medicinal products, and a hyperlink to the website of the EMA. The EMA's website also has to contain information about the common logo and the risks related to illegally supplied medicines. Furthermore, it should provide information on the respective EU legislation and it should refer to the Member States' websites and the information that is provided there. The Member State authorities and the EMA will promote information campaigns on the function of the common logo and in general on the dangers of counterfeit medicines supplied illegally via the internet. These campaigns shall enhance consumer awareness of the hazard related to counterfeit medicinal products. In addition, the Member States shall ensure that effective, proportionate and dissuasive penalties to punish counterfeiters are implemented. [69][145]

1.3.1 Pharmacovigilance framework

1.3.1.1 Definition of pharmacovigilance

Medicinal products have to meet highest standards with respect to safety, quality, and efficacy, as the basis for the receipt and the preservation of the marketing authorization.

[143] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

[144] European Commission, "EU logo for online sale of medicines," 27 June 2014. [Online]. Available: http://ec.europa.eu/health/human-use/eu-logo/index_en.htm. [Accessed 6 January 2015].

[145] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

[1][146] In the European Union (EU), former European Economic Commission (EEC) established in 1957, the submission of data regarding the safety, efficacy and quality of a medicinal product to at least one competent authority within the EEC for approval, prior marketing, became mandatory by law with the passage of the directive 65/65/EEC, in 1965. [87][147] [88][148]

In addition to the accomplishment of clinical studies prior to the marketing authorization of a medicinal product, it is the marketing authorization holder's duty to implement a post-marketing surveillance system, also denoted as pharmacovigilance system, to examine if the authorized product remains within its established benefit-risk balance. [1][149] This examination is based on the evaluation of collected data with regard to suspected adverse reactions of medicinal products. Therefore, pharmacovigilance has been defined by the World Health Organization as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem*". [89][150]

1.3.1.2 Purpose of pharmacovigilance

In 1968 the WHO promoted a pilot research project for International Drug Monitoring. At the end of 2010, already 134 countries were part of it. The initial reason why the WHO established the program for International Drug Monitoring was the thalidomide disaster detected in 1961. [10][151] At that time, the documentation of and investigation in adverse events concerning medicinal products, as well as the communication of potential safety signals across countries were insufficient. The quick implementation of corrective and preventive actions, based on an appropriate evaluation of the adverse event reports

[146] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].
[147] H. Rahalkar, "Historical Overview of Pharmaceutical Industry and Drug Regulatory," 29 September 2012. [Online]. Available: http://www.omicsgroup.org/journals/historical-overview-of-pharmaceutical-industry-and-drug-regulatory-affairs-2167-7689.S11-002.pdf. [Accessed 11 November 2013].
[148] "Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products," (OJ L 22, 9.2.1965, p. 369). [Online]. Available: http://www.echamp.eu/fileadmin/user_upload/Regulation/Directive_65-65-EEC__-__Consolidated_Version.pdf. [Accessed 11 November 2013].
[149] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].
[150] "Volume 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use," September 2008. [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. [Accessed 30 October 2013].
[151] "The Importance of Pharmacovigilance - Safety Monitoring of medicinal products, WHO 2002," [Online]. Available: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. [Accessed 29 October 2013].

concerning thalidomide, could have saved thousands [90][152] of children of being malformed. For that reason, the need for an internationally applicable detection system for evaluation of information about adverse effects of medicines was reaffirmed on the Sixteenth World Health Assembly in 1963. [10][153] As a result, the WHO pharmacovigilance program came into effect. In 1971 the WHO held a consultation meeting where it was decided to advocate the establishment of national centers for drug monitoring, to provide guidelines and to identify potential contribution by national centers to the international system. [10][154]

Today, the WHO Collaborating Center for International Drug Monitoring, set in Uppsala, Sweden, coordinates the membership of the WHO program for International Drug Monitoring and provides essential resources for regulatory agencies, health professionals, researchers and the pharmaceutical industry. [91][155] It is also known as the Uppsala Monitoring Center (UMC). Requirements on pharmaceutical systems have been included into drug regulations worldwide.

At present, every competent authority of the WHO Member States as well as every marketing authorization holder for medicinal products have implemented systems [10][156] wherein data of adverse event reports concerning pharmaceutical products is collected and evaluated. Hence, national drug regulatory authorities are informed immediately if a report points to a serious safety signal of adverse effects that demand rapid corrective actions to ensure public health. Due to negative historical examples, it is the aim of today's pharmacovigilance to enhance patient safety in relation to the use of medicines and to support public health by providing reliable, balanced information for the effective assessment of the benefit-risk balance of medicines. [92][157]

1.3.1.3 MAH's obligations

In the Directive 2001/83/EC, articles 101 to 108, the EU gives instructions how to handle the surveillance of authorized medicinal products. According to this Directive all Member States

[152] J. H. Kim and A. R. Scialli, "Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease (Oxford Journals; Toxicological Sciences Volume 122, Issue 1, pp. 1-6)," 2 April 2011. [Online]. Available: http://toxsci.oxfordjournals.org/content/122/1/1.full. [Accessed 22 November 2013].
[153] "The Importance of Pharmacovigilance - Safety Monitoring of medicinal products, WHO 2002," [Online]. Available: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. [Accessed 29 October 2013].
[154] "The Importance of Pharmacovigilance - Safety Monitoring of medicinal products, WHO 2002," [Online]. Available: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. [Accessed 29 October 2013].
[155] "WHO-UMC homepage," [Online]. Available: http://www.who-umc.org/DynPage.aspx. [Accessed 30 October 2013].
[156] "The Importance of Pharmacovigilance - Safety Monitoring of medicinal products, WHO 2002," [Online]. Available: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. [Accessed 29 October 2013].
[157] "WHO - Pharmacovigilance," [Online]. Available: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. [Accessed 30 October 2013].

of the European Union and marketing authorization holders of medicinal products have to establish a pharmacovigilance system in order to collect and to evaluate all information about potential risks regarding medicinal products, with particular reference to adverse reactions and interactions. [1][158] However, not only information about adverse drug reactions under normal conditions of use shall be in scope of the pharmacovigilance system, but also any data on misuse and abuse of the drugs that may have an impact on the benefit-risk balance of the products. [1][159] Such information is summarized in a risk management plan including the safety risk assessment and defined risk minimization measures. The marketing authorization holders are expected to provide a succinct update of the worldwide safety experience of a medicinal product together with a critical evaluation of its benefit-risk balance considering new or changing information to the competent authorities at defined time points post-authorization. These reports are called periodic safety update reports (PSURs) [89][160], nowadays also denoted as periodic benefit-risk evaluation reports (PBRERs) since the reports provide a greater emphasize on the benefit of medicinal products. [93][161]

Every marketing authorization holder is obliged to appoint a qualified person for pharmacovigilance (QPPV) who is responsible for the permanently and continuously post authorization surveillance. [1][162] The duties and responsibilities of the QPPV are clarified in the Directive 2001/83/EC, as well. Beyond the territory of the EU the Directive affects also all other countries. Marketing authorization holders located in non-EU countries have reporting requirements towards the competent authorities within the EU with respect to medicinal products that are authorized in at least one EU country. The marketing authorization holder is required to record and report suspected serious adverse reactions promptly to the competent

[158] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].
[159] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].
[160] "Volume 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use," September 2008. [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. [Accessed 30 October 2013].
[161] European Medicines Agency, "ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)," January 2013. [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500136402.pdf. [Accessed 27 January 2014].
[162] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].

authority, latest within 15 calendar days[163], regardless whether the incident occurred within the territory of an EU Member State or in a country outside of the EU. [1][164]

In the context of the already mentioned Pharmaceutical Package the new pharmacovigilance legislation, comprising a directive (Directive 2010/84/EU) and a regulation (Regulation EU No 1235/2010), was adopted by the European Parliament and the European Council in December 2010. The new legislation serves the purpose to strengthen and to simplify the European pharmacovigilance system and to provide the public with helpful information about the benefit-risk aspects of medicinal products. In October 2012, the new pharmacovigilance legislation was amended again by Directive 2012/26/EU and Regulation EU No 1027/2012. The amendment's purpose is to further support the protection of patient health. It refers e.g. to the marketing authorization holder's obligation to notify the EMA immediately in case of the withdrawal of a medicinal product. The notification also has to include the reasons for the withdrawal of the respective product from the market. [94][165] To provide specific guidelines regarding the provisions related to the EU safety monitoring system and the requirements with respect to pharmacovigilance procedures, the EMA released the good pharmacovigilance practice (GVP) guidelines which comprise multiple modules. 12 modules (I – X, XV and XVI) are already effective. 3 modules (XI, XII and XIV) are still in development, while the development of module XIII was stopped. Its contents will be included in module XII. [95][166] Thus, the document Volume 9A of "The rules governing medicinal products in the European Union - Pharmacovigilance" is being replaced by the 15 GVP modules. [96][167]

In Germany the handling of pharmacovigilance is settled in the AMG, §§ 62-63c. The German competent authorities such as the BfArM and the Paul-Ehrlich-Institute (PEI) collaborate closely and interact with the WHO, the EMA and FDAs of other countries, amongst others. [53][168] Every health facility, e.g. pharmacies and medical practices, is

[163] 15 calendar days for serious cases, 90 calendar days for non-serious cases
[164] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].
[165] European Medicines Agency, "2010 Pharmacovigilance Legislation," 2013. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&mid=WC0b01ac058033e8ad. [Accessed 3 December 2013].
[166] European Medicines Agency, "Good Pharmacovigilance Practices," 2014. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp. [Accessed 31 January 2015].
[167] European Commission, "The EU Phamacovigilance System," 2013. [Online]. Available: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm. [Accessed 3 December 2013].
[168] "German Medicinal Products Act; Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG)," as announced on 12 December 2005 (Federal Law Gazette I p. 3394); last amended on 10 October 2013 (Federal Law Gazette I p. 3813). [Online]. Available: http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf. [Accessed 26 November 2013].

obliged to report any adverse drug reaction, which is brought to their attention, pursuant to the graduated scheme which is given by governance as a guide so that everyone knows to whom the information has to be provided. [53][169]

The law includes special regulations with respect to pharmaceutical companies. According to § 63a every company must implement and continuously run a pharmacovigilance system. A named qualified person, responsible for pharmacovigilance, has to account for the required qualification and to ensure the pharmacovigilance system is managed according to the legislative regulations. Furthermore, the qualified person is the interface to the competent authorities. [53][170]

[169] "German Medicinal Products Act; Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG)," as announced on 12 December 2005 (Federal Law Gazette I p. 3394); last amended on 10 October 2013 (Federal Law Gazette I p. 3813). [Online]. Available: http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf. [Accessed 26 November 2013].

[170] "German Medicinal Products Act; Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG)," as announced on 12 December 2005 (Federal Law Gazette I p. 3394); last amended on 10 October 2013 (Federal Law Gazette I p. 3813). [Online]. Available: http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf. [Accessed 26 November 2013].

CHAPTER TWO – PHARMACEUTICAL COMPANYS' ANTI-COUNTERFEITING MEASURES

As counterfeit medicines pose a major risk to the safety of patients, and thus to public health, pharmaceutical companies should endeavor to contribute to the combat against counterfeiting of medicinal products, far beyond the obligations that are laid down in statutory provisions. There are several options for pharmaceutical companies to implement anti-counterfeiting measures. Some examples of these measures are explained below including data monitoring and evaluation, collaboration with authorities, investigative measures, legal measures, technological measures, awareness-raising, review of established anti-counterfeiting procedures and activities.

2.1 Monitoring and data evaluation

Besides the monitoring and reporting obligation of marketing authorization holders regarding suspected counterfeit reports towards the competent authorities, the MAH should also establish a monitoring system for the purpose of internal decision-making with respect to the implementation of required anti-counterfeiting actions. The monitoring and evaluation of counterfeit-relevant data provide basic information about affected products of the company's portfolio and about the countries in which the market is definitely affected by the counterfeit problem. Based on this information, respective needs for the implementation of anti-counterfeiting measures can be identified and a better decision made with regard to the focus and the markets in scope of the anti-counterfeiting activities to be conducted.

2.1.1 Monitoring concept

Various concepts regarding the monitoring and evaluation of counterfeit-related data are possible. One suggestion for an appropriate concept would be the combination of an ad-hoc monitoring with a long-term monitoring of counterfeit incidents. The ad-hoc monitoring should be conducted within short time intervals, e.g. on a weekly basis. Its purpose would be the identification of counterfeit incidents related to serious consequences, e.g. serious injury of a patient, which would require immediate investigative measures or respective actions. The long-term monitoring should be conducted within greater time intervals, e.g. on a monthly or quarterly basis, to serve the purpose of identifying counterfeit incidents which may be connected to one or multiple aspects, and therefore could point to an increase in counterfeit occurrences. The respective aspects to be considered include the following:

- Affected products
- Affected countries
- Batch numbers
- Incident types
- Reporter types

The monitoring concept should further comprise a notification concept in case of the identification of respective counterfeit incidents or clusters of linked counterfeit incidents. The notification concept should include standards, detailing the required information to be contained in the notification and the named recipient of the notification.

2.2 Collaboration with authorities

Besides the reporting obligations the marketing authorization holders have towards the competent health authorities, other collaborative activities with regard to the topic of counterfeit medicines can be carried out by pharmaceutical companies. Such activities serve the purpose of supporting the authorities with the exchange of knowledge, information and experience. The collaboration is not just limited to health authorities only. Customs, criminal investigation offices and the police can also be included. A pharmaceutical company can support authorities with regard to case-related requests. In case the authorities examine a cargo of medicinal products and become suspicious, they can contact the respective marketing authorization holder for information regarding the cargo e.g. valid batch numbers or designated distribution routes. If the authorities discover medicinal products of which the authenticity is in doubt, the respective marketing authorization holder can dispatch a representative. The representative can carry out a first assessment by comparing the visual characteristics of the suspected product with a retention sample or he can check if required anti-counterfeiting safety features have been applied to the suspected product. Another possibility is chemical analysis of the suspected product by the pharmaceutical company with the results being forwarded to the authorities. Furthermore, possible case-related actions can be discussed and agreed upon with the authorities in this context.

In general, marketing authorization holders can also provide the authorities with informative literature about their products. This information could contain details about product-specific visual properties, e.g. tablet dimensions, pictures of the single product parts including primary and secondary packaging as well as the dosage form and pictures of overt (visible) anti-counterfeiting security features applied to the respective product. Through these means,

the authorities are able to conduct a first assessment. Moreover, pharmaceutical companies can provide topic-specific training about counterfeit medicines to the authorities and they can communicate topic-specific contact persons within their companies which further improves the collaboration and the exchange of information. In addition, when authorities conduct raids pharmaceutical companies can support them by providing required informative literature or by dispatching an expert in that field to participate.

Pharmaceutical companies can also collaborate by joining forces and thus, support authorities substantially and financially in conducting anti-counterfeiting campaigns e.g. education campaigns which inform patients about the risks counterfeit medicinal products can cause. The Pharmaceutical Industry Initiative to Combat Crime, coordinated by INTERPOL, is one current example for such a public private partnership between the authorities and the pharmaceutical industry.

Moreover, marketing authorization holders can approach the customs and fill in an application for action. As a result, the customs are requested to take action if they detect medicinal products that are suspected to be falsified or are suspected to infringe on the intellectual property rights of the marketing authorization holder. The applications for action to be submitted to the customs have to contain product-specific information provided by the respective pharmaceutical companies. The collaboration of the private sector and the customs has gained in importance. Over the years from 2000 to 2010, the number applications of action, submitted to the EU Customs by holders of intellectual property rights, increased from about 1000 to over 18.000. [11][171]

2.3 Investigative measures

Pharmaceutical companies can collect information about suspicious sources of counterfeit medicinal products which can be based on the information of a case report or a cluster of case reports with respect to counterfeit incidents related to a specific source. Another possibility to detect suspicious sources of counterfeit drugs is the targeted search for dubious online providers of medicinal products using search engines. The marketing authorization holder may look for internet pharmacies offering products from its portfolio and check if the respective online pharmacies show characteristics that would raise the suspicion that they are acting illicitly e.g. hiding a physical address or offering prescription-only medicines without demanding a prescription. Additionally, the pharmaceutical companies can conduct

[171] "Report on EU customs enforcment of intellectual property rights - Results at the EU borders - 2010," 2011. [Online]. Available: http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/statistics_2010.pdf. [Accessed 13 November 2013].

"active online listening" reading comments in public internet forums in the search for references to potential providers of counterfeit medicines. After suspicious sources have been identified, the marketing authorization holders can then try to compile more detailed information about the respective providers using publicly accessible data or by hiring a specialized consultant agency to conduct the investigation.

In collaboration with the authorities test purchases can be initiated. Consequently, the purchased products are analyzed visually and chemically to investigate if the identified suspicious sources in fact offer and provide counterfeit medicines.

This information can be compared with data from other known cases of a suspected or even confirmed criminal activity regarding counterfeit medicines. The compiled and edited data can be provided to the respective authorities for further investigation or if the information is sufficient, the pharmaceutical company can press charges.

2.4 Legal measures

As mentioned before a marketing authorization holder can press charges against persons or potentially criminal organizations under suspicion of violating its intellectual property rights or patents.

2.5 Technological measures

The purpose of anti-counterfeiting technologies and security features is to exacerbate the access of counterfeit medicinal products to the supply chain without being detected. Security features that are applied to the packaging materials of medicinal products or are even included in the formulation of a drug, allow a check of authentication of the respective product. The characteristics of security features should make their imitation difficult with regard to highly sophisticated or very cost-intensive technologies. Hence, anti-counterfeiting security features have the purpose to enable the distinction between genuine and counterfeit medicinal products. Depending on the type of technology that is used, industrial experts, authorities or the public should be able to check the authenticity. [97][172]

[172] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

2.5.1 Features for products authentication

2.5.1.1 Overt security features

Overt security features are visible markers that are usually applied on the outer packaging and the primary packaging of a medicinal product. Such features are meant to be used by the end-user for the verification of authenticity of the product, comparable to the visible security features applied to banknotes. Overt security features require sophisticated technologies, or special raw materials to be produced, to ensure that the attempt to copy them is as difficult as possible. One condition for the correct and successful use of these features is the education of the end-user about their visual characteristics and the products to which they are applied. Otherwise, there is the risk that barely sophisticated copies of overt security features are sufficient to deceive the end-user.

Examples for overt security features:

- Holograms (images with some kind of 3-dimensional illusion including a range of colors and designs)
- Optical variable device (similar to holograms, but mostly without the 3D component)
- Color shifting inks (inks based on metallic components in an opaque layer shifting colors depending on the angle of the viewer)
- Security graphics (fine line color printing incorporating several design elements e.g. guilloches, line modulation and line emboss; semi-overt as e.g. a magnifier is required)
- Sequential product numbering (unique number applied to each single pack in a batch and to be checked accessing data in a database; semi-overt)
- On-product marking (special images or codes placed on solid dosage forms) [97][173]

2.5.1.2 Covert security features

Covert security features are hidden features usually applied to the packaging materials of a medicinal product. The information about the characteristics of these features, their location on the packaging and the products on which they are applied is confidential. The purpose of covert security features is to allow an in-house verification of the product's authenticity. The verification is done by authorized experts, usually company-internal personnel. In addition to

[173] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

the necessary knowledge about the hidden security features, devices including magnifiers or UV-light are required to conduct the verification.

Examples for covert features:

- Invisible printing (printings not visible to the naked eye but only under special conditions e.g. UV illumination)
- Embedded images (invisible images that require a filter to be viewed)
- Digital watermarks (digitally encoded data that require the use of a reader and special software to be verified)
- Hidden marks and printing (features require special attention to be detected and therefore are dependent on secrecy)
- Anti-copy or anti-scan design (fine line background patterns, invisible to the naked eye, that only show a latent image when scanned or copied)
- Laser coding (codes can include e.g. variable data and can be applied to different materials including metal, plastic and carton)
- Substrates (markers e.g. chemical reagents, UV fluorescing fibers or metallic threads are incorporated within parts of the products' packaging material)
- Odor (micro-encapsulated distinctive odors) [97][174]

2.5.1.3 Forensic markers

Forensic markers may be considered as a sub-group of the covert security features as they are as well hidden to the naked eye. But the highly sophisticated technologies that are required for the verification of authenticity present the difference. Dedicated field test kits or laboratory tests are necessary to conduct the check of authentication based on forensic markers. Due to the special technologies in use, this kind of anti-counterfeiting security features is cost-intensive; however very secure against duplication. Usually, forensic markers are undetectable by normal analytical methods.

Examples for forensic markers:

[174] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

- Chemical taggants (require the use of highly specific reagent systems to be detected)
- Biological taggants (detectable at extremely small amounts using highly specific "lock and key" reagent kits)
- DNA taggants (reaction of the DNA taggant with a recombinant strand is detectable with a dedicated device)
- Isotope ratios (laser fluorescence or magnetic resonance techniques are used to determine the composition of isotopes which acts as a fingerprint of the compounds of the product)
- Micro-taggants (require the use of a microscope to examine the coded information that the microscopic particles contain) [97][175]

2.5.2 Tamper-evident packaging

"*Tamper-evident packaging means packaging that has an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible or audible evidence to consumers that tampering may have occurred*." [98][176]

Examples for tamper-evident packaging features:

- Transparent film wrappers (entire product pack is wrapped securely in the transparent film, which is of a distinctive design to make sure it cannot be replaced unnoticed)
- Blister or strip packs (individual doses e.g. tablets are sealed in plastic and / or foil so that the access to the single doses is not possible without leaving visible evidence of entry)
- Heat shrink bands or wrappers (seal the union of the cap and outer packaging of a product tightly after being shrunk by heat)
- Pouches and sachets (have to be broken or ripped to get access to the contained product)

[175] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

[176] TGA - Therapeutic Goods Administration (Australia), "Code of Practice for Tamper-Evident Packaging (TEP) of Therapeutic Goods," June 2003. [Online]. Available: http://www.tga.gov.au/pdf/packaging-tamper-evident-cop.pdf. [Accessed 10 January 2014].

- Breakable caps and tear-away caps (caps include a component that breaks away on opening or has to be torn away in order to gain access to the product)
- Tape seals (tape with a distinctive design seals all flaps of a folding box or the cap of a bottle)
- Container mouth inner seals and sealed metal tubes (nozzle of the primary packaging is sealed which makes gaining access to the product impossible without breaking the seal and thus leaving visible evidence) [98][177]

2.5.3 Track and trace technologies

In the pharmaceutical sector track and trace applications have the purpose of enhancing the supply chain control with regard to medicinal products. During the manufacture of a pharmaceutical product a unique identity is assigned to each stock unit, which usually comprises product-specific information including the product name and strength, and unit-specific information including batch number and expiry date. The unique identity is meant to remain with the stock unit through the entire distribution chain to the final dispenser, e.g. pharmacist or physician, and to the end-user. The unique identity may be assigned to the product unit in form of a code that can be read using a dedicated device. Then, the respective information included in the code can be accessed via a secure database. Using track and trace technologies allows the authentication of the coded data at any time. Moreover, the application enables the tracking of product units through the supply chain and provides the traceability on the history of product units. Therefore, track and trace applications present another opportunity to exacerbate counterfeit or diverted medicinal products from entering the supply chain without being detected. Some examples for track and trace applications are provided below. [97][178]

2.5.3.1 Serialization

The serialization should be based on non-sequential numbering. The level of security is enhanced if the sequence of numbers to be applied, to the product units, is not predictable. Random serialization, based on highly secure algorithms, provides the maximum in security. The serial number is, in fact, not immune from being copied or adulterated; however by means of the data check in the database duplicates or invalid serial numbers can be

[177] TGA - Therapeutic Goods Administration (Australia), "Code of Practice for Tamper-Evident Packaging (TEP) of Therapeutic Goods," June 2003. [Online]. Available: http://www.tga.gov.au/pdf/packaging-tamper-evident-cop.pdf. [Accessed 10 January 2014].

[178] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

identified. Units with invalid product details, expired units or those which appear in the wrong market will also be detected and raise a system alert.

2.5.3.2 Bar codes

Bar codes are security features that are meant to be applied to the packaging material of a medicinal product. Their use allows the verification of the product identity down to the unit pack level by incorporating the respective information for each unique pack in a high-density linear or 2-dimensional bar code, which is applied to the pack and can be read by a dedicated scanner. The scanned information is compared to the reference information in a central database. One popular example of the bar codes is the 2D data matrix code. [97][179] As already mentioned in paragraph 1.3, this kind of code shall serve as one of the anti-counterfeiting security features that are stipulated according to the Falsified Medicines Directive to be applied to the most prescription-only medicines and eventually some non-prescription medicines in the EU.

2.5.3.3 Unique surface marking or topography

A unique fingerprint is applied to the surface of each single pack of a batch which is registered in a database using a dedicated device. This process is done at batch manufacture. Afterwards the fingerprint can be used for the check of authentication of each single pack. Another possibility to mark each single pack of a batch for later verification is to apply a pseudo-random image to each pack. The image may consist of a specific pattern of dots or lines printed on one part of the product packaging e.g. the carton. Then each image is scanned into the batch database to serve as a reference for the product identity check. [97][180]

2.5.3.4 Radio frequency identification (RFID)

A radio frequency identification tag is an electronic tag which can be applied to a medicinal product and can be read using radio waves emitted by the reader. The tag has a microchip in its center which contains product-specific information that allows the identification of a single pack. The major advantage of the RFID technology in comparison to the use of bar codes or unique surface markings is the readability of the RFID tag at a distance. The tag does not need to be in line of sight of the reader considering that the range and sensitivity are

[179] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].
[180] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

dependent on the radio frequency. The disadvantage of the RFID technology is that some materials and liquids have the potential to absorb radio signals, thus making it unsuitable for certain medicinal products or packaging materials. [99][181] [97][182]

2.5.3.5 Portable devices for the detection of counterfeit medicines

Portable devices for the detection of counterfeit medicinal products allow the verification of authenticity of pharmaceutical products in the field and within a short time of investigation. Additionally, such portable technologies are also designed to be used by non-experts as the analysis methods save the complex sample preparation. Moreover, samples can be analyzed directly at points of the supply chain, e.g. at transit or distribution, or at places of detection of suspicious goods without sending the samples to central laboratories for investigation. To guarantee that the verified samples remain undamaged, non-destructive testing is required. The demand for such portable devices comes particularly from health authorities and other law enforcement agencies, as well as security personnel of pharmaceutical companies. Many portable devices are based on vibrational spectroscopies such as Raman spectroscopy and infrared (IR) spectroscopy. The generated spectra then act as fingerprints which can be compared with spectra collected in a reference library to verify if the analyzed sample complies with the genuine product. Raman methods use a single-frequency laser and are very specific. Therefore, the methods are suitable for the detection of specific chemical compounds e.g. the API in a sample. If a broader analysis is needed to verify if a sample complies with the genuine product, the IR spectroscopy is more suitable. The IR analysis covers the API and non-active ingredients of samples so that fine differences of similar formulations can be detected. Many Raman and some near-IR devices can measure through packaging materials e.g. clear plastic while the signals from such materials often interfere with the signals of the API in the mid-IR spectrum. [100][183]

[181] US Food and Drug Administration, "Radio Frequency Identification (RFID)," 13 August 2013. [Online]. Available: http://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/ElectromagneticCompatibilityEMC/ucm116647.htm. [Accessed 13 January 2014].

[182] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available: http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

[183] A. M. Thayer, "Chemical & Engineering News "Instrumentation Firms Develop Portable Technology To Detect Counterfeit Drugs" Volume 90, Issue 33, pp.11-15," 13 August 2012. [Online]. Available: http://cen.acs.org/articles/90/i33/Instrumentation-Firms-Develop-Portable-Technology.html. [Accessed 14 January 2014].

In the following table some examples for portable devices are given.

Analytical method / device	Device name	Company name
Raman spectroscopy	TruScan RM	Thermo Fisher Scientific Inc.
Near-IR spectroscopy	MicroPhazir	Thermo Fisher Scientific Inc.
FTIR spectroscopy	Multipurpose analyzer	Bruker Optics (Bruker Cooperation)
FTIR microscope	Lumos	Bruker Optics (Bruker Cooperation)
FTIR spectroscopy	ExoScan 4100	Agilent Technologies
IR spectroscopy	Spectrum Two portable IR system	PerkinElmer Inc.
Visible / near-IR spectrometer	LabSpec	ASD Inc.

Table 1: Examples for portable devices for the detection of counterfeit medicines [100][184]

2.5.4 Recommendation regarding technological ACF measures

A combination of multiple anti-counterfeiting technological measures may be the best approach to minimize the opportunities of counterfeiters to copy medicinal products and enter the supply chain unnoticed. Therefore, track and trace technologies should be used to control the supply chain by authorities, stakeholders of the supply chain and, at best, also by the end-user. Furthermore, security features with the purpose to ascertain the authenticity of a product should be applied to medicinal products in combination with tamper-evident packaging to make sure that a product tampered with is detected immediately.

2.6 Awareness-raising

Awareness-raising is equally as important in the protection against counterfeiting of medicines. As already mentioned, overt security features help the patients, healthcare professionals, or any other stakeholder of the legal supply chain to distinguish between genuine and counterfeit medicinal products. If there is no awareness of the overt security features or the visual characteristics of a genuine package, no doubt of authenticity will be raised if the respective security features are missing. Therefore, education of the stakeholders, especially patients, on what to be aware of and whom to report to, is of utmost importance.

Furthermore, it is necessary to caution patients against the hazard counterfeit medicines pose to their health. To this extend, there is the need for public understanding of the major differences between counterfeit luxury goods e.g. clothing and accessories and counterfeit medicinal products and the impact they can have on health and safety. The difference

[184] A. M. Thayer, "Chemical & Engineering News "Instrumentation Firms Develop Portable Technology To Detect Counterfeit Drugs" Volume 90, Issue 33, pp.11-15," 13 August 2012. [Online]. Available: http://cen.acs.org/articles/90/i33/Instrumentation-Firms-Develop-Portable-Technology.html. [Accessed 14 January 2014].

between original drugs (non-generic), approved generic drugs and counterfeit drugs also needs to be explained.

2.7 Review of anti-counterfeiting procedures within a pharmaceutical company

Adopting measures to raise awareness of counterfeit medicines will influence the reporting behavior of patients and healthcare professionals in a positive way. This will result in a higher number of suspected counterfeit incident reports. A global pharmaceutical company, being active in terms of awareness-raising, has to ensure that all these case reports are collected and processed with the same due diligence in all its affiliates. Thus, a consistent knowledge on the topic, responsible functions and contact persons, required obligations, and standardized processes is essential for a gapless case handling, as well as high data consistency and quality. This is necessary to ensure that data monitoring and evaluation activities lead to results which in turn represent the basis for decision-making on further required actions. In order to check if all affiliates comply with the respective requirements a pharmaceutical company should carry out appropriate measures to review the current status of all implemented anti-counterfeiting procedures and activities. As a result, gaps and needs for support can be identified and required measures can be adopted.

CHAPTER THREE – DATA MONITORING AND EVALUATION

3.1 Influence of counterfeit medicines on the benefit-risk profiles of genuine drugs

The evaluation of the benefit-risk profile of a medicinal product is based on the collection and evaluation of all adverse event (AE) reports related to the respective product. Since counterfeit medicines mimic genuine medicinal products, it can be assumed that adverse drug reactions, caused by undetected counterfeit drugs, can falsely impact the benefit-risk profile of the respective genuine medicinal products.

According to the WHO and the UMC an adverse event is defined as:

> "*Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment*" [101][185]

According to the WHO and the UMC an adverse drug reaction is defined as:

> "*A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function*" [101][186]

Based on the results of counterfeit seizures major quantities of counterfeit medicines can be expected to be on the market. Since only rather few suspected counterfeit incidents are reported by patients and healthcare professionals, it is assumed that the majority of counterfeit medicinal products is consumed without questioning whether the medicines are genuine or not.

Therefore, concerning its portfolio, a marketing authorization holder may receive reports about the occurrence of adverse events that were actually caused by counterfeits of the respective genuine products. If such an AE report is received in relation to a suspected counterfeit incident, the respective complaint sample will be analyzed and its authenticity checked. In addition to the authentication check, it is assed if the reported adverse event is actually related to the complaint sample. In the case that no sample is available, its authenticity cannot be checked. Thus, the MAH is obliged to include the respective report in

[185] World Health Organization, Uppsala Monitoring Center, "Glossary of terms used in Pharmacovigilance," January 2013. [Online]. Available: http://www.who-umc.org/graphics/27400.pdf. [Accessed 6 February 2014].
[186] World Health Organization, Uppsala Monitoring Center, "Glossary of terms used in Pharmacovigilance," January 2013. [Online]. Available: http://www.who-umc.org/graphics/27400.pdf. [Accessed 6 February 2014].

the respective genuine product's benefit-risk evaluation, since the report could not be confirmed to be related to a counterfeit product. If the AE report is received without the suspicion of a counterfeit incident and also no suspicion is raised after the receipt of the complaint sample, the authentication check is omitted, as the authenticity of the reported product is not in doubt. Thus, it is possible that a marketing authorization holder collects adverse event cases which are actually not related to the genuine medicines, the MAH is responsible for, but to their counterfeits. As it remains unknown, that the adverse events were actually caused by counterfeits of the genuine medicinal products, the reports are included in the evaluation of all AE reports related to the respective genuine products to assess the products' benefit-risk profiles. Hence, the counterfeit products would have an influence on the evaluation of the benefit-risk profiles of the genuine medicines.

Based on this assumption, one aim of this thesis is to examine if a correlation between documented AE data and documented counterfeit incidents data can be identified. And, if this is the case, if AE data can serve as a basis for the monitoring of the potential counterfeit presence on the market. For that reason, an analysis of the AE data and the counterfeit incidents data, collected in the company's global pharmacovigilance data base and the company's global technical complaint database, has been conducted.

3.2 Framework of data analysis

3.2.1 Data sources

The adverse event data represents the basis for the data analysis. The collected data has been examined and compared to the collected counterfeit incidents data, serving as reference data.

All case reports, related to the suspicion of a counterfeit incident concerning the company's portfolio, that are brought to the company's attention are collected and documented in its global, company-internal technical complaint database. This database holds all reports that are related to technical complaints and suspected counterfeit incidents. In case, a reporter – e.g. a patient, a healthcare professional (HCP) or an authority – questions the authenticity of a medicinal product and reports the suspicious product to the company, the case report is entered as a suspected counterfeit incident in the global technical complaint database and is assessed accordingly, i.e. all (available) parts of the suspicious product are investigated to confirm or refuse its authenticity. Subsequently, the reporter is informed about the result of investigation, except national limitations prohibit the direct contact to the reporter.

All adverse event reports, concerning the company's portfolio, that are brought to its attention are collected and documented in its global, company-internal pharmacovigilance database. All AE reports are investigated to confirm or refuse the correlation between the reported adverse event and the reported medicinal product. Also, the reporter is informed about the result of investigation, except national limitations prohibit the direct contact to the reporter.

The Pharmacovigilance organization is the owner of the global pharmacovigilance database and the Quality organization is the owner of the global technical complaint database.

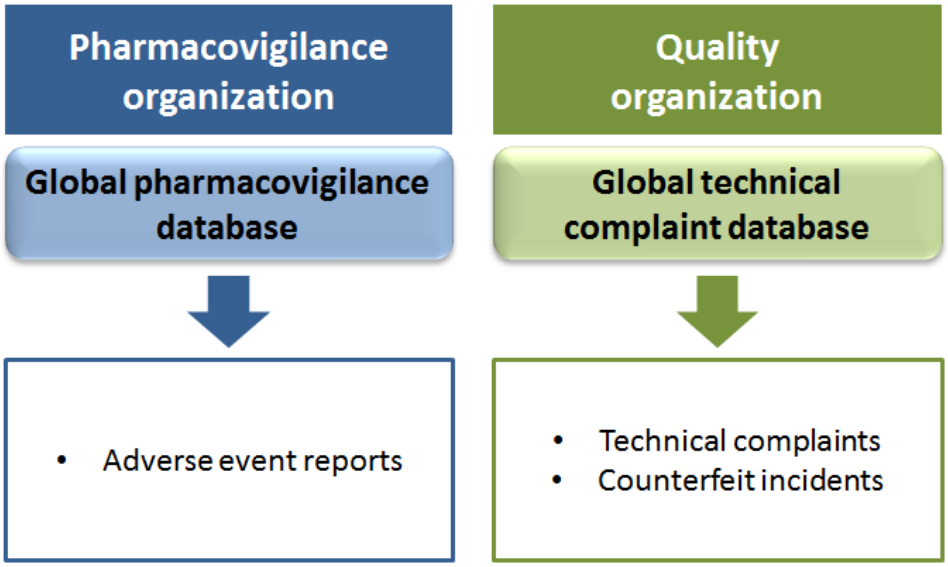

Figure 11: Data sources of AE cases and counterfeit incidents

Case reports related to both, one or multiple adverse events and a suspected counterfeit incident, are entered into both, the global pharmacovigilance database and the global technical complaint database and are marked and assed accordingly.

In the context of this thesis specific data has been selected that was considered suitable to serve as the basis for the analysis of a potential correlation between AE reports and confirmed counterfeit incidents. With respect to the counterfeit incidents all data related to a confirmed falsification has been selected from the global complaint database. Regarding the adverse event reports all data related to a lack of drug effect has been selected from the global pharmacovigilance database.

3.2.2 Special focus on falsifications

As outlined in paragraph 1.1.2.1, this incident type refers to counterfeit medicines which have been completely or partly manufactured by an unauthorized third party. The counterfeit part can be the dosage form, the packaging materials or both. The dosage form can contain the wrong ingredients, the wrong amount of the correct API or no API, at all. Moreover, it could

"*have been manufactured in unsanitary, unsafe conditions"* [7][187]*.* Even if the dosage form is genuine, any manipulation including illegal repackaging and bad storage conditions can have a negative impact on the medicinal product's quality. Therefore, the quality and with it the safety and efficacy of such medicines are not or no longer guaranteed. As a result, falsifications have the highest potential to impact health in a negative way and thus, to cause adverse events, or to lack the desired pharmaceutical effect, when administered.

3.2.3 Special focus on lack of drug effect reports

As outlined in paragraph 1.1.3, counterfeit medicines can impact patients in different ways depending on the characteristics of the counterfeit medicine and the characteristics and indication(s) of the genuine medicinal product that has been counterfeited. Adverse events possibly caused by counterfeit medicines show a broad variety and can be very unspecific. For instance, impurities, allergenic or toxic ingredients can cause adverse events including head ache, nausea or gastrointestinal disorders and (allergic) skin reactions. Such reactions can be caused by genuine medicinal products, as well, and are often even listed adverse drug reactions for the respective drug.

According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) a listed adverse drug reaction is defined as:

"*An ADR whose nature, severity, specificity and outcome are consistent with the information in the CCSI*" [102][188]

[187] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].

[188] International Conference on Harmonization, "Guidance for Industry E2C Clinical Data Safety Management: Periodic Safety Update Reports for Marketed Drugs," November 1996. [Online]. Available: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073102.pdf. [Accessed 12 February 2014].

The ICH defines the Company Core Safety Information (CCSI) as:

> "*All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.*" [102][189]

The ICH defines the Company Core Data Sheet (CCDS) as:

> "*A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology, and other information concerning the product.*" [102][190]

As already presented in figure 4 "What exactly is in counterfeit medicines?" (paragraph 1.1.3.2), the majority of identified imitations contain no active ingredients. The results of in-house analyses of detected and confirmed imitations also revealed that the majority of the respective samples contained too little of the declared API or no API, at all. With regard to medicines for hormonal contraception also wrong amounts of the declared API have been found, e.g. in combined oral contraceptives the content of one of the hormones was too high while the content of the other one was too low. The expected adverse event caused by this type of counterfeit medicines would be the failure of the desired pharmaceutical effect, also denoted as lack of efficacy or lack of drug effect (LODE).

According to the WHO and the UMC efficacy is defined as:

> "*The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research conditions*". [101][191] Therefore, the lack of efficacy or lack of drug effect is the "*evidence of less than the expected effect of a product*". [103][192]

[189] International Conference on Harmonisation, "Guidance for Industry E2C Clinical Data Safety Management: Periodic Safety Update Reports for Marketed Drugs," November 1996. [Online]. Available: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073102.pdf. [Accessed 12 February 2014].

[190] International Conference on Harmonisation, "Guidance for Industry E2C Clinical Data Safety Management: Periodic Safety Update Reports for Marketed Drugs," November 1996. [Online]. Available: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073102.pdf. [Accessed 12 February 2014].

[191] World Health Organization, Uppsala Monitoring Center, "Glossary of terms used in Pharmacovigilance," January 2013. [Online]. Available: http://www.who-umc.org/graphics/27400.pdf. [Accessed 6 February 2014].

A failure of the expected drug effect can occur regardless of the indication of the pharmaceutical product. Moreover, it is the expected adverse drug reaction of the majority of counterfeit medicinal products. For that reason, LODE reports are considered suitable to serve as a basis for the analysis of a potential correlation between AE reports and confirmed counterfeit incidents. Hence, LODE reports were selected for the data analysis in this dissertation.

To identify AE cases that are related to a LODE, they are coded using respective preferred terms (PT) of the Medical Dictionary for Regulatory Activities (MedDRA), when they are entered into the company's pharmacovigilance database. Detailed information regarding MedDRA, including MedDRA terms and the MedDRA hierarchy are outlined in paragraph 3.2.5. Respective preferred terms are listed in the following table. An AE case is coded using a LODE PT when the "*evidence of less than the expected effect of the product*" [103][193] is estimated after medical judgment or if the reporter explicitly stated that the drug did not work. [104][194]

MedDRA PT for LODE (examples)
• Drug ineffective • No therapeutic response • Therapeutic product ineffective

Table 2: Examples for MedDRA PTs for LODE

3.2.4 Lack of drug effect type of events

As defined above, a lack of drug effect is the "*evidence of less than the expected effect of a product*". [103][195]

Adverse events, occurring under the treatment of a medicinal product, that point to a failure of the pharmaceutical effect but do not give the evidence are not defined as a LODE.

[192] National Center for Biomedical Ontology, "Medical Dictionary for Regulatory Activities - Lack of efficacy," [Online]. Available: http://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMDR%2F20000032. [Accessed 6 February 2014].

[193] National Center for Biomedical Ontology, "Medical Dictionary for Regulatory Activities - Lack of efficacy," [Online]. Available: http://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMDR%2F20000032. [Accessed 6 February 2014].

[194] International Conference on Harmonisation, "MedDRA Term Selection: Points to Consider," 1 October 2013. [Online]. Available: http://www.meddra.org/sites/default/files/guidance/file/9491-1610_termselptc_r4.6_sep2013.pdf. [Accessed 24 February 2014].

[195] National Center for Biomedical Ontology, "Medical Dictionary for Regulatory Activities - Lack of efficacy," [Online]. Available: http://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMDR%2F20000032. [Accessed 6 February 2014].

Therefore, case reports related to such an event are not coded with a LODE-specific PT, when entered into the database. Hence, such case reports would not be included in the results of a retrieval of LODE cases from the database. Nevertheless, cases that have been reported in correlation with adverse events pointing to a failure of the desired pharmaceutical effect of a medicinal product could hint at a potential counterfeit presence and thus, should be included in the analysis of the potential correlation between AE cases and confirmed counterfeit incidents. In this dissertation these adverse events are denoted as lack of drug effect type of events (LODE TOE).

LODE type of events are very product-specific and depend on the indication of the respective medicinal product. For that reason, LODE TOE were selected separately for each product in scope of the analysis. The selection of the respective events was done in the context of this thesis using MedDRA preferred terms.

In the following, some examples for products of different indications and the appropriate MedDRA PTs for LODE type of events are given.

3.2.4.1 Combined oral contraceptives

Indication / drug effect	MedDRA PT (examples)
Contraception	• Pregnancy • Pregnancy on contraceptive • Unintended pregnancy • Unwanted pregnancy • Pregnancy test positive • Human chorionic gonadotropin increased
Irregular menstrual bleeding / Regulation of menstrual bleeding	• Bleeding time abnormal • Abnormal withdrawal bleeding • Dysfunctional uterine bleeding • Menstruation irregular
Anti-androgen effects	• Acne • Alopecia • Hirsutism • Seborrhoea • Virilism

Table 3: Lack of drug effect type of events - oral contraceptives

3.2.4.2 Anti-diabetics

Indication / drug effect	MedDRA PT (examples)
Diabetes mellitus (Typ 2) / Regulation of blood glucose	• Diabetes mellitus inadequate control • Increased insulin requirement • Hyperglycaemia • Hyperglycaemic unconsciousness • Blood glucose increased • Glycosylated haemoglobin increased • Diabetic ketoacidosis • Diabetic hyperglycaemic coma

Table 4: Lack of drug effect type of events - anti-diabetics

3.2.4.3 Erectile dysfunction pharmaceuticals

Indication / drug effect	MedDRA PT (examples)
Erectile dysfunction	• Ejaculation disorder • Ejaculation failure • Erectile dysfunction • Male sexual dysfunction

Table 5: Lack of drug effect type of events - erectile dysfunction pharmaceuticals

3.2.4.4 Antibiotics

Indication / drug effect	MedDRA PT (examples, depending on the spectrum of the antibiotic API)
Bacterial infection	• Abscess bacterial • Bacterial diarrhea • Bacterial sepsis • Bronchitis bacterial • Cystitis bacterial • Otitis bacterial • Pneumonia bacterial • Sinusitis bacterial • Urinary tract infection bacterial

Table 6: Lack of drug effect type of events - antibiotics

3.2.5 MedDRA

MedDRA stands for Medical Dictionary for Regulatory Activities. The dictionary was developed by the ICH in the late 1990's with the purpose to provide a standardized medical terminology to "*facilitate sharing of regulatory information internationally for medical products used by humans*". [105][196] All institutions, including regulatory authorities, pharmaceutical companies, clinical research organizations and health care professionals, can access MedDRA "*for use in the registration, documentation and safety monitoring of medical*

[196] "ICH MedDRA homepage - basics," [Online]. Available: http://www.meddra.org/how-to-use/support-documentation/english. [Accessed 05 August 2013].

products, both, before and after the product's marketing authorization". [105][197] The scope of the tool covers pharmaceuticals, biologics, vaccines and drug-device combination products. [105][198]

To guarantee the integrity of MedDRA, the ICH has created a governance structure. The ICH MedDRA Maintenance and Support Services Organization (MSSO) is responsible for the maintenance, development, and distribution of MedDRA and is controlled by the ICH MedDRA Management Board, which is appointed by the ICH Steering Committee. MedDRA is available in multiple languages: Chinese, Czech, Dutch, English, French, German, Hungarian, Italian, Japanese, Portuguese and Spanish. Each MedDRA term is associated to an 8-digit numerical code, which defines the same term in every language. Thus, it is much easier to share safety-relevant information internationally. On a half-year basis an updated MedDRA version is provided to the users. [105][199]

All MedDRA terms are arranged in a hierarchical structure of 5 levels from "system organ class" (SOC) as the highest level over "high level group term" (HLGT), "high level term" (HLT) and "preferred term" (PT) down to "low level term" (LLT) as the lowest and most specific level, as illustrated in figure 12. All in all, MedDRA comprises more than 70,000 terms at the LLT level aggregated in 26 system organ classes. [106][200] But one low level term is not mandatorily allocated under only one system organ class. Branches are possible at several levels, e.g. see figure 13. Therefore, the possible paths are classified as primary path and secondary path(s).

[197] "ICH MedDRA homepage - basics," [Online]. Available: http://www.meddra.org/how-to-use/support-documentation/english. [Accessed 05 August 2013].
[198] "ICH MedDRA homepage - basics," [Online]. Available: http://www.meddra.org/how-to-use/support-documentation/english. [Accessed 05 August 2013].
[199] "ICH MedDRA homepage - basics," [Online]. Available: http://www.meddra.org/how-to-use/support-documentation/english. [Accessed 05 August 2013].
[200] "ICH MedDRA homepage - structure," [Online]. Available: http://www.meddra.org/how-to-use/basics/hierarchy. [Accessed 21 August 2013].

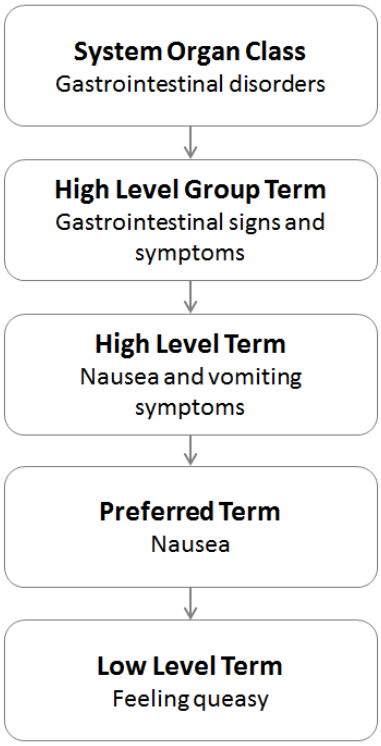

Figure 12: MedDRA hierarchy [106][201]

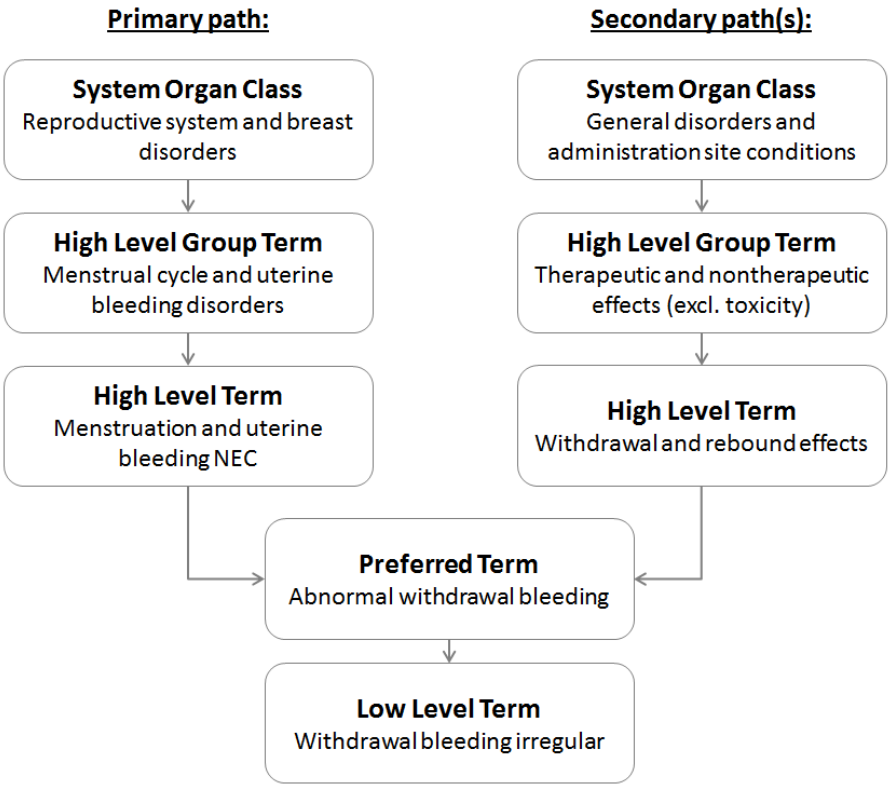

Figure 13: MedDRA hierarchy - branches (MedDRA version 17.1)

[201] "ICH MedDRA homepage - structure," [Online]. Available: http://www.meddra.org/how-to-use/basics/hierarchy. [Accessed 21 August 2013].

3.2.6 Methodology

The data analysis, including the selection of the products and countries in scope, the preparation and retrieval of the required data, the data presentation, as well as the selection of a suitable statistical method and the statistical evaluation, including all calculations were accomplished in the context of this thesis.

3.2.6.1 Scope: Products, countries, time frame

The data analysis was done with respect to a selection of products, for which confirmed counterfeit incidents have already been received and thus, a high counterfeit presence in specific countries is known. Therefore, the respective data in the company's global technical complaint database served as reference data regarding the confirmed counterfeit incidents, particularly confirmed falsifications which are in the focus of the analysis.

In order to maintain data protection, the 6 selected prescription-only medicines are encrypted with the terms "Product A-F". The dosage forms of the selected products are all solid formulations for oral administration. The time period in scope of the data analysis was determined on 4 years; from 2009 to 2012.

3.2.6.2 Data retrieval

All LODE cases and all LODE type of event cases regarding the products in scope were retrieved from the company's global pharmacovigilance database, based on the entry date of the reports, i.e. the reports were entered into the database within the time period in scope. The LODE cases were retrieved using LODE-specific preferred terms, which are used to code LODE cases in the database, as mentioned above. In order to select appropriate LODE type of event terms for each product in scope, an event count query was run in the global pharmacovigilance database for each of the products. The results of the event count queries contain all preferred terms that have ever been reported with regard to the respective product since the beginning of the company's data collection. The result lists were reviewed for preferred terms that would serve the required characteristics of a LODE type of event for the respective products. Based on the selected terms the MedDRA browser was examined for similar, appropriate terms which also should be included in the LODE type of event lists for the respective products in scope. Additionally, the Company Core Safety Information of the respective products was used as an orientation for the selection of appropriate preferred terms. Finally, the compiled LODE type of event lists were discussed with the responsible Global Safety Leader (GSL) of each of the products and were adapted, if necessary.

As mentioned above, the lists of the defined product-specific MedDRA terms are not presented in the dissertation to guarantee that the evaluated products remain confidential according to data protection.

3.2.6.3 Data presentation

The LODE + LODE TOE cases of each product in scope were calculated as case counts in a long-term view over the 4 years period on a quarterly basis for the respective country of known counterfeit presence. As the reference, the confirmed falsifications of each product in scope were displayed in the same way for the respective country. Due to country-specific circumstances, a data evaluation across countries is not reasonable. Hence, the data evaluation was done separately for each of the product-country combinations to exclude influencing factors that are based on country-specific circumstances. For each product-country combination the described AE data and counterfeit incidents data were displayed in one joint figure. The statistical method used to calculate if a correlation between the respective data can be identified is Spearman's rank correlation coefficient.

Furthermore, the LODE + LODE TOE cases are calculated in counts per million (CPM) for each product-country combination over the time period in scope. The consideration of the CPM rates was done to offset increases in the adverse event case counts that were caused by increasing sales quantities and, thus, a higher number of patients who have been treated with the respective pharmaceutical products. A probable temporal delay between the sale of the medicines and the reporting of potentially related adverse events has to be taken into account. This has to be considered in particular with respect to medicinal products which are subject to a seasonal dependency, e.g. vaccines. However, no seasonal dependency is expected for the 6 selected products in scope as the consumption of these products is stable during the course of the year. The CPM rates were calculated based on the sales quantities documented in the company's global sales database.

3.2.6.4 Statistical method: Spearman's rank correlation coefficient

A company-internal statistician was consulted to gain information about statistical methods, possibly applicable to the planned data evaluation. In the context of this dissertation the proposed statistical methods were checked with respect to their suitability. As a result, Spearman's rank correlation coefficient, also denoted as Spearman's *rho* (r_s or ρ), was selected to examine if there is a correlation between the confirmed falsification cases and the LODE + LODE type of event cases regarding the example products.

Spearman's rank correlation coefficient is a non-parametric measure of the statistical dependence between two variables. This means that it is examined if there is a monotonic relation between the two variables. Spearman's *rho* ranges from -1 to +1, with ρ = -1 describing a perfect negative monotonic relation (one variable increases while the other decreases) and ρ = +1 describing a perfect positive monotonic relation (one variable increases and the other does, too). ρ = 0 means that there is no monotonic relation between the variables. Spearman's rank correlation coefficient is derived from Pearson's correlation coefficient. For both, the same formula is used. However, for Spearman's rank correlation coefficient the data, to be evaluated, does not need to be normally distributed, as it is required for Pearson's correlation coefficient. The main difference between the two methods is that Spearman's rank correlation coefficient is based on the ranks of the variables' values to be evaluated, while Pearson's correlation coefficient is based directly on the variables' values. The values of one variable are sorted in an ascending order. Then each of the values is assigned a rank according to its position in the ascending order. If there are identical values of one variable, also denoted as rank ties, these values are assigned a rank corresponding to the average of the positions which these values have in the ascending order. [107][202] [108][203] For the first example product an auxiliary table, containing all data required for the calculation, is given. For all other example products only the result of ρ is given.

Levels of absolute results of ρ, describing the relationship between the variables [109][*204*]:

- 0.00 – 0.19 "very weak"
- 0.20 – 0.39 "weak"
- 0.40 – 0.59 "moderate"
- 0.60 – 0.79 "strong"
- 0.80 – 1.00 "very strong"

[202] G. Buttler and K. Oeckler, "Zusammenhang von Rangmerkmalen," in *Einführung in die Statistik*, Rowohlt-Verlag GmbH, 2010, pp. 224-233.
[203] D. Rumsey, "Korrelationen mit dem Spearman'schen Rang bestimmen," in *Statistik II für Dummies*, Weinheim, WILEY-VCH Verlag GmbH & Co. KGaA, 2013, pp. 327-330.
[204] "Spearman's correlation," [Online]. Available: http://www.statstutor.ac.uk/resources/uploaded/spearmans.pdf. [Accessed 30 January 2014].

Formula of Spearman's *rho* (ρ) [107][205] [108][206]:

$$\rho = \frac{\frac{1}{n}\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\frac{1}{n}\sum_i (rx_i - \overline{rx})^2}\sqrt{\frac{1}{n}\sum_i (ry_i - \overline{ry})^2}} = \frac{s_{rxry}}{s_{rx}s_{ry}}$$

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

with

n	Number of value pairs
i	Index of the value pair; from 1 to n; n = sample size
rx_i	Ranks of the x-values
$\overline{rx}$	Mean (arithmetic) of all ranks of the x-values
ry_i	Ranks of the y-values
$\overline{ry}$	Mean (arithmetic) of all ranks of the y-values
s_{rxry}	Covariance of the ranks of the x-values and y-values
s_{rx}	Standard deviation of the ranks of the x-values
s_{ry}	Standard deviation of the ranks of the y-values

Testing the significance of the results of ρ, the figure "Significance of Spearman's rank correlation coefficient" was used. The significance level is a measure for the likelihood that the null hypothesis is falsely rejected, i.e. the likelihood that the result of *rho* is only due to chance. The power of the test depends on the sample size, in this case the number of value pairs. If *rho* is greater than the 5% significance level corresponding to the sample size (or degrees of freedom = number of value pairs – 2) the likelihood that the null hypothesis is falsely rejected is too high. Therefore, it should not be rejected. [110][207]

[205] G. Buttler and K. Oeckler, "Zusammenhang von Rangmerkmalen," in *Einführung in die Statistik*, Rowohlt-Verlag GmbH, 2010, pp. 224-233.
[206] D. Rumsey, "Korrelationen mit dem Spearman'schen Rang bestimmen," in *Statistik II für Dummies*, Weinheim, WILEY-VCH Verlag GmbH & Co. KGaA, 2013, pp. 327-330.
[207] Barcelona Field Studies Center, "Spearman's Rank Correlation Coefficient," 12 May 2013. [Online]. Available: http://geographyfieldwork.com/SpearmansRank.htm. [Accessed 30 January 2014].

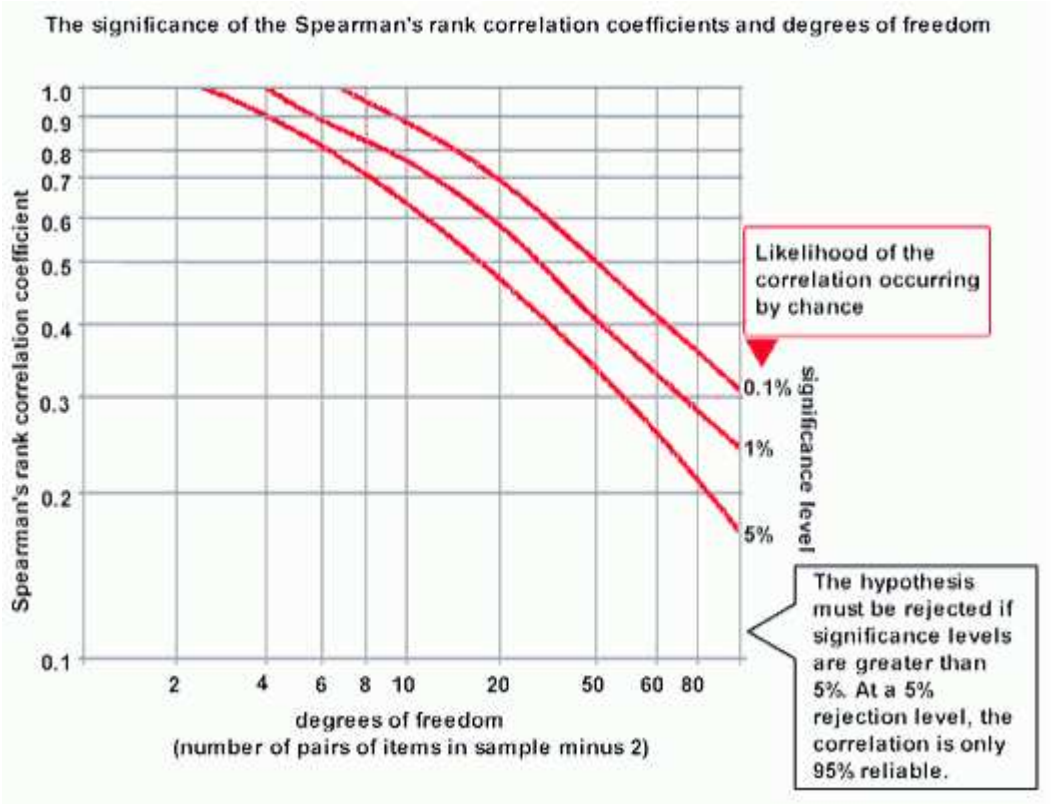

Figure 14: Significance of Spearman's rank correlation coefficient [111][208]

[208] Barcelona Field Studies Center, "Significance of Spearman's Rank Correlation Coefficient," 11 May 2013. [Online]. Available: http://geographyfieldwork.com/SpearmansRankSignificance.htm. [Accessed 30 January 2014].

3.3 Data analysis and statistical evaluation

First, the reference data was evaluated in order to identify the product-country combinations of known high counterfeit presence concerning the 6 products in scope. For each product in scope all confirmed falsifications received in the time period of 2009 to 2012 are displayed as case counts with regard to all respective reporting countries.

3.3.1 Product A

Confirmed counterfeit presence in Colombia

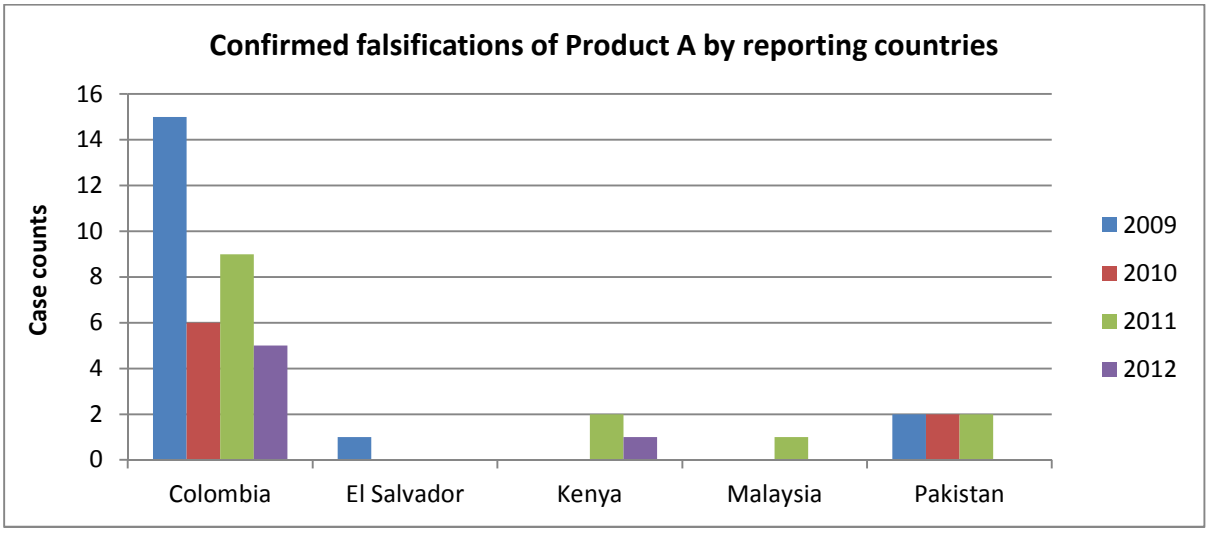

Figure 15: Confirmed falsifications of Product A by reporting countries

The data evaluation shows that the country with the highest number of confirmed falsifications of Product A is Colombia.

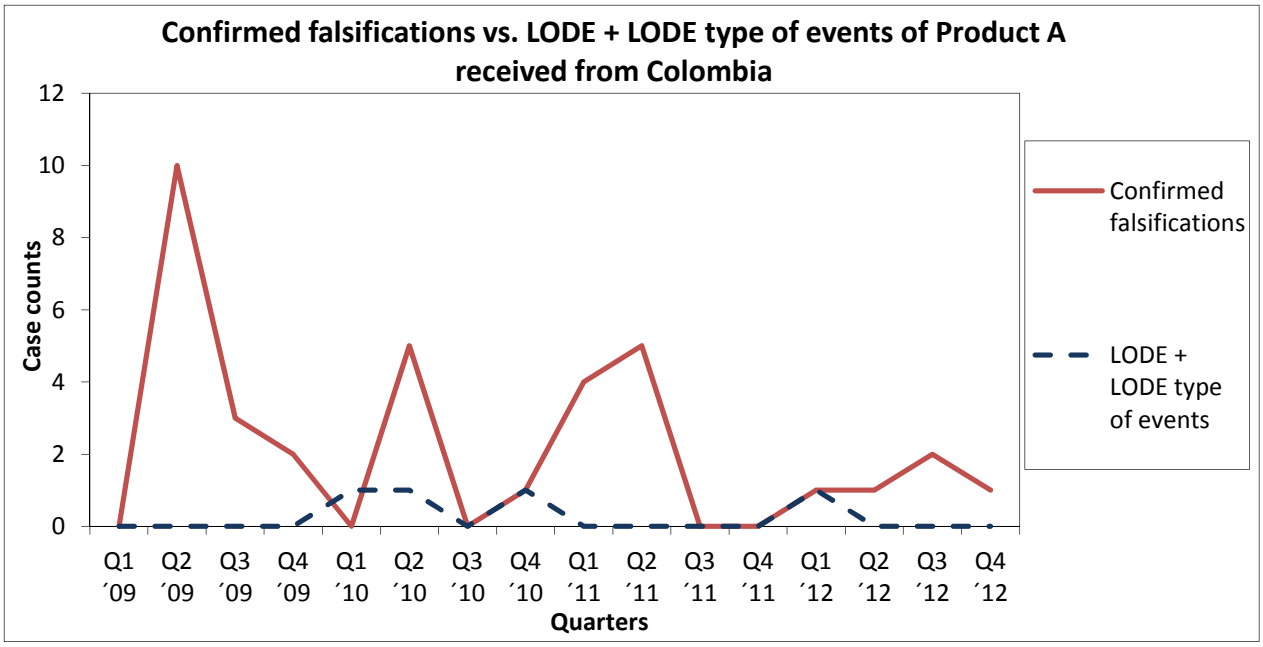

Figure 16: Confirmed falsifications vs. LODE + LODE type of events of Product A received from Colombia

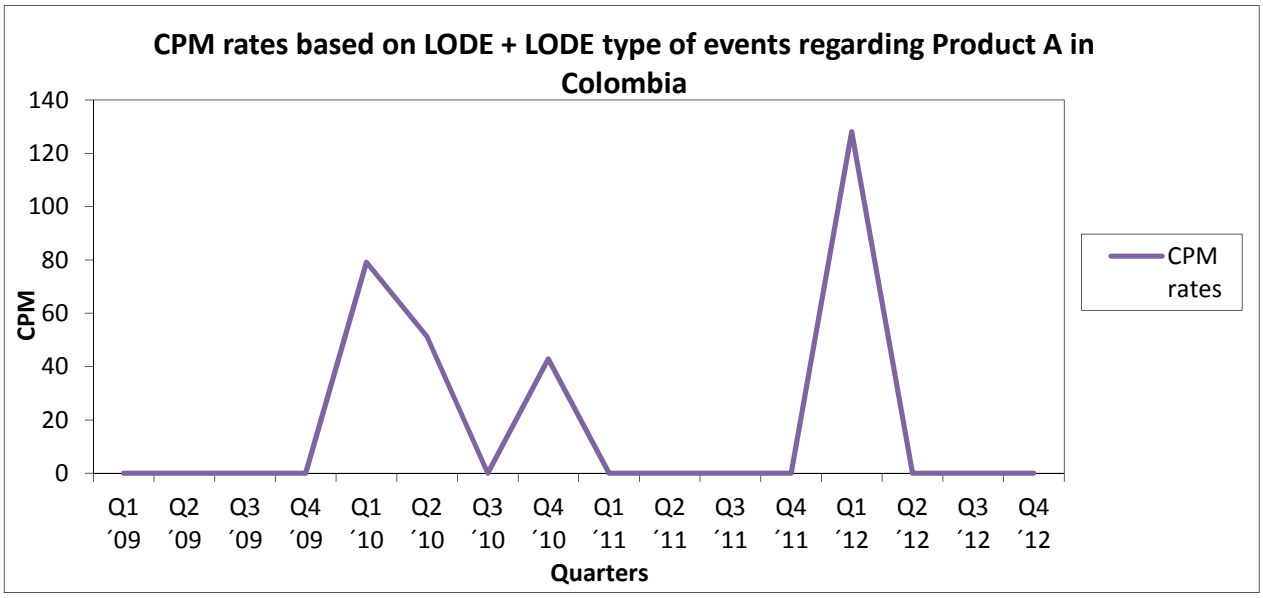

Figure 17: CPM rates based on LODE + LODE type of events regarding Product A in Colombia

To check if the number of received LODE + LODE type of event cases is influenced by the sales quantities, the CPM (counts per million) rates were calculated for the respective product with respect to the time period in scope. According to the calculation ($CPM\ rates = \frac{Number\ of\ LODE{+}LODE\ TOE\ cases}{Sales\ quantity\ (of\ the\ respective\ quarter)} \times 1000000$) the CPM rates behave inversely proportional to the sales quantities at constant numbers of received LODE + LODE type of event cases, i.e. increasing sales quantities lead to decreasing CPM rates, when the number of received LODE + LODE type of event cases remains stable and vice versa.

In 2010 the CPM rates of Product A slightly decreased while the number of received LODE + LODE type of event cases remained stable, i.e. the sales quantities slightly increased. In Q1 2012 the CPM rates increased, i.e. the sales quantities decreased in comparison to the sales quantities in 2010, but the number of received LODE + LODE type of event cases still remained stable. No influence of the sales quantities on the number of LODE + LODE type of event cases was identified.

Regarding the example of Product A all necessary data for the calculation of Spearman's *rho* is given in the table below.

x Values of the confirmed falsification cases

y Values of the LODE + LODE type of event cases

x	rx_i	y	ry_i	$rx_i - \overline{rx}$	$ry_i - \overline{ry}$	$(rx_i - \overline{rx})(ry_i - \overline{ry})$	$(rx_i - \overline{rx})^2$	$(ry_i - \overline{ry})^2$
0	3	0	6.5	-5.5	-2	11	30.25	4
10	16	0	6.5	7.5	-2	-15	56.25	4
3	12	0	6.5	3.5	-2	-7	12.25	4
2	10.5	0	6.5	2	-2	-4	4	4
0	3	1	14.5	-5.5	6	-33	30.25	36
5	14.5	1	14.5	6	6	36	36	36
0	3	0	6.5	-5.5	-2	11	30.25	4
1	7.5	1	14.5	-1	6	-6	1	36
4	13	0	6.5	4.5	-2	-9	20.25	4
5	14.5	0	6.5	6	-2	-12	36	4
0	3	0	6.5	-5.5	-2	11	30.25	4
0	3	0	6.5	-5.5	-2	11	30.25	4
1	7.5	1	14.5	-1	6	-6	1	36
1	7.5	0	6.5	-1	-2	2	1	4
2	10.5	0	6.5	2	-2	-4	4	4
1	7.5	0	6.5	-1	-2	2	1	4
	$\overline{rx}$ = 8.5		$\overline{ry}$ = 8.5			Σ = -12	Σ = 324	Σ = 192

Table 7: Data for calculation of Spearman's *rho* for Product A

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{-12}{\sqrt{324}\sqrt{192}}$$

$$\rho = -0.048$$

The value of ρ is -0.048, i.e. the relationship between the variables is very weak.

H_0: There is no correlation between the variables (confirmed falsification cases and LODE + LODE type of event cases), i.e. ρ = 0.

For the sample size n = 16, and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.048. The significance level of I ρ I = 0.048 is greater than the 5% significance level, i.e. the likelihood that the null hypothesis is falsely rejected is too high. Therefore, it is not rejected.

There is no correlation between the variables regarding Product A.

3.3.2 Product B

Confirmed counterfeit presence in Colombia

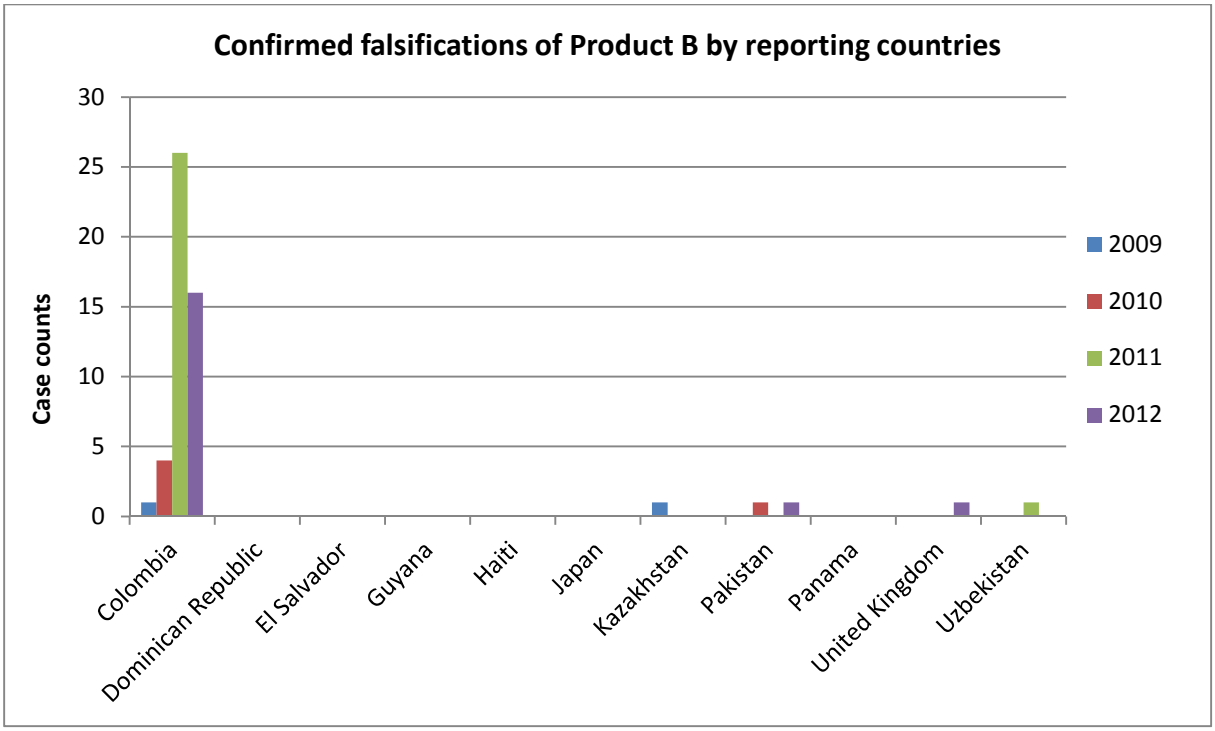

Figure 18: Confirmed falsifications of Product B by reporting countries

The data evaluation shows that the country with the highest number of confirmed falsifications of Product B is Colombia.

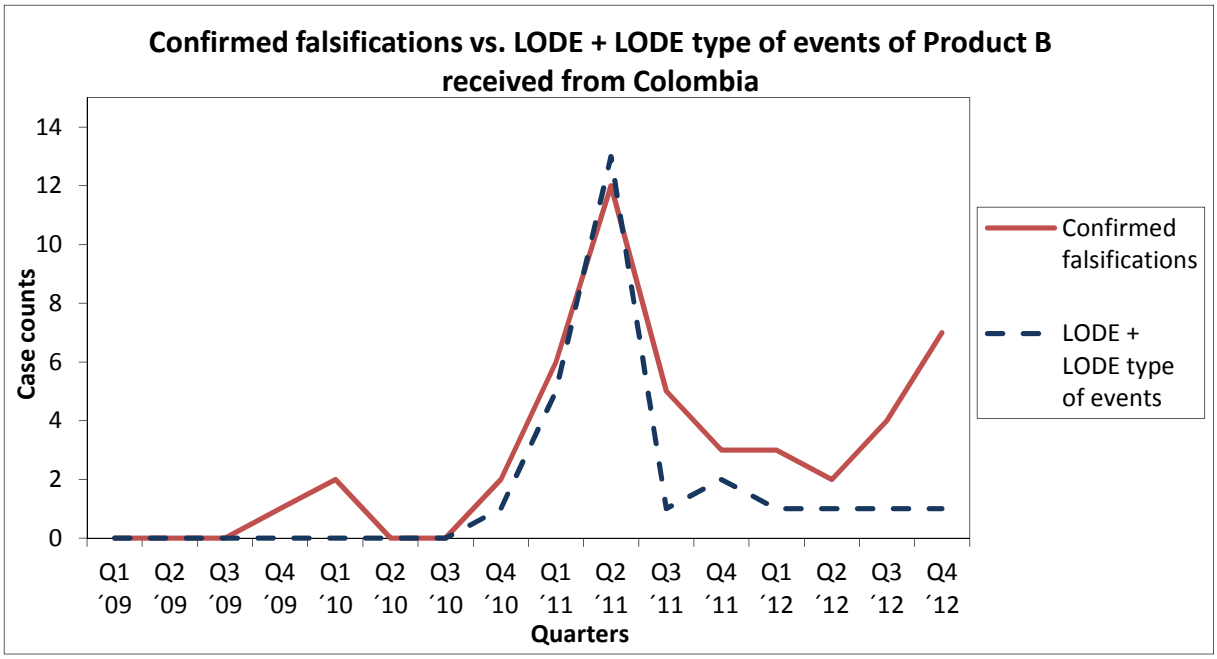

Figure 19: Confirmed falsifications vs. LODE + LODE type of events of Product B received from Colombia

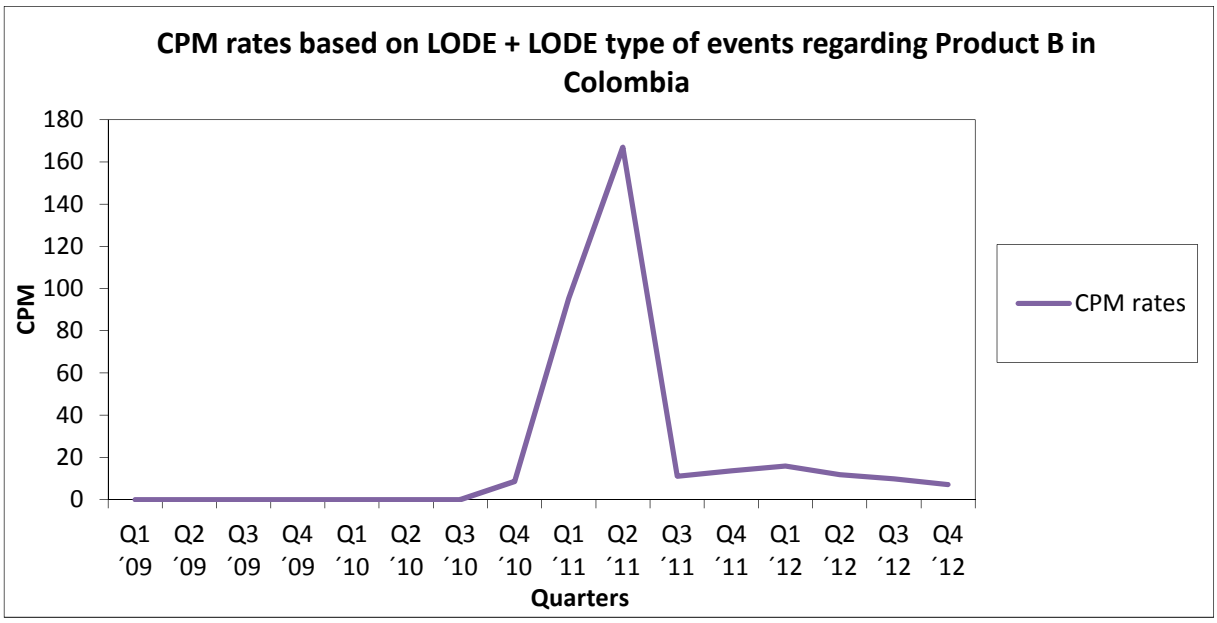

Figure 20: CPM rates based on LODE + LODE type of events regarding Product B in Colombia

The comparison of the curve shapes of the confirmed falsifications and the LODE + LODE type of event cases regarding Product B reveals a distinct match of the peaks in 2011. Hence, a correlation between the data is assumed. The sales quantities in 2011 remained stable as the CPM rates increase according to the increase of the received LODE + LODE type of event cases. No influence with respect to the sales quantities was identified.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{271.25}{\sqrt{327.5}\sqrt{294.5}}$$

$$\rho = 0.873$$

The value of ρ is 0.873, i.e. the relationship between the variables is very strong.

H_0: There is no correlation between the variables (confirmed falsification cases and LODE + LODE type of event cases), i.e. ρ = 0.

For the sample size n = 16 and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.873. The significance level of I ρ I = 0.873 is smaller than the 0.1% significance level, i.e. the likelihood that the null hypothesis is correctly rejected is 99.9%. Therefore, the null hypothesis is rejected.

There is a correlation between the variables regarding Product B.

3.3.3 Product C

Confirmed counterfeit presence in China

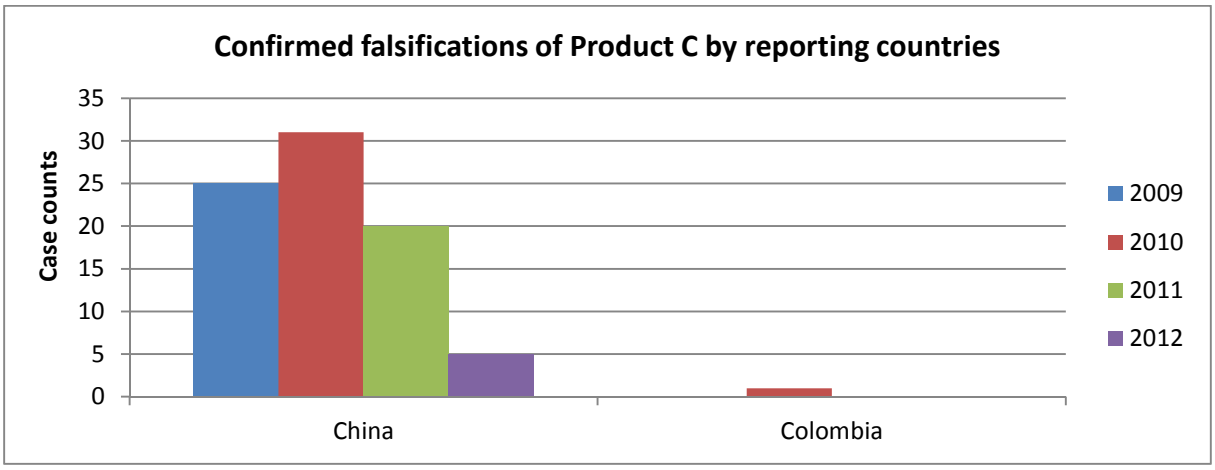

Figure 21: Confirmed falsifications of Product C by reporting countries

The data evaluation shows that the country with the highest number of confirmed falsifications of Product C is China.

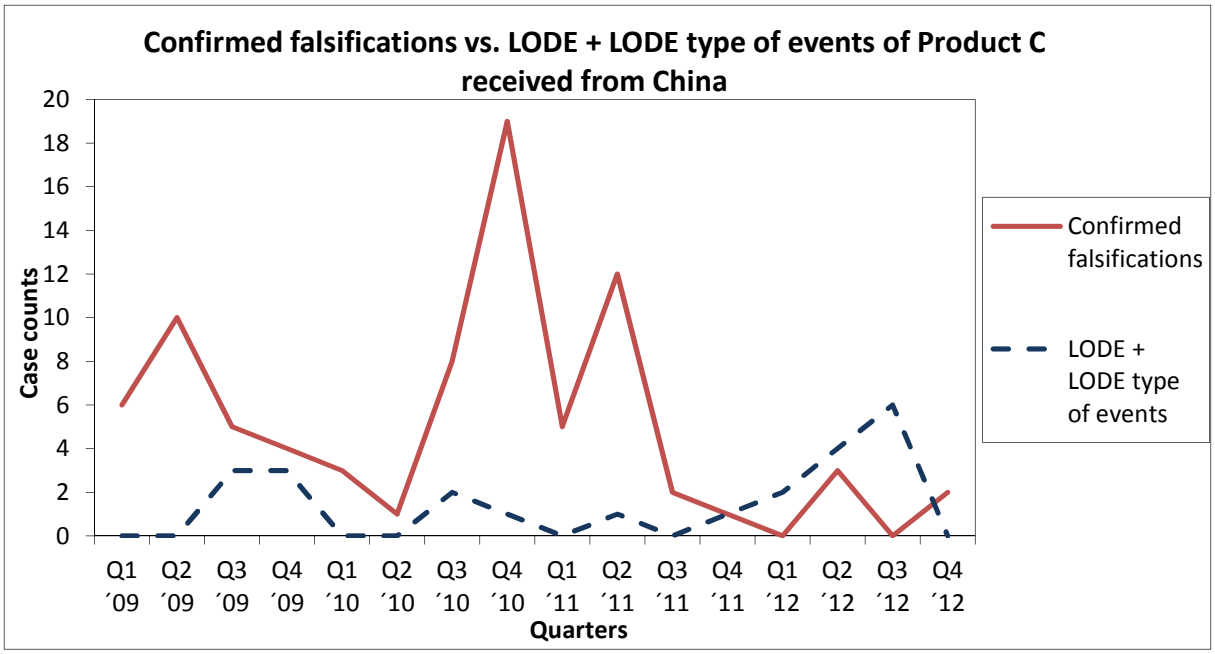

Figure 22: Confirmed falsifications vs. LODE + LODE type of events of Product C received from China

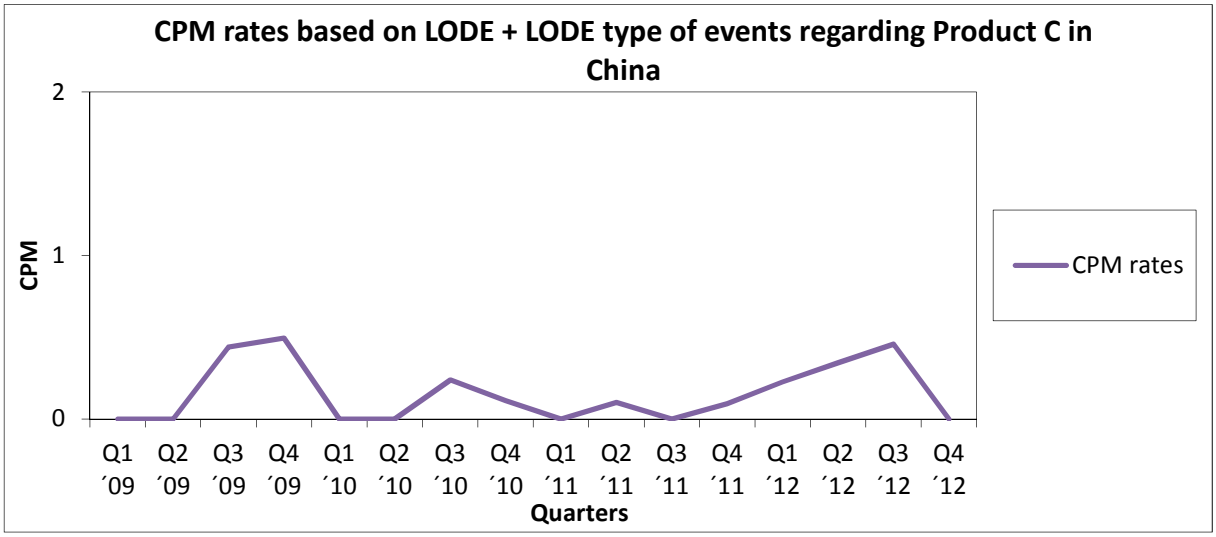

Figure 23: CPM rates based on LODE + LODE type of events regarding Product C in China

The CPM rates curve is shaped similar to the LODE + LODE type of event cases curve, i.e. the sales quantities remained stable, except in 2012. In comparison to the previous years the peak in the CPM rates in 2012 is slightly lower, i.e. the sales quantities slightly increased in 2012 and could have had an influence on the increased number of reported LODE + LODE type of event cases in 2012.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{-45}{\sqrt{337.5}\sqrt{309}}$$

$\rho = -0.139$

The value of ρ is -0.139, i.e. the relationship between the variables is very weak.

H_0: There is no correlation between the variables (confirmed falsification cases and LODE + LODE type of event cases), i.e. ρ = 0.

For the sample size n = 16 and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.139. The significance level of I ρ I = 0.139 is greater than the 5% significance level, i.e. the likelihood that the null hypothesis is falsely rejected is too high. Therefore, the null hypothesis is not rejected.

There is no correlation between the variables regarding Product C.

3.3.4 Product D

Confirmed counterfeit presence in Japan, Germany and Israel

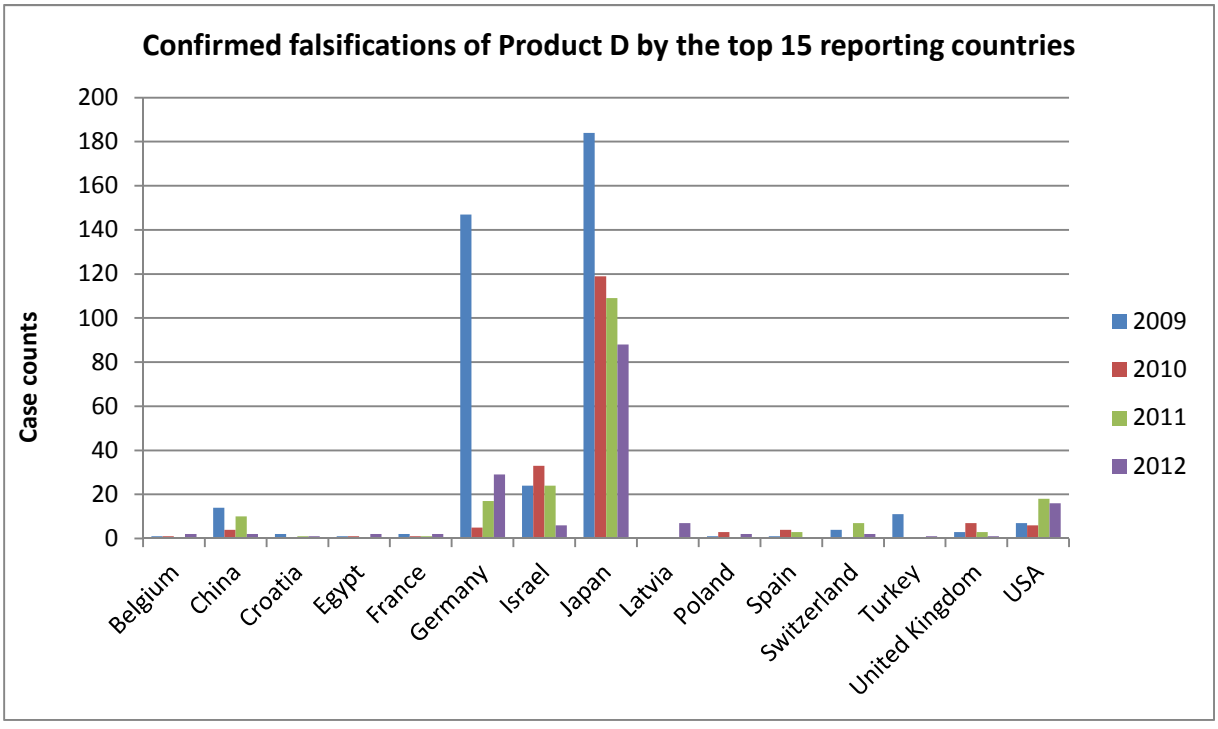

Figure 24: Confirmed falsifications of Product D by reporting countries

Regarding Product D confirmed falsifications were reported by 47 countries. In figure 24 the case counts regarding the top 15 reporting countries are displayed. With respect to the remaining 32 countries, the case counts of the confirmed falsifications are below 4 cases considering the sum of cases reported within the 4 years in scope. The data evaluation shows that there is more than one country with a significantly increased number of confirmed

falsifications of Product D. A high counterfeit presence is confirmed for Japan, Germany and Israel.

Japan

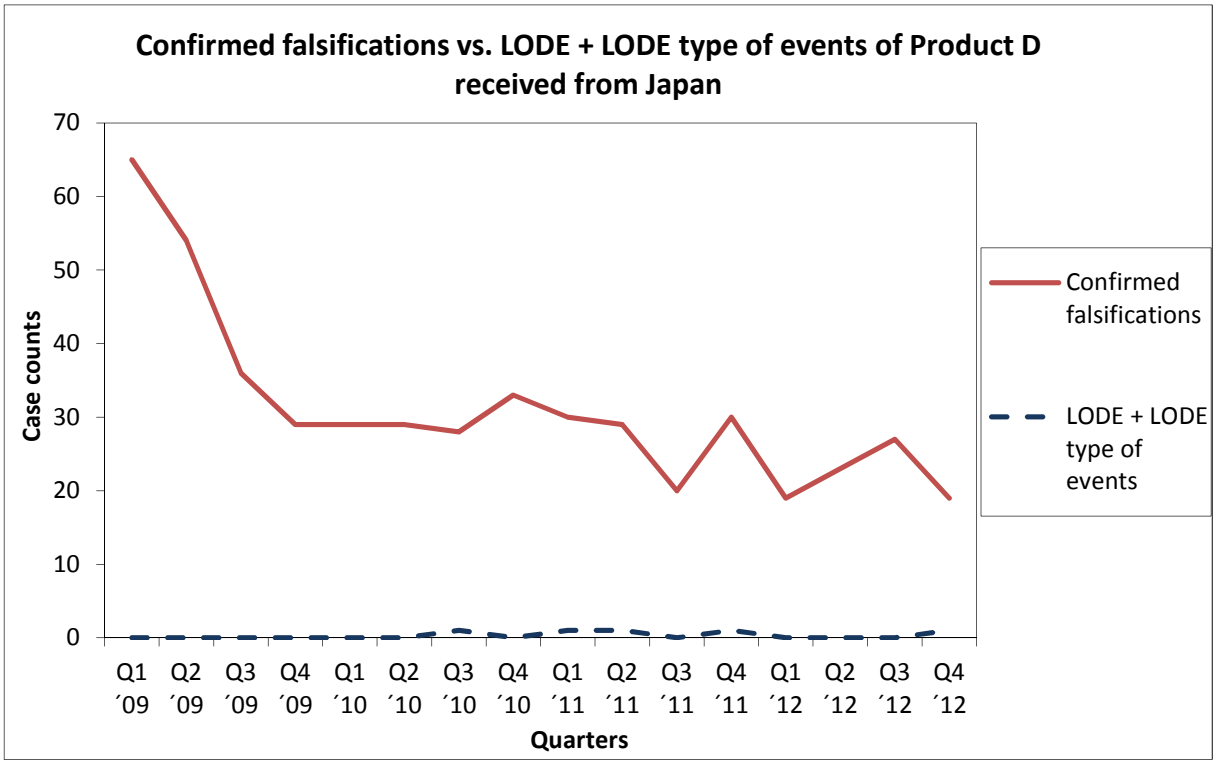

Figure 25: Confirmed falsifications vs. LODE + LODE type of events of Product D received from Japan

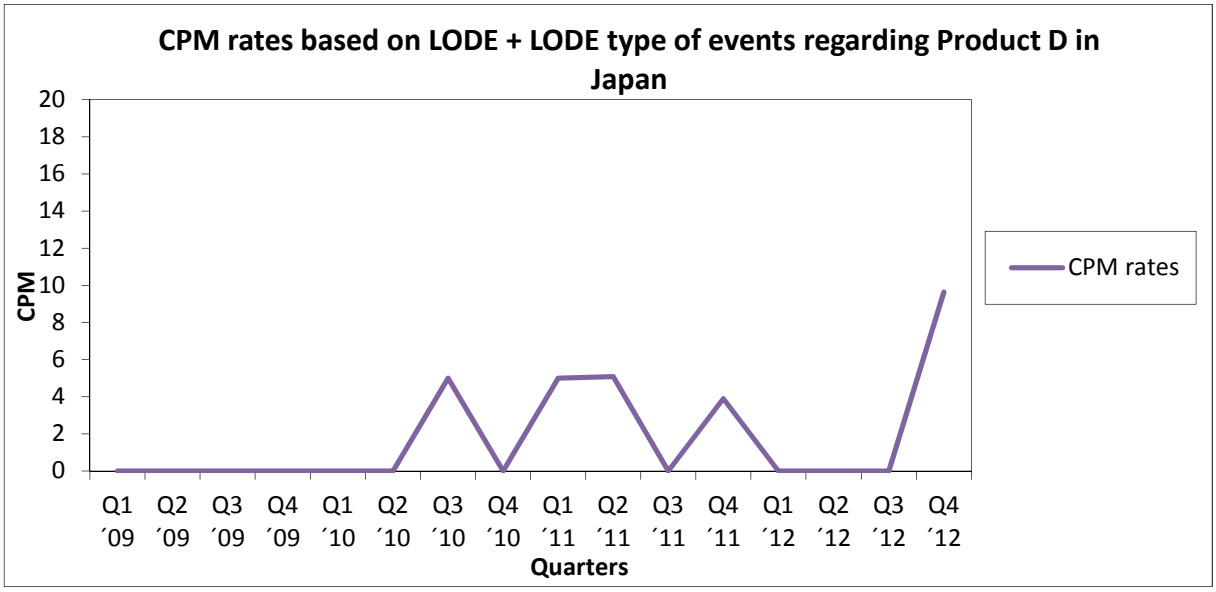

Figure 26: CPM rates based on LODE + LODE type of events regarding Product D in Japan

The CPM rates curve is shaped similar to the LODE + LODE type of event cases curve, i.e. the sales quantities remained stable, except in Q4 2012. Then, the CPM rates increased, i.e. the sales quantities decreased in Q4 2012. However, the number of reported LODE + LODE

type of event cases remained at the same level as in the quarters of the previous years. No influence with respect to the sales quantities was identified.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{-28}{\sqrt{334}\sqrt{220}}$$

$$\rho = -0.103$$

The value of ρ is -0.103, i.e. the relationship between the variables is very weak.

H_0: There is no correlation between the variables (confirmed falsification cases and LODE + LODE type of event cases), i.e. ρ = 0.

For the sample size n = 16 and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.103. The significance level of I ρ I = 0.103 is greater than the 5% significance level, i.e. the likelihood that the null hypothesis is falsely rejected is too high. Therefore, the null hypothesis is not rejected.

There is no correlation between the variables regarding Product D (cases received from Japan).

Germany

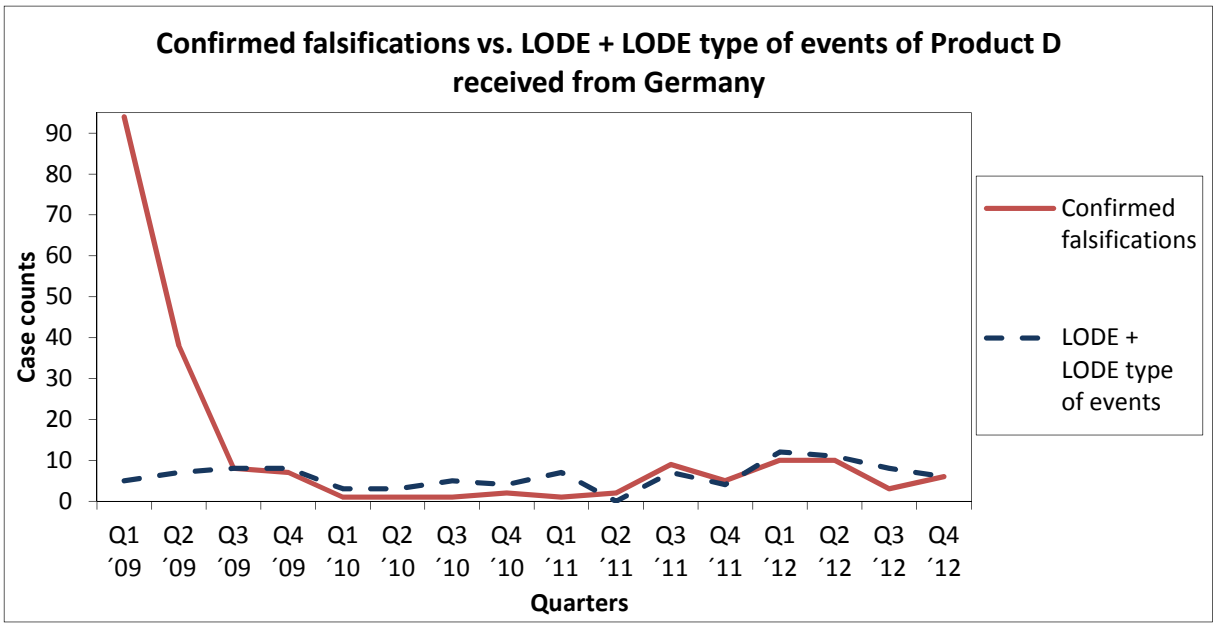

Figure 27: Confirmed falsifications vs. LODE + LODE type of events of Product D received from Germany

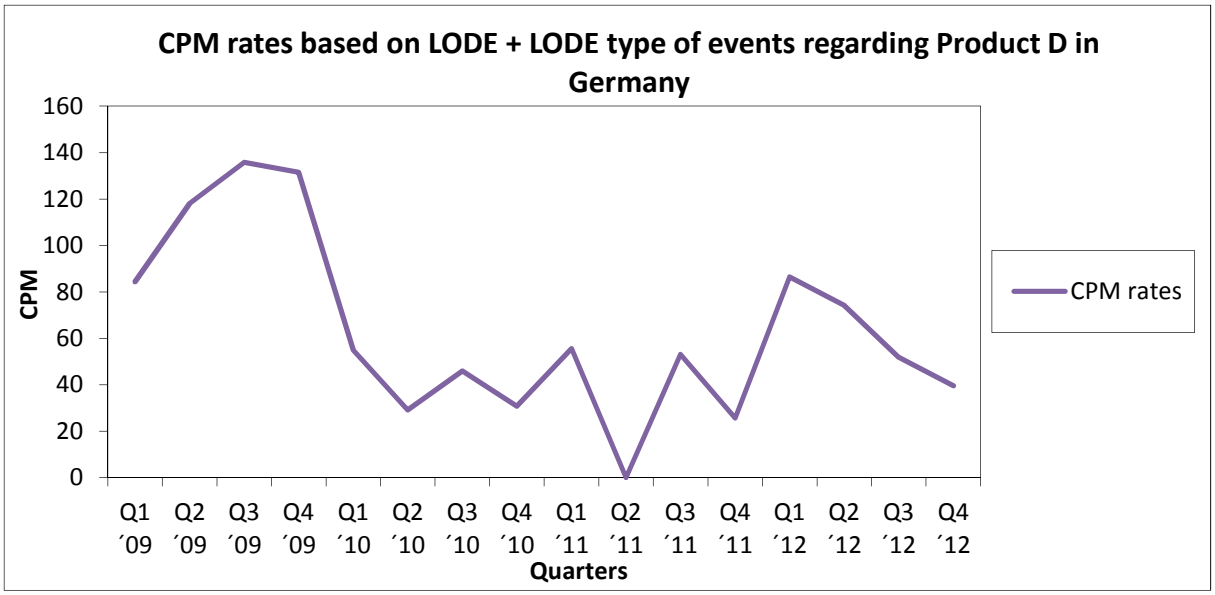

Figure 28: CPM rates based on LODE + LODE type of events regarding Product D in Germany

In 2009, the sales quantities were lower than in the following 3 years. For that reason, the CPM rates are increased in 2009 in comparison to the time period of 2010 – 2012. However, the increased sales quantities had no enhancing effect on the number of received LODE + LODE type of event cases.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{192.5}{\sqrt{334}\sqrt{334.5}}$$

$$\rho = 0.576$$

The value of ρ is 0.576, i.e. the relationship between the variables is moderate.

H_0: There is no correlation between the variables (confirmed falsification cases and LODE + LODE type of event cases), i.e. ρ = 0.

For the sample size n = 16 and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.576. The significance level of I ρ I = 0.576 is slightly smaller than the 5% significance level, i.e. the likelihood that the null hypothesis is correctly rejected is 95%. Therefore, the null hypothesis can be rejected.

There is a correlation between the variables regarding Product D (cases received from Germany).

This is a special case since the number of confirmed falsifications is biased by a high number of test purchases which were carried out in the first two quarters of 2009 with respect to Product D. Test purchases are initiated by the company, itself. Moreover, such cases are not related to reports of any adverse events. Therefore, the *rho* was calculated again taking only the data into consideration that was received in the time period of Q3 2009 – Q4 2012.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{165}{\sqrt{221.5}\sqrt{224}}$$

$$\rho = 0.741$$

The value of ρ is 0.741, i.e. the relationship between the variables is strong.

For the sample size n = 14 and the respective degrees of freedom df = 12, the absolute value of *rho* is I ρ I = 0.741. The significance level of I ρ I = 0.741 is distinctly smaller than the 5% significance level, i.e. the likelihood that the null hypothesis is correctly rejected is 95%. Therefore, the null hypothesis is rejected.

There is a correlation between the variables regarding Product D (cases received from Germany).

Israel

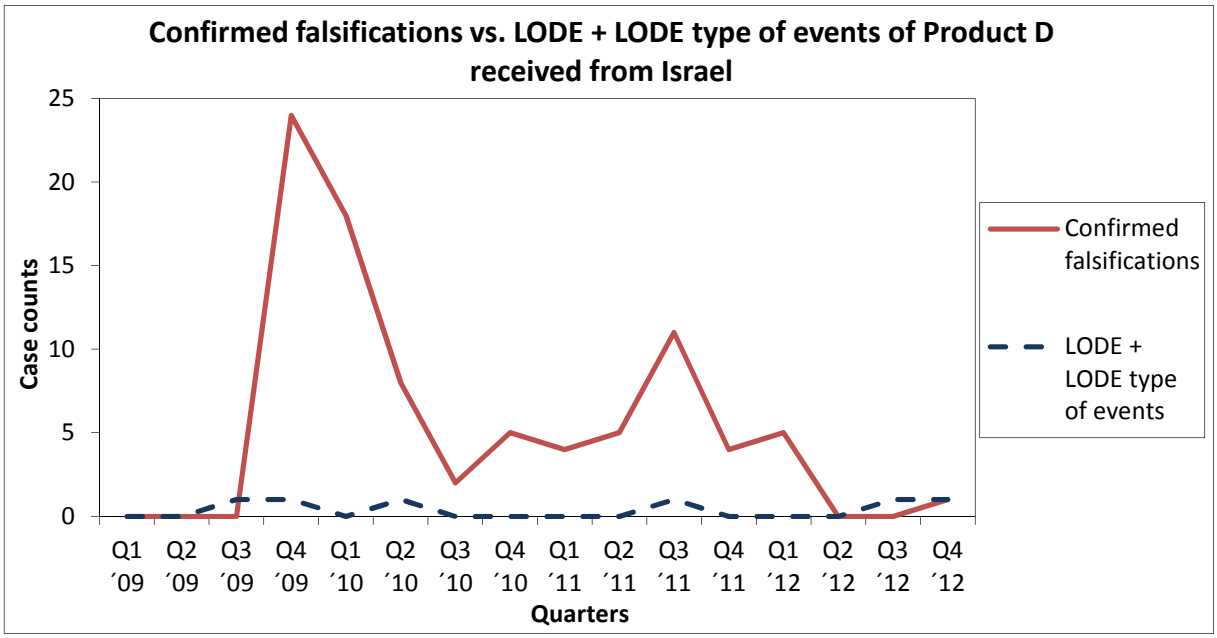

Figure 29: Confirmed falsifications vs. LODE + LODE type of events of Product D received from Israel

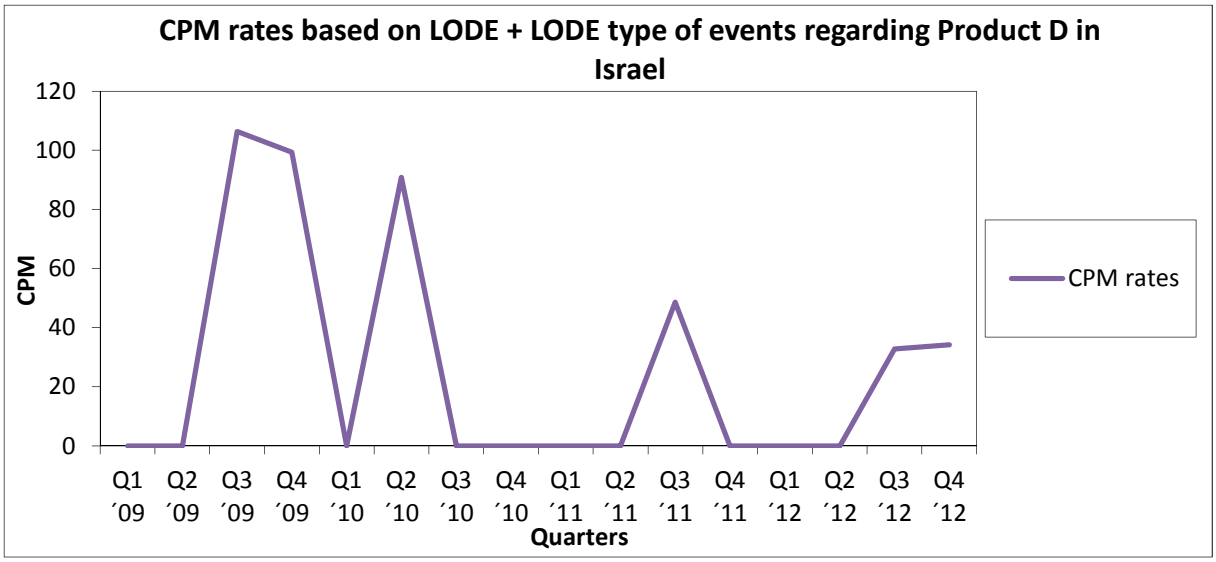

Figure 30: CPM rates based on LODE + LODE type of events regarding Product D in Israel

In 2011 and 2012, the CPM rates are lower in comparison to the years 2009 and 2010, i.e. the sales quantities were increased in 2011 and 2012. However, the increased sales quantities had no enhancing effect on the number of received LODE + LODE type of event cases.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{32}{\sqrt{327.5}\sqrt{240}}$$

$$\rho = 0.114$$

The value of ρ is 0.114, i.e. the relationship between the variables is very weak.

For the sample size n = 16 and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.114. The significance level of I ρ I = 0.114 is greater than the 5% significance level, i.e. the likelihood that the null hypothesis is falsely rejected is too high. Therefore, the null hypothesis is not rejected.

There is no correlation between the variables regarding Product D (cases received from Israel).

3.3.5 Product E

Confirmed counterfeit presence in Colombia

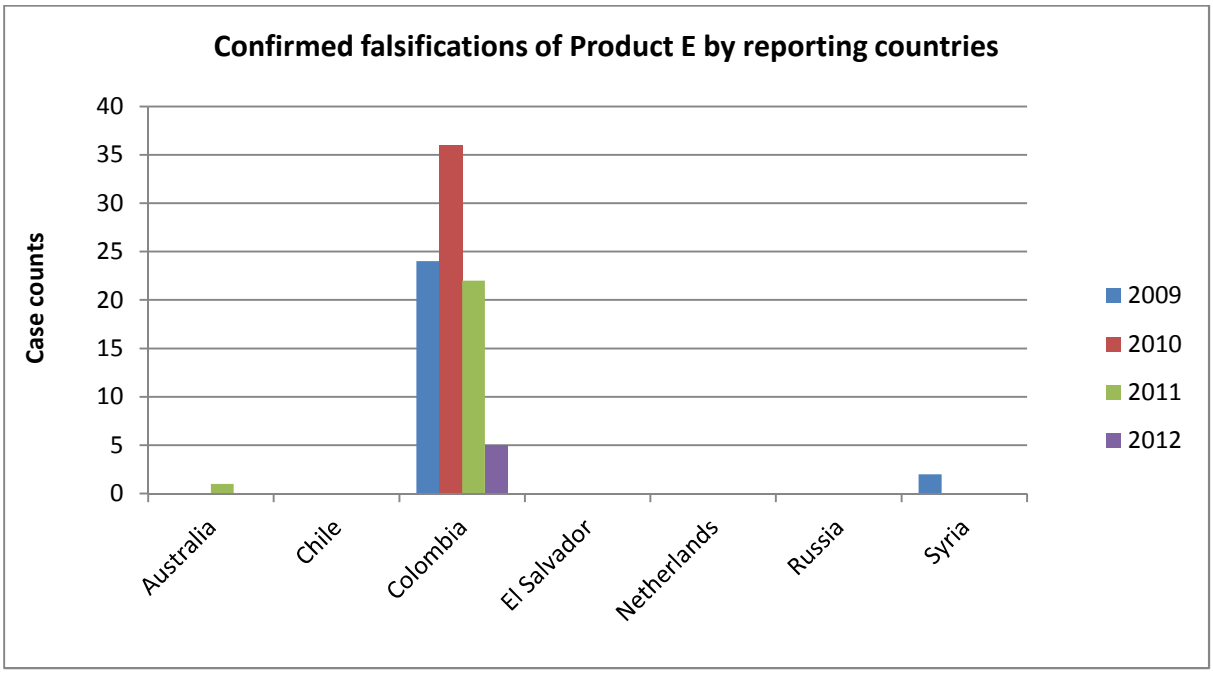

Figure 31: Confirmed falsifications of Product E by reporting countries

The data evaluation shows that the country with the highest number of confirmed falsifications of Product E is Colombia.

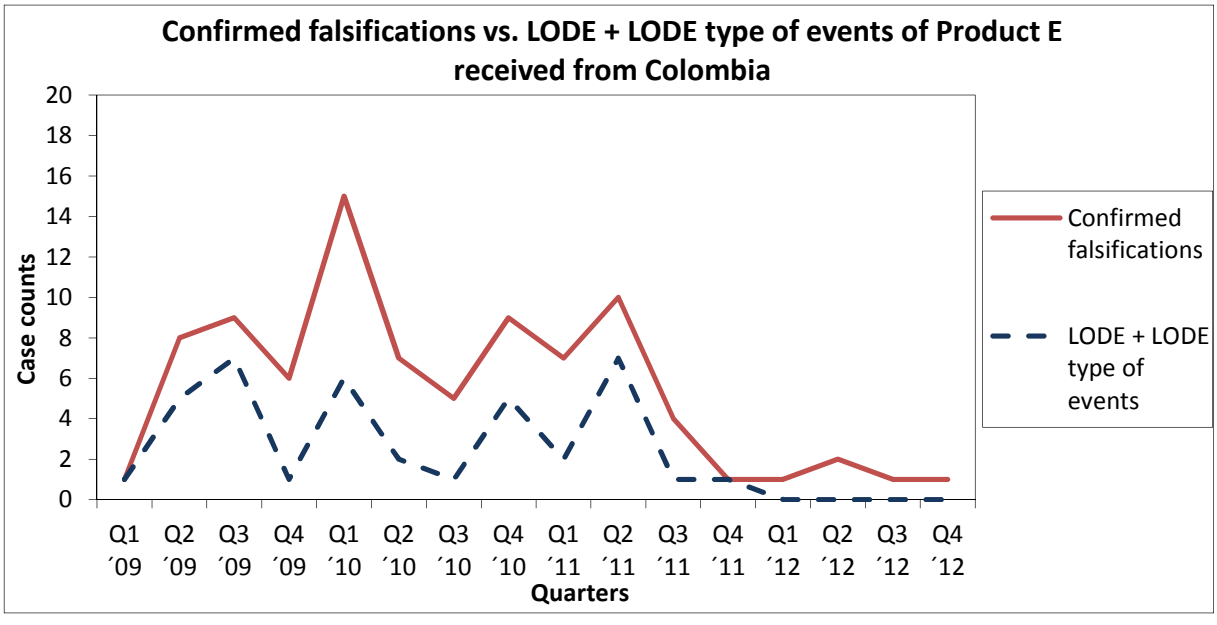

Figure 32: Confirmed falsifications vs. LODE + LODE type of events of Product E received from Colombia

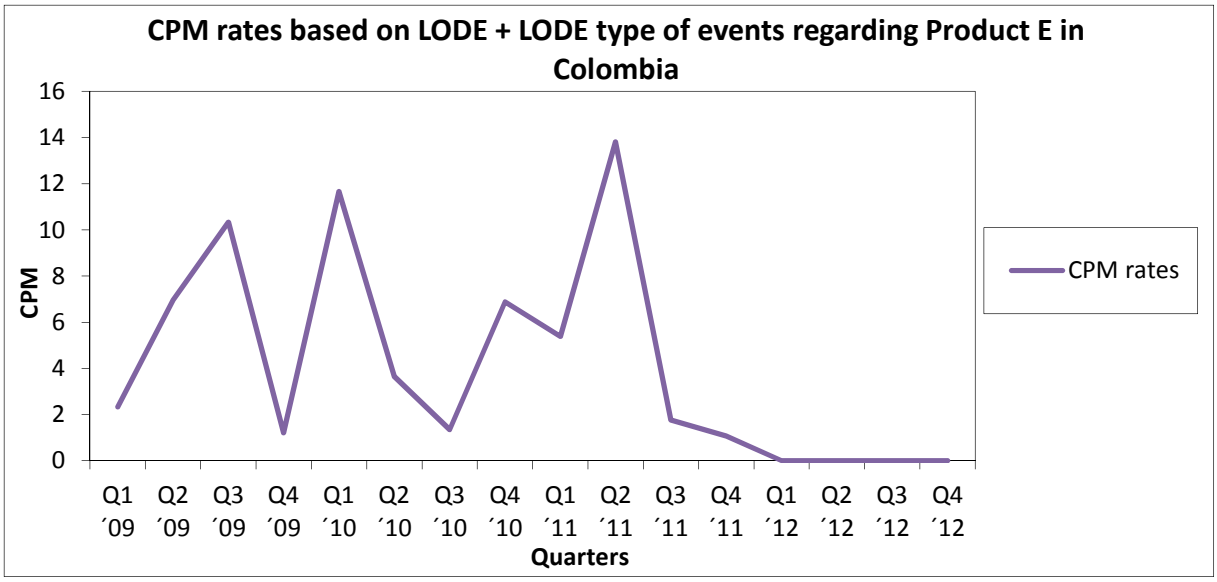

Figure 33: CPM rates based on LODE + LODE type of events regarding Product E in Colombia

The CPM rates curve is shaped similar to the LODE + LODE type of event cases curve, i.e. the sales quantities remained stable, except in Q1 2010 and Q2 2011. Then, the CPM rates slightly increased, i.e. the sales quantities decreased in these two quarters. However, the number of reported LODE + LODE type of event cases remained at almost the same level. No influence with respect to the sales quantities was identified.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{296.5}{\sqrt{329}\sqrt{323.5}}$$

$$\rho = 0.909$$

The value of ρ is 0.909, i.e. the relationship between the variables is very strong.

For the sample size n = 16 and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.909. The significance level of I ρ I = 0.909 is smaller than the 0.1% significance level, i.e. the likelihood that the null hypothesis is correctly rejected is 99.9%. Therefore, the null hypothesis is rejected.

There is a correlation between the variables regarding Product E.

3.3.6 Product F

Confirmed counterfeit presence in Colombia

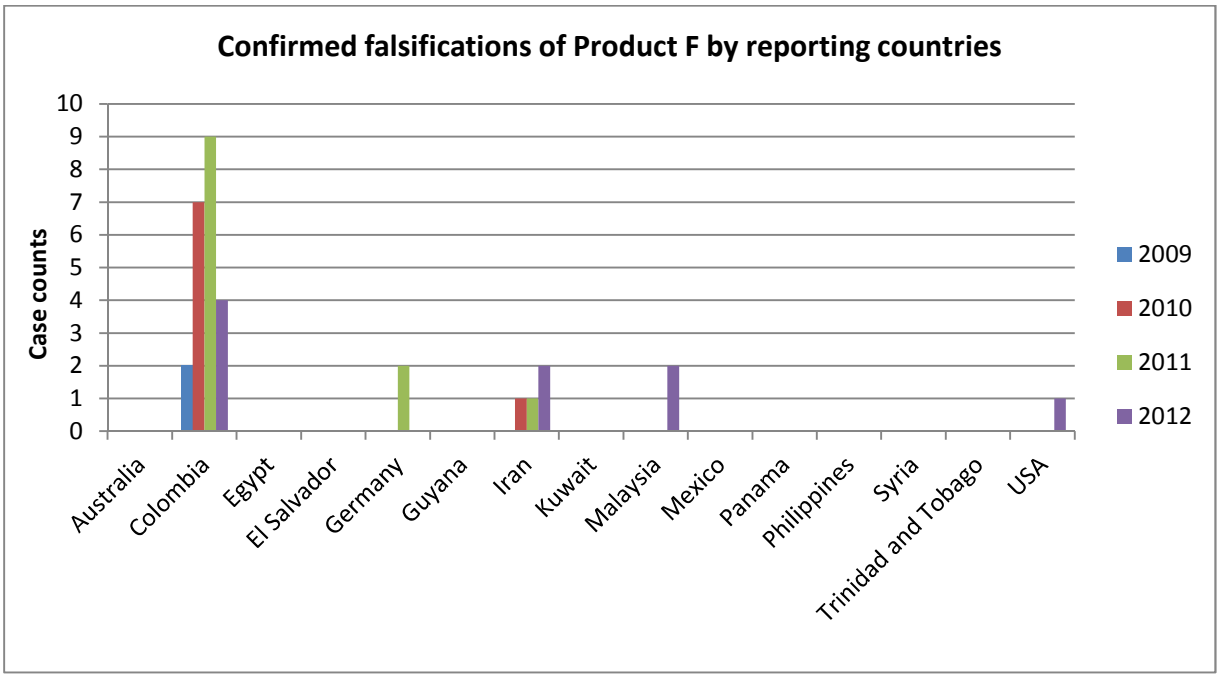

Figure 34: Confirmed falsifications of Product F by reporting countries

The data evaluation shows that the country with the highest number of confirmed falsifications of Product F is Colombia.

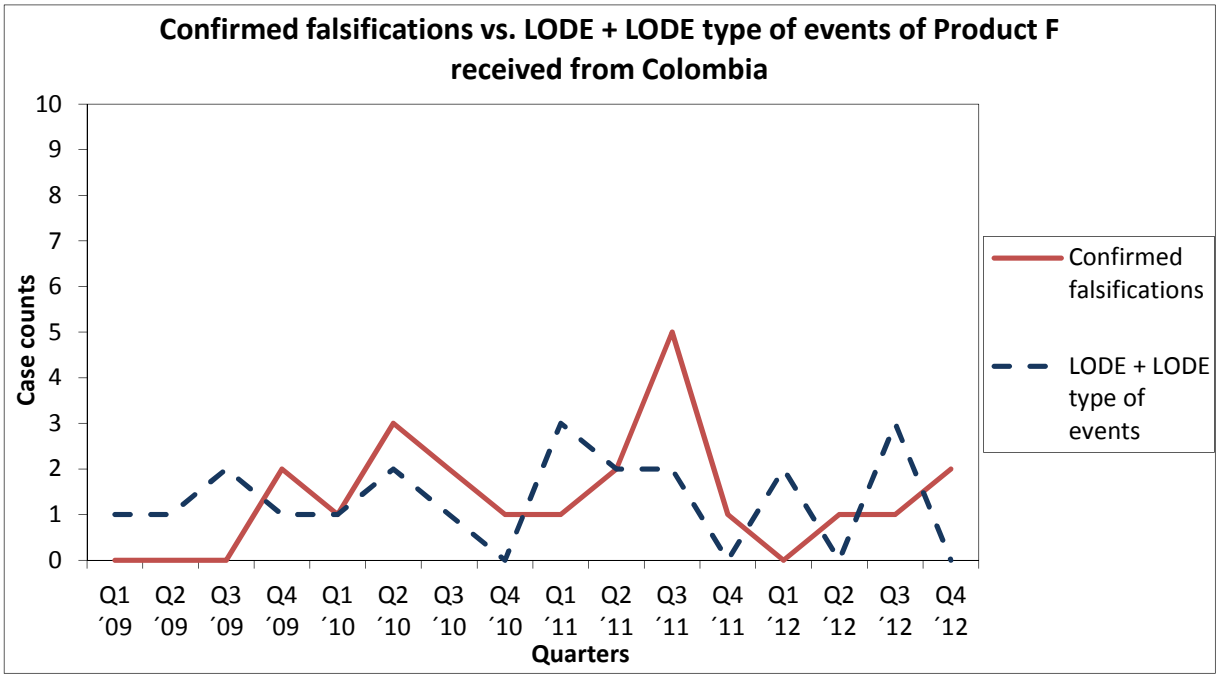

Figure 35: Confirmed falsifications vs. LODE + LODE type of events of Product F received from Colombia

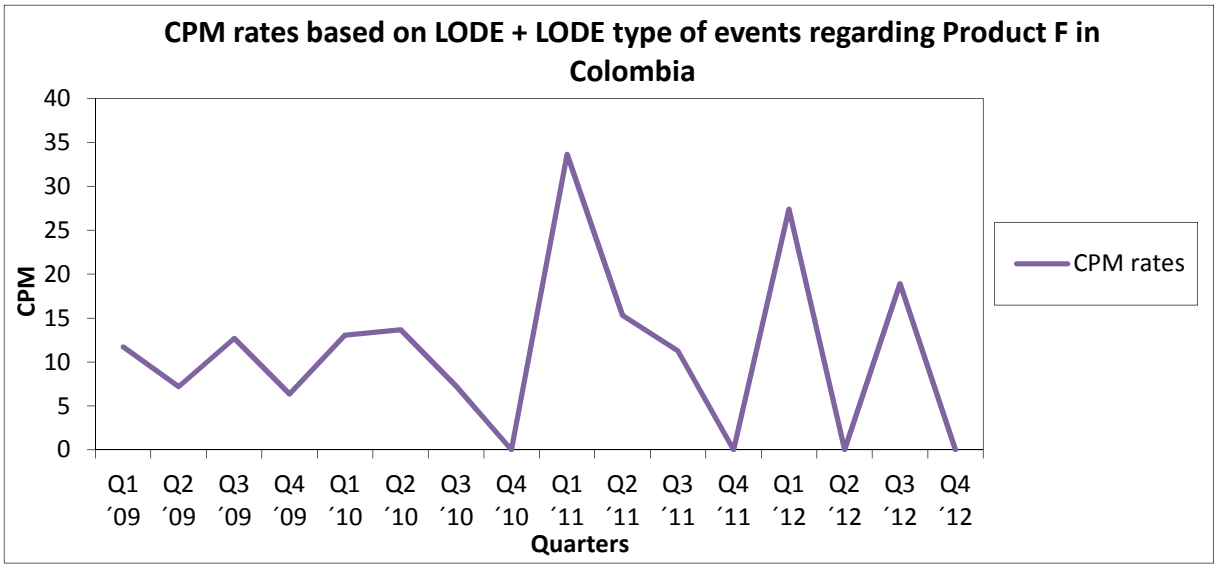

Figure 36: CPM rates based on LODE + LODE type of events regarding Product F in Colombia

In 2011 and 2012, the CPM rates are increased in comparison to 2009 and 2010, i.e. the sales quantities were decreased in 2011 and 2012. However, the decreased sales quantities had no weakening effect on the number of received LODE + LODE type of event cases.

$$\rho = \frac{\sum_i (rx_i - \overline{rx})(ry_i - \overline{ry})}{\sqrt{\sum_i (rx_i - \overline{rx})^2}\sqrt{\sum_i (ry_i - \overline{ry})^2}}$$

$$\rho = \frac{8.5}{\sqrt{312.5}\sqrt{314.5}}$$

$$\rho = 0.027$$

The value of ρ is 0.027, i.e. the relationship between the variables is very weak.

For the sample size n = 16 and the respective degrees of freedom df = 14, the absolute value of *rho* is I ρ I = 0.027. The significance level of I ρ I = 0.027 is greater than the 5% significance level, i.e. the likelihood that the null hypothesis is falsely rejected is too high. Therefore, the null hypothesis is not rejected.

There is no correlation between the variables regarding Product F.

3.4 Results

Based on the evaluation of the confirmed falsifications regarding the 6 products in scope 8 product-country combinations of a high counterfeit presence were identified. For each of the 8 product-country combinations it was examined if a correlation between the confirmed falsification cases and the LODE + LODE type of event cases can be identified. A correlation

between the respective data could be confirmed for 3 out of the 8 product-country combinations.

Product	Country	*rho*	H_0 rejected	Correlation confirmed
A	Colombia	-0.048	no	no
B	Colombia	**0.873**	yes	**yes**
C	China	-0.139	no	no
D	Japan	-0.103	no	no
D	Germany	**0.741**	yes	**yes**
D	Israel	0.114	no	no
E	Colombia	**0.909**	yes	**yes**
F	Colombia	0.027	no	no

Table 8: Results of the statistical evaluation (overview)

It can be concluded that an increase in LODE + LODE type of event cases is not mandatorily indicative for the presence of counterfeits of the respective drug in the monitored market. However, the examples where a correlation between the data could be confirmed revealed that the adverse event data can serve as a source for hints at a potential counterfeit presence. For that reason, the monitoring of AE data regarding a potential counterfeit presence in a specific market can be a helpful measure to complete the assessment of a medicinal product's benefit-risk profile taking all possible influences into consideration. In this context, it is also necessary to examine the data, on which the evaluation of a medicinal product's benefit-risk profile is based, regarding all potential influencing factors, as far as possible. Furthermore, the analysis results show that a monitoring concept regarding a potential counterfeit presence based on adverse event data has to be set up in a very detailed and product-specific way to exclude as many errors as possible.

3.5 Influencing factors

3.5.1 Reporting behavior

The conducted data analysis, as well as all monitoring and data evaluation activities, carried out by a pharmaceutical company are based on the reports the company collects and documents. However, the case reporting regarding both, adverse events and suspected counterfeit incidents is influenced by several factors. A pharmaceutical company can only collect, process, monitor, and evaluate what is brought to its attention. The collection of case reports is rather a passive process, except the follow-up processes to actively collect more information with regard to a received case. Only a minor amount of the case collection is - in the first place - based on investigative activities conducted by the pharmaceutical company to actively collect cases. One example of such an investigative activity with respect to

counterfeit incidents is the conduct of test purchases. Another example with regard to adverse events is the implementation of patient assistant programs (PAP), also denoted as patient support programs (PSP), where patients are guided and actively asked if they have any problems with the respective medicinal product. For that reason, the data collection depends mainly on the reporting behavior of all reporters, including patients, healthcare professionals and authorities, all over the world. Measures like patient support programs and trainings provided to healthcare professionals can have a positive influence on the reporting behavior with respect to AE cases in a country or region. A close collaboration with health authorities, enforcement bodies and customs and the conduct of public education campaigns regarding counterfeit medicines can also cause an increase in the reporting of suspected counterfeit incidents. Such an increase is described as “stimulated reporting”. Cultural differences, the knowledge about the possibility to report cases and about the respective contacts, awareness of potential risks regarding medicinal products and the circumstances with respect to the established medical and medial infrastructure can influence the reporting behavior.

High-income countries

Patients or consumers report mainly lifestyle or high price (private fee) medicines directly to the MAH in order to claim reimbursement. Adverse events regarding other prescription or non-prescription medicines are usually discussed with the respective HCP (physician, pharmacist, nurse, etc.) who in turn decides whether the AE will be reported or not. A certain proportion may not be aware of having the possibility to address their adverse event directly to the MAH. Regarding the reporting of suspected counterfeit incidents, the public may have the opinion that counterfeiting of medicines is a problem affecting only low-income countries. Therefore, they may not question the authenticity of their medicines and check them for any suspicious characteristics.

Low-income countries

A major amount of the population has limited access to medicines, at all. The poor population is lucky when they receive any treatment. Limited access to media, including telephone and internet or great distances to HCPs because of a narrow medical infrastructure regarding secluded places would constrain the reporting of adverse events or suspected counterfeit incidents. Based on the counterfeit incidents known from literature and the narrow regulatory system regarding the distribution of pharmaceutical products, a higher number of suspected counterfeit incident reports would be expected to be received from this region. However, the reporting regarding these countries is mainly rather low.

CHAPTER FOUR – AWARENESS-RAISING

4.1 Influence of awareness-raising measures on the reporting behavior regarding suspected counterfeit incidents

In the context of this dissertation the company-internal data concerning suspected counterfeit incidents was assessed to examine the influence of awareness-raising measures on the reporting behavior with regard to such cases. The graphical evaluation of the received suspected counterfeit incidents in the years 2009 to 2012 with regard to the reporters of the received cases shows that there is a high amount of cases reported by authorities (health authorities, enforcement bodies and customs) and company-internal staff. The number of reports received from patients and healthcare professionals is rather low taking their high ratio of contact with medicines into consideration (see figure 37). Moreover, 90% of the reports received from patients, all over the world, are related to only 7 countries: Colombia, the US, Germany, China, Brazil, Russia and the UK. Of all the received suspected counterfeit incident reports from patients, those from Colombia alone account for 47% (see figure 38).

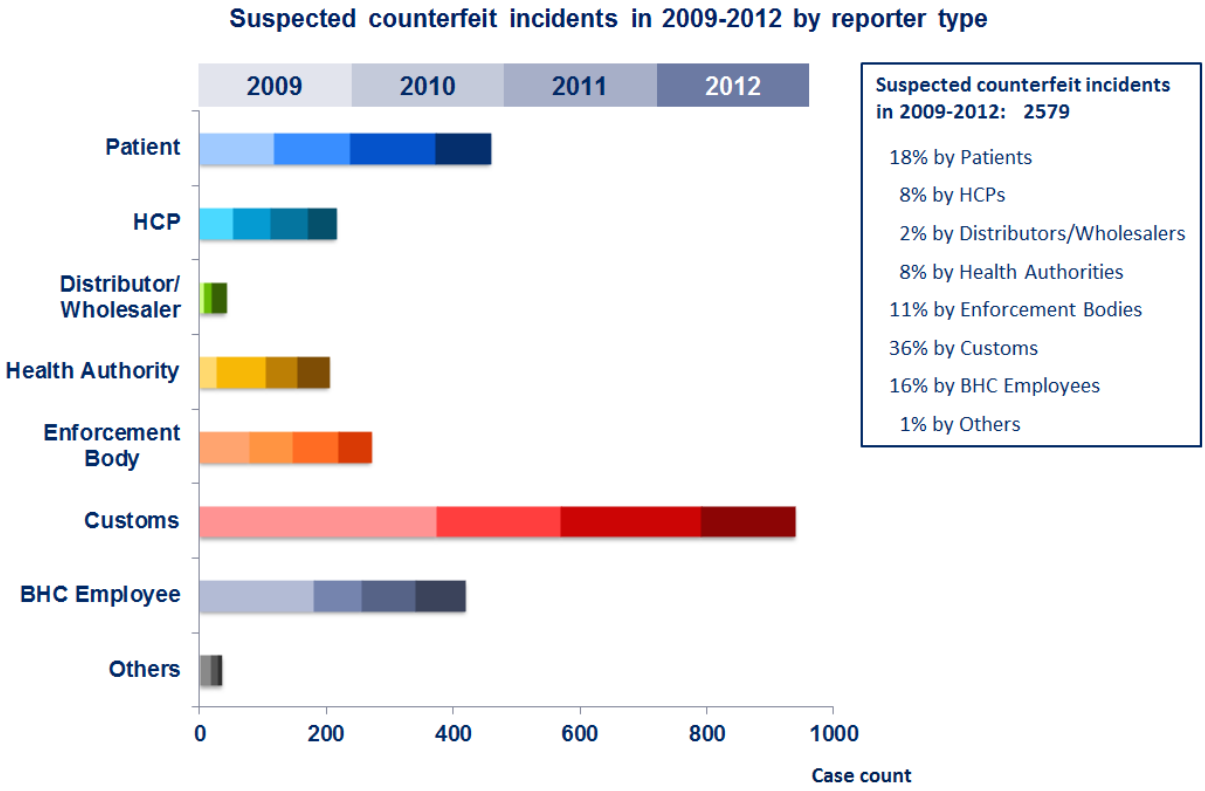

Figure 37: Suspected counterfeit incidents in 2009-2012 by reporter type

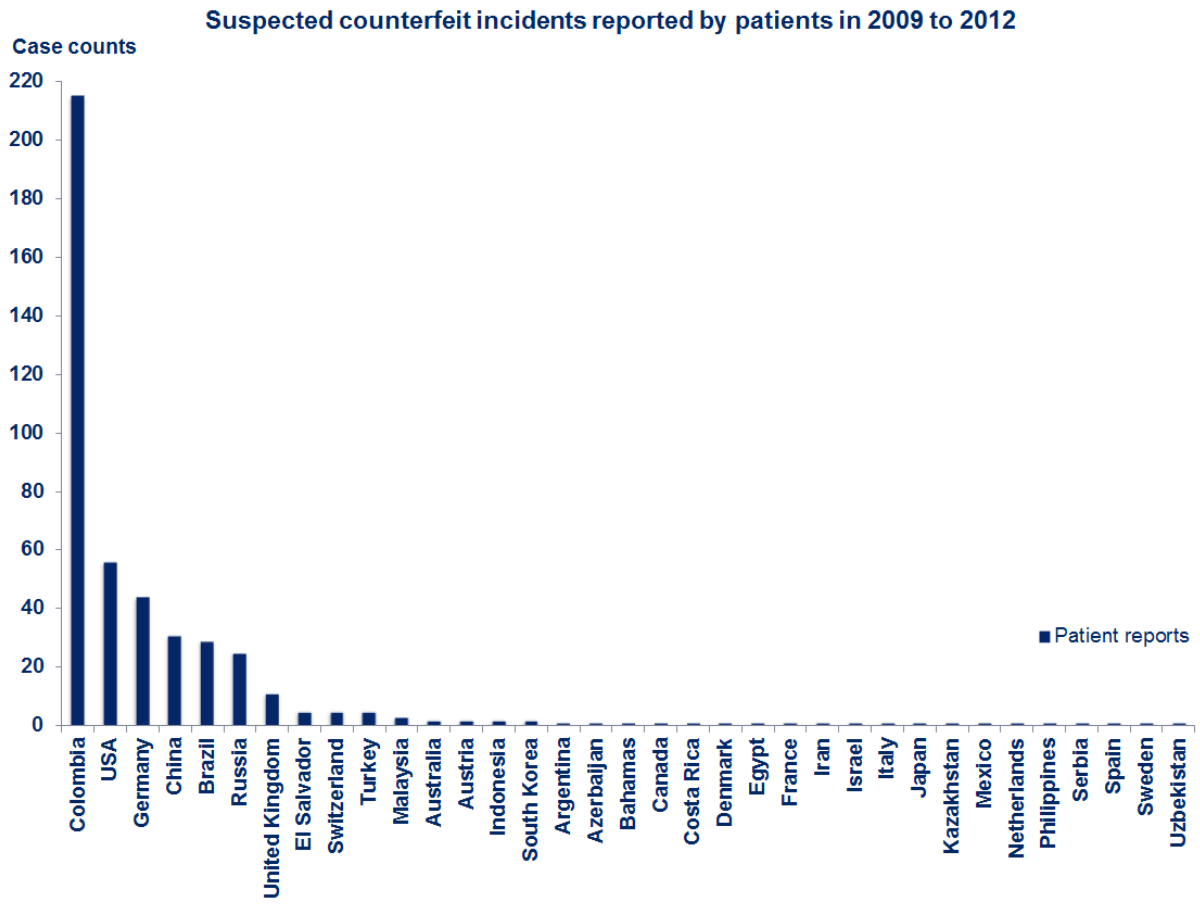

Figure 38: Suspected counterfeit incidents reported by patients in 2009 to 2012

Having a closer look on the situation in Colombia, the local affiliate goes to great efforts to raise awareness of the counterfeit problem among the public. Furthermore, the local affiliate collaborates closely with the local authorities and routinely provides its internal staff with counterfeit-specific training. When a counterfeit incident report concerning a falsification is received and could be confirmed after investigation the local competent authority is informed immediately. In accordance with the competent authority an “awareness note” is published in the main newspapers of the country containing relevant information including the name and the batch number of the affected product. Additionally, the “awareness note” contains the web address of the local anti-counterfeiting website where more information (e.g. about the overt security features applied to the product) is available. The effect of the public “awareness notes” is exhibited by the increased reporting of suspected counterfeit incidents by patients after the release of the “awareness notes” in the newspapers (see figure 39).

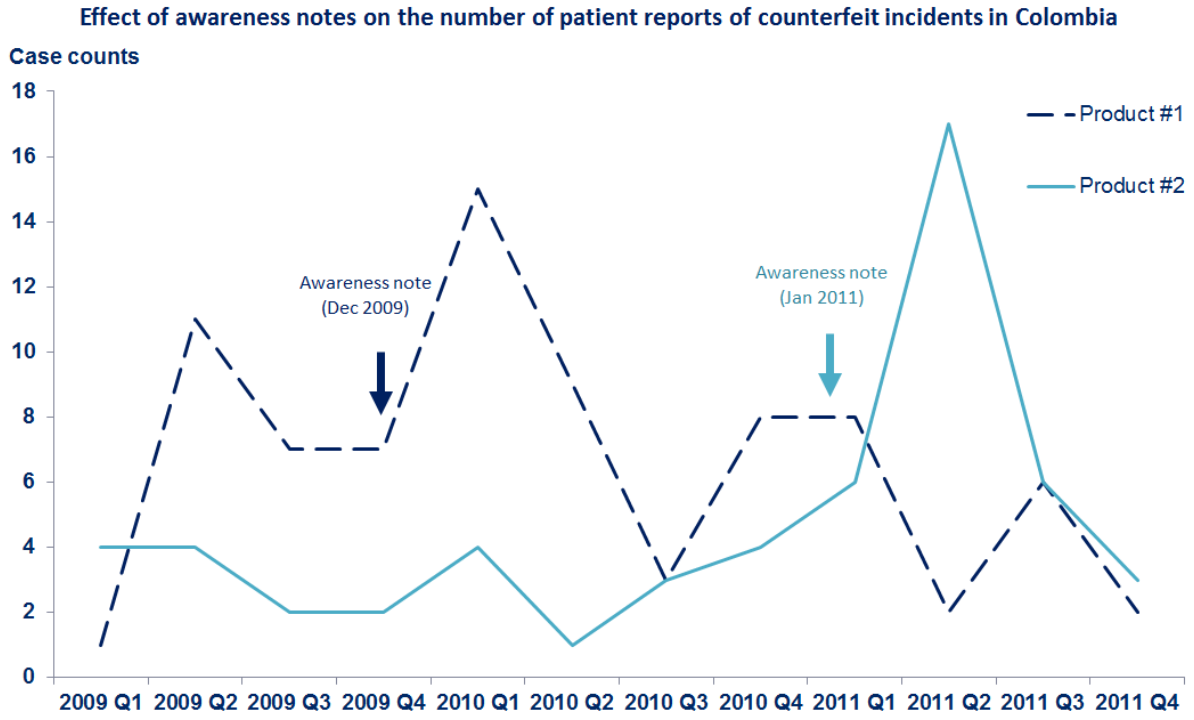

Figure 39: Effect of awareness notes on patient reports of counterfeit incidents in Colombia

Taking the given example into consideration, it becomes clear that anti-counterfeiting measures conducted with the purpose to raise awareness are very effective to inform and educate the public about the counterfeit problem in general and about current issues. Thereby, patients are able to protect themselves, as they know what to be aware of. Additionally, by reporting suspected counterfeit incidents, patients can help the pharmaceutical company to collect more valuable information that can be used for the decision about further required actions. Therefore, a pharmaceutical company should take action to raise awareness of the risks related to counterfeit medicines among the public, e.g. by conducting public education campaigns. The successful conduct of such a campaign depends very much on a good preparation, planning and consideration of potential influencing or limiting aspects. Based on the detailed consideration of these aspects two options to prepare an education campaign, including their comparison against each other, have been elaborated in the context of the thesis and are outlined in the following paragraphs.

4.2 Education campaign as an example for ACF measures with regard to awareness-raising

Conducting a public education campaign is one major option for a pharmaceutical company to raise awareness of counterfeit medicines and the risks that are related to the problem. But, as mentioned above, it requires a good preparation and a lot of preliminary considerations

with respect to contents, structure, used media and potential limitations to develop and conduct a successful campaign.

The contents of the campaign depend on the current state of knowledge the public already has and which should be extended by means of the campaign. Furthermore, it is necessary to consider if the information to be communicated should be general or product-specific information regarding the counterfeit issue. The choice of the target group or groups of the campaign also influences the selection of its contents. Additionally, the pharmaceutical company has to decide whether to conduct the campaign under its own name or rather neutrally in collaboration with authorities, associations or other pharmaceutical companies under the name of the respective entity or the group of companies. This again affects the selection of the campaign's contents.

There are various kinds of media which can be used for the conduct of a public education campaign, including print media e.g. newspapers, brochures and posters, broadcast media e.g. TV and radio, and web-based media e.g. websites and social media. However, it has to be examined if the use of such media with regard to a health-related topic is in accordance with valid regulatory requirements. Hence, an education campaign regarding counterfeit medicines has to be adapted according to country-specific limitations, e.g. national legislation concerning the publication of health-related information. Moreover, the selection of appropriate media and its successful use also depends on the public's view what kind of media is reliable. This opinion probably differs from country to country and requires further country-specific adaptation of the campaign's concept.

Economic aspects also have to be taken into consideration to assess the practicability of this kind of anti-counterfeiting measure.

4.2.1 Option #1: Determination of suitable campaign contents by means of a patient survey

One means to prepare an education campaign is to conduct a survey to gain information about several facts, as mentioned above, that are relevant with respect to the concept and the contents of the campaign. The characteristics of such a survey and the different options of realization have been elaborated and are outlined in the following.

Contents

The information gained by means of the survey should provide an idea about the present extend of awareness of the counterfeit problem among the respondents of the survey. For that reason, questions about the awareness of the existence of counterfeit drugs, about the

risks they pose to safety and health and about previous contact with counterfeit medicines should be included in the survey.

The survey should also contain questions with regard to the current extend of knowledge about the counterfeit issue, including questions with regard to the purpose of anti-counterfeiting security features, known anti-counterfeiting security features, known affected product groups and questions about suspicious providers of counterfeit medicines (e.g. illicit online pharmacies and street vendors).

Moreover, it is valuable to know to what extend patients purchase medicines via the internet, what kind of medicines they purchase, how often and for what reasons they use this distribution way. The question about the respective product groups should be a multiple choice question containing, among others, all product groups relevant with respect to the pharmaceutical company's portfolio.

Another aspect that should be addressed in the survey is the reporting attitude. Therefore, the respondents should be asked if they ever reported a complaint - a suspected counterfeit incident or an adverse event - to the respective marketing authorization holder, a healthcare professional or an authority. Additionally, they should be asked for the motivation for reporting the complaint, in case they have ever reported one, and if not, they should be asked for reasons why they never reported a complaint. Again, possible answers can be provided in the form of a multiple choice question, e.g.:

- I never experienced an adverse event or had a suspected counterfeit product
- I never thought about or doubted the authenticity of the medicines I used and therefore never checked it
- I did not know that I could report a complaint
- I did not know whom to contact
- There are no appropriate tools in use to report a complaint

In this context, the survey should include questions about whom patients would first approach in case of an adverse event or a suspected counterfeit product and where they would get the contact information from. In addition, the respondents should be asked if - in their view - the existent reporting tools (e.g. hotline and e-mail contact) are sufficient or if better reporting tools are needed and what kind of tools the respondents would prefer (e.g. reporting app via mobile phone).

The last topic that should be included in the survey is the use of media with regard to counterfeit-specific and, in general, health-related information. It should be asked if the respondents have ever used the websites provided by the authorities and by pharmaceutical companies to inform themselves about the counterfeit issue. If the answer is no, a question about the reasons why they did not access the available information should be posed, providing multiple choice answers, e.g.:

- I have no interest in the topic
- I was not aware of the problem
- I did not know that such information is available

Additionally, the respondents should be asked about what kind of media they judge as reliable with regard to health-related matters and how often they use these media.

Setup

With regard to a proper setup of the patient survey the company-internal “Global Market Research” function has been asked for experiences and advice.

Usually, a consultant agency is assigned by the pharmaceutical company to conduct the survey. The respondents of the survey should be representative for the population of the region or country in scope with regard to socio-demographic criteria, including number of respondents, gender, age group, region (in the country), salary, household size and education. Appropriate correction factors for the respective population should be included for the result evaluation. In terms of a proper practicability it was suggested to conduct a web-based survey. This implies that only the online population of the respective country or region is represented. The acquisition of respondents is done off-line via phone calls or face-to-face. Usually, consultant agencies have participant databases and do acquisition to extend them.

Conduct options and duration

The preliminary phase covers the consultation with the consultant agency, the desk research, the preliminary considerations regarding the contents of the survey and the resulting development of an appropriate questionnaire. There are two main options to conduct such a survey. One option is to interview a focus group first to check if the developed questionnaire is well understood by the respondents and therefore is suitable to gain the required information. Otherwise, the questionnaire can be reviewed and adapted before it is used for the main survey. The other option is to carry out the main survey without

the previous suitability check of the questionnaire. Another aspect to be considered is the decision if the main survey should be conducted in only one or in multiple countries. In case of a multiple countries-survey, there is also the option to interview a focus group in each of the countries in scope to check the comprehensibility of the questions before the main study is carried out.

The previous survey of the focus group would comprise 10 respondents, each country, and would be of 120 min duration to provide enough time for queries. This survey type would be conducted face-to-face. The main survey would comprise 1000 respondents, each country, and would be of 30 min duration. The questionnaire would be web-based. In figure 40 the sequence of the different steps is shown if both, the main survey and the previous survey are conducted, including the required time of the different steps (according to the estimations and experiences of the Global Market Research function).

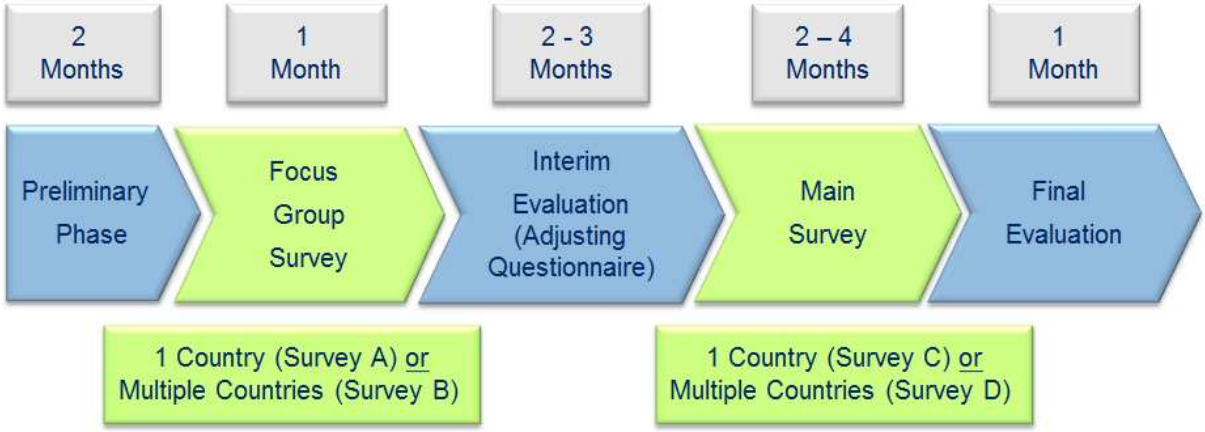

Figure 40: Survey types of the patient survey and duration of the conduct

The advantages and disadvantages of the different survey types are summed up in table 9.

Survey type	Advantages	Disadvantages
A*	• Suitability check of the questionnaire is carried out • The probability to receive a comprehensive result of the main survey is enhanced	• Suitability check only with regard to a single country
B*	• Suitability check of the questionnaire is carried out in multiple countries • Check if the questionnaire has to be adapted with regard to the different countries to achieve maximum result quality	• Additional costs in comparison to survey A
C**	• Minor expenses in comparison to conduct the main survey in several countries	• No information about the country specific differences
D**	• Results from multiple countries, better overview, • Possibility to compare between regions and countries	• Additional costs in comparison to survey C
* 10 respondents each country ** 1000 respondents each country		

Table 9: Advantages and disadvantages of the different survey types

Based on the information gained in the patient survey the education campaign can be planned and structured aligned to the situation in the country or countries in scope.

4.2.2 Option #2: Determination of suitable campaign contents by the means of preliminary considerations and the conduct of a pilot project

Another option with respect to gaining experience about an appropriate setup and conduct of a successful education campaign would be the trial and error principal by implementing a product-specific pilot project within one country in scope to serve as an orientation for further education campaigns regarding other products and countries. The selection of the medicinal product for the anti-counterfeiting education campaign pilot project depends on several aspects. First of all, the potential safety hazard to the patient if the product was counterfeited is relevant for the decision. Secondly, there should be an indication of the counterfeit presence or planned counterfeit activities regarding the respective product, e.g. case reports concerning the diversion or the falsification of the product. Thirdly, economic aspects have to be considered since the price of the product has an impact on the profitable appeal for counterfeiters and on the economic loss of the MAH if counterfeits of the respective medicinal product are on the market. The selection of the country, where the campaign should take place, mainly depends on the fact if reports regarding the counterfeit presence or planned counterfeit activities have already been received from this country. Another aspect

that should be considered is the number of patients potentially affected by counterfeits of the selected product.

4.2.3 Comparison of advantages and disadvantages of option #1 and #2

	Advantages	Disadvantages
Option #1: Patient survey	• Gaining profound information about: − The current state of knowledge and awareness of the counterfeit topic among the public − Patient reporting behavior and their use habits of media regarding health-related issues − Purchasing behavior with respect to medicinal product groups via the internet • Option to gain information comparable across countries	• Additional (high) expenses prior to the conduct of the education campaign • Major time effort → delayed implementation of the education campaign, itself • No gain of product-specific information (only product groups)
Option #2: Pilot project	• Immediate gaining of information and experiences regarding: − Planning and scheduling required steps − Net-working and collaborating with several functions of different areas − Country-specific requirements (e.g. national legislation, cultural aspects) • Possibility to use product-specific programs as a means for the education campaign (e.g. patients assistant programs, if permitted) • Implementation of the campaign in a timely manner • Saving additional expenses	• Contents and setup of the campaign are based on assumptions, not on gained facts → minor risk a of less successful campaign • Gained experiences are not all suitable for other country and product combinations → need to adapt further campaigns

Table 10: Advantages and disadvantages of option #1 and #2

Based on the comparison of the advantages and disadvantages the conduct of a product- and country-specific pilot project was selected as the preferred option at choice.

4.2.4 Approval process

In the context of this dissertation a presentation for the required approval process in the pharmaceutical company was created. Such a presentation has to comprise information about the background of the problem, an analysis of the current state of knowledge based on literature and company-internal data, the framework of the necessity of the project which is asked approval for and a comparison of the advantages and disadvantages of the different options at choice as given in the previous paragraphs, including a proposal of the preferred option and its scope. This business case was presented to the different function heads whose areas would be affected by the project: Head of Counterfeit Protection Management, Head of Global Pharmacovigilance, Head of Global Medical Affairs & Pharmacovigilance, Head of Quality Assurance and Head of Product Supply Pharma (including necessary management levels).

All function heads gave approval to conduct the preferred option of the project, the product- and country-specific education campaign, including the proposal of the selected product and country in scope.

4.3 Pilot project: Product- and country-specific education campaign

4.3.1 Preparation of the pilot project

The selected medicinal product in scope of the education campaign is the oral multikinase inhibitor Nexavar® which is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) and patients with hepatocellular carcinoma (HCC). [112][209] Moreover, the US FDA approved Nexavar® for the treatment of patients with differentiated thyroid carcinoma (DTC) in the US, in 2013. [113][210] In 2014, Nexavar® was approved for this indication also by the EC in the EU [114][211] and by the Japanese Ministry of Health, Labour and Welfare (MHLW) in Japan [115][212]. According to studies that compared the efficacy of Nexavar® to placebo in patients with HCC and RCC, the results show that statistically Nexavar® significantly prolonged the progression-free survival. [116][213] [117][214] Thus, counterfeits of this medicinal product could shorten patients' already shortened lifespan.

The country in scope of the campaign is China. Nexavar® was approved in China for RCC in 2007 and for HCC in 2008. [118][215] In 2012, more than 7500 RCC and HCC patients were treated with Nexavar® in China. In 2010 and 2011, 2 confirmed counterfeit incidents were received from China with respect to Nexavar®. Both incidents were related to the imitation of product-specific packaging materials in a larger scale. Imitations of the complete medicinal product, including the dosage form, have not yet been identified. However, the confirmed

[209] Bayer AG, "Nexavar.com," October 2011. [Online]. Available: http://www.nexavar-international.com/home/index.php. [Accessed 19 February 2014].
[210] Bayer AG, "Nexavar zur Behandlung von differenziertem Schilddrüsenkrebs in den USA zugelassen," February 2014. [Online]. Available: http://www.nexavar.de/de/fachkreise/rcc/aktuelles/news/news.php/15303. [Accessed 19 February 2014].
[211] Bayer AG, "Bayer erhält EU-Zulassung für Nexavar zur Behandlung des differenzierten Schilddrüsenkarzinoms," 30 May 2014. [Online]. Available: http://www.nexavar.de/de/fachkreise/rcc/aktuelles/news/news.php/15517. [Accessed 13 June 2014].
[212] Bayer AG, "Bayer erhält in Japan die Zulassung für Nexavar® (Sorafenib) zur Behandlung von differenzierten Schilddrüsenkarzinomen," 20 June 2014. [Online]. Available: http://www.nexavar.de/de/fachkreise/rcc/aktuelles/news/news.php/15543. [Accessed 4 July 2014].
[213] Bayer AG, "Nexavar — Demonstrated a Statistically Significant Advantage in Overall Survival (OS) vs Placebo in HCC," [Online]. Available: http://www.nexavar-international.com/home/hcp_nexavar_hcc/index.php. [Accessed 19 February 2014].
[214] Bayer AG, "Nexavar — A Multikinase Inhibitor Approved for the Treatment of Patients With Advanced RCC," [Online]. Available: http://www.nexavar-international.com/home/nexavar_for_advanced_rcc/index.php. [Accessed 19 February 2014].
[215] Bayer AG, "Nexavar Approved for Liver Cancer in China," 28 July 2008. [Online]. Available: http://pharma.bayer.com/scripts/pages/en/news_room/news_room/news_room64.php. [Accessed 19 February 2014].

counterfeit incidents regarding the packaging materials indicated the presence of counterfeit activities with respect to Nexavar® on the Chinese market. For that reason, this product-country combination was selected for the pilot project.

Such a project requires the collaboration of several functions, including Quality, Pharmacovigilance, Medical Affairs, Legal, Communications and Marketing. The respective global and local responsible colleagues have to be asked for their support. Most of the involved functions were already introduced to the project during the approval process. Therefore, a telephone conference was scheduled with the responsible colleagues of Global Marketing Oncology to introduce them to the planned project, too, and to ask for their support and the respective local responsible contacts. Subsequently, a telephone conference was held with the local responsible colleagues in China. The project contents were presented with respect to the selected product and the information to be published. The local colleagues agreed to the proposed suggestion and offered their support with regard to the further preparation of the required informative literature and the realization of the project. In the subsequent follow-up meetings, via telephone conference, the following aspects have been discussed:

- The target groups of the campaign
- Suitable media
- The distribution way(s) to be used for print media
- The contents regarding the different types of media

4.3.2 Implementation of the pilot project

Based on the groundwork done in the context of the dissertation the project was carried out in collaboration with the local colleagues in China. It was decided to distribute the informative literature to local drug distribution points (hospitals, pharmacies and charity federations) to reach out to patients and healthcare professionals. In this context, it was decided to include general information regarding the counterfeit problem, specific information regarding overt anti-counterfeiting security features applied to the packaging material of the Chinese Nexavar® presentation and contact information regarding the company hotline and the SFDA

respectively CFDA hotline. In March 2013, the SFDA (State Food and Drug Administration) became the CFDA (China Food and Drug Administration). [119][216]

As a result, a hand-out (2-pages, front and back) and a poster (one-page), containing the mentioned information including pictorial material, were created in English (see annex 1-3). Afterwards the local colleagues translated the hand-out and the poster into Chinese and initiated the reproduction of the informative literature for its distribution to 39 drug distribution points all over China. It was scheduled that each distribution point would be provided with minimum 100 copies of the hand-out and minimum one poster. Larger cities e.g. Beijing and Shanghai would receive a higher number of materials.

Furthermore, a “floating icon” was added to the local website of the Nexavar® patient support program in China (see figure 41). By clicking on the icon, the user was forwarded to a digital version of the described hand-out. The icon was active from January 11, 2013 to June 20, 2013.

Figure 41: Floating icon applied to local PAP website

Moreover, it was decided to train the local marketing staff regarding the purpose and contents of the education campaign. 180 sales representatives were trained in January 2013.

After the review of the informative literature by the Quality, Medical Affairs and Legal functions at the beginning of 2013, the distribution of the materials started on March 1, 2013.

4.3.3 Results

The Nexavar®-specific education campaign in China was very successful. The target groups of the campaign showed very high interest in the information which was provided to them. Only three month after the beginning of the distribution of the Nexavar® informative literature the first printing was already exhausted and it was ordered to print and distribute a second printing. Furthermore, the traffic on the Nexavar® patient assistant program website reached 4306 clicks on the floating icon in the time period of January 11, 2013 to June 20, 2013. The

[216] A. Gaffney, "RF Regulatory Focus," 25 March 2013. [Online]. Available: http://www.raps.org/focus-online/news/news-article-view/article/3073/chinas-sfda-becomes-cfda-amidst-consolidation-of-power-and-new-leadership.aspx. [Accessed 26 August 2013].

number of clicks exceeds the number of Nexavar® PAP patients in China in 2013. Thus, it can be assumed that the majority of the respective patients accessed the provided information.

Moreover, the project which was initiated in the framework of the thesis lead to a raised awareness of the anti-counterfeiting topic among the different involved functions due to the broad collaboration between Global Pharmacovigilance, the global Quality Assurance responsible for anti-counterfeiting and multiple responsible persons of the local functions, including Medical Affairs, PV, Quality Assurance, Legal and Marketing. Additionally, the public education campaign was reason to provide the local personnel with counterfeit-specific training to enhance their knowledge about the topic.

CHAPTER FIVE – REVIEW OF INTERNAL ANTI-COUNTERFEITING PROCEDURES

5.1 Company-wide affiliate survey

As mentioned in paragraph 2.7, a global pharmaceutical company has to ensure that all procedures required with respect to its established anti-counterfeiting concept are consistent in all its affiliates, all over the world. This includes knowledge about the counterfeit topic, responsible functions and contact persons, required obligations and established processes and activities. Consistent procedures are the basis for the effective implementation of the company's anti-counterfeiting concept. However, country-specific circumstances have to be attended and, as a consequence, local adaptations of the required procedures have to be established.

Therefore, a survey was planned and a respective questionnaire was developed, in the context of the dissertation, to gain information about the current state of the mentioned aspects in the company's affiliates. To this extent further questions, e.g. regarding locally implemented anti-counterfeiting activities need to be answered. If a pharmaceutical company plans to carry out anti-counterfeiting measures regarding awareness-raising, e.g. an education campaign in a specific country, it is valuable to know if a public campaign has ever been done to address this issue. The information, if the public has ever been confronted with the topic before or not, has an impact on the decision on the contents of the planned campaign. In this context, it should be clarified if the local affiliate was ever involved in such anti-counterfeiting activities or if it collaborates otherwise with local authorities or associations with regard to the problem of counterfeit medicines.

Furthermore, the survey should provide the surveyed employees the opportunity to address support needs with respect to the topic. Thus, the central functions are better informed about the needs of the local employees and can better respond to these needs with appropriate supportive measures.

5.1.1 Preparation, contents and conduct of the affiliate survey

To conduct a global company-internal survey it is required to obtain approval by the heads of all involved functions. As the counterfeit medicines topic affects multiple functions, the following functions are in scope of the survey and needed to be asked for approval:

- Medical Affairs
- Pharmacovigilance

- Quality Assurance
- Legal
- Marketing
- Medical information

With regard to the approval process the business case of the survey, including its purpose, background, the setup options and the functions in scope was compiled in the context of this thesis.

With regard to the setup the company's function of Business Services was approached to clarify the setup options and the procedure of the planned project. There are two possible options to conduct a web-based survey which are presented in the following table. Their advantages and disadvantages were evaluated and are included in the table with respect to the business case presentation.

Survey Type	Explanation	Advantages	Disadvantages
Personalized	• Fixed number of respondents (address list) • Every link to access the questionnaire is codified to only one respondent • Results are provided anonymized	• Data privacy is guaranteed • Data is directly entered into a database (ext. server, consultant agency) • Response rate can be defined • Automatic reminder e-mails to all invitees can be set up and sent out during the field time • Extended chance of a high response rate	• Limited number of respondents (target recipients)
Anonymized	• Links to the questionnaire are not codified • Invitation incl. the link can be forwarded by the invitee to further respondents • Number of respondents who receive an invitation is unknown	• Data privacy is guaranteed • Data is directly entered into a database (ext. server, consultant agency) • Opportunity for the invitees to forward the invitation incl. the link to further respondents possibly involved in the topic • No limitations regarding the number of respondents	• Evaluation of response rate not possible • No opportunity to send out reminder e-mails since not all recipients of the invitation are known • Higher risk of a low response rate

Table 11: Advantages and disadvantages of the personalized and the anonymized survey type

Based on the comparison of the advantages and disadvantages of the given options, the personalized survey was selected and presented as the preferred option in the approval process.

The Business Services function was also asked about the estimated duration of the survey procedure. The procedure requires the following steps to prepare and carry out the survey. First of all, an English and a German version of the questionnaire to be distributed has to be provided to the company's works committee, located in Berlin and Leverkusen, for approval. The works committee checks the contents of the questionnaire and gives its approval if the questionnaire adheres to the works committee's guidelines on data privacy regarding personal data. Then, the Business Services function programs the questionnaire, after which the contents are checked and its performance tested by the initiator of the survey. The invitations are prepared based on the respondents list which has to be compiled by the initiator and provided to the Business Services function. The field time describes the time period in which the questionnaire is online and can be accessed by the respondents, i.e. from the day of distribution of the invitations to the close-out of the survey. The responses are transferred into a database. In the last step, the Business Services function exports the data from the database and compiles the raw data in a Microsoft® Excel file which is then provided to the initiator for evaluation. In the following figure the described steps and their estimated duration are depicted.

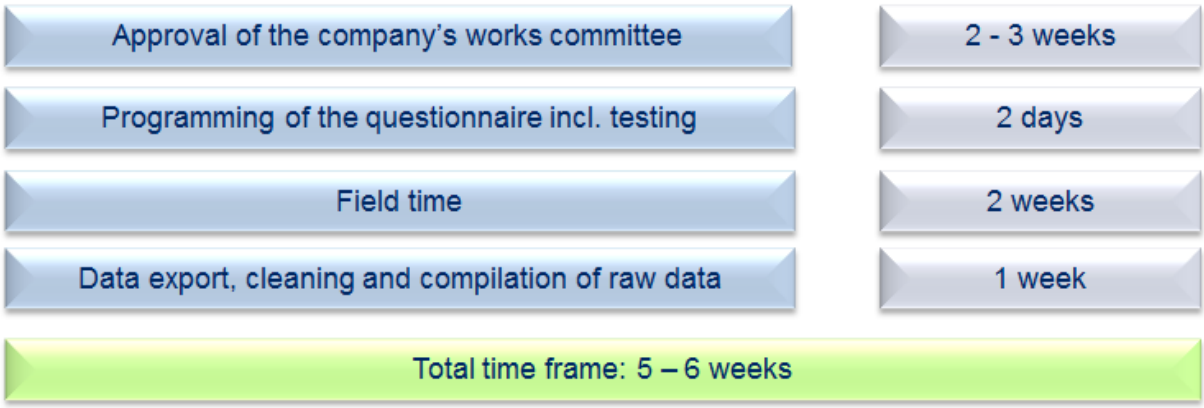

Figure 42: Procedure of the affiliate survey

The information on the setup options and the procedure, received from the Business Services function, as well as all prepared information on the purpose and the background of the survey, including the functions in scope and the preferred setup option was compiled and a presentation created in the context of this dissertation. According to the approval process the presentation was held to the heads of all functions to be involved in the survey to ask for their approval and support. The approval has been received from all required functions, including the Head of Medical Affairs & Pharmacovigilance, Head of Pharmacovigilance Regions, Head of Product Supply Pharma, Head of Quality Assurance, Head of Global Anti-Counterfeiting, Head of Counterfeit Protection Management and Head of Global Marketing Operations.

Acting as the initiator of the survey a questionnaire, comprising 20 questions with respect to all mentioned aspects of interest, was developed in English in the context of this dissertation. Its phrasing was reviewed by a native speaker to check the comprehensibility of the questions. The English and the German version of the questionnaire were provided to the company's works committee for approval, which was permitted. The invitation e-mail for the web-based survey, the "landing page" of the questionnaire and the reminder e-mail were also phrased in English and were reviewed by a native speaker. Based on the functions in scope of the survey, a list of all affected employees was compiled, including their roles, names and e-mail addresses, to be provided to the responsible colleague of the Business Services function. The list served as the basis for the coding of the links to the digital version of the questionnaire. All prepared material was provided to the Business Services colleague, who programmed the digital questionnaire. Afterwards, the web-based survey was tested and checked for correctness.

In order to achieve maximum participation in the planned survey an announcement of the survey was phrased, including its purpose, all functions in scope, all supportive function heads and the request to inform all affected employees about the planned survey and to encourage them to participate. This announcement was sent out to all function heads of the affected functions prior to the invitation. The survey invitation e-mails, including the personalized link to the web-based questionnaire, were sent out on October 30, 2012. After the end of the field time of the survey the Business Services function compiled the raw data, which was then evaluated in detail in the context of this thesis, as outlined in the following paragraphs.

5.1.2 Survey results

In addition to the employees of the mentioned functions in scope, the head of the local organization of each country was invited to the survey as he / she represents the main responsible person of the respective affiliate. The survey invitations were sent out to 272 employees in 84 countries. It has to be mentioned that the number of invitees per country differs for the following reason: In some countries more than one of the roles in scope is assigned to one employee. Furthermore, the roles are not always allocated to only one country. One Pharmacovigilance Country Head (PVCH), for example, can be responsible for multiple countries. In this case the respective employee should answer the questionnaire with regard to his or her country of main responsibility (mostly the country of residence). Out of the 272 invitees 149 participated in the survey which makes a response rate of 55%. Regarding the countries, employees of 70 out of the 84 invited countries took part which makes a response rate of 83%. In the following chart the response rate of the countries is

displayed by regions. The results show that the participation in the survey and hence, the interest in the counterfeit topic is high (above 70%) across all regions.

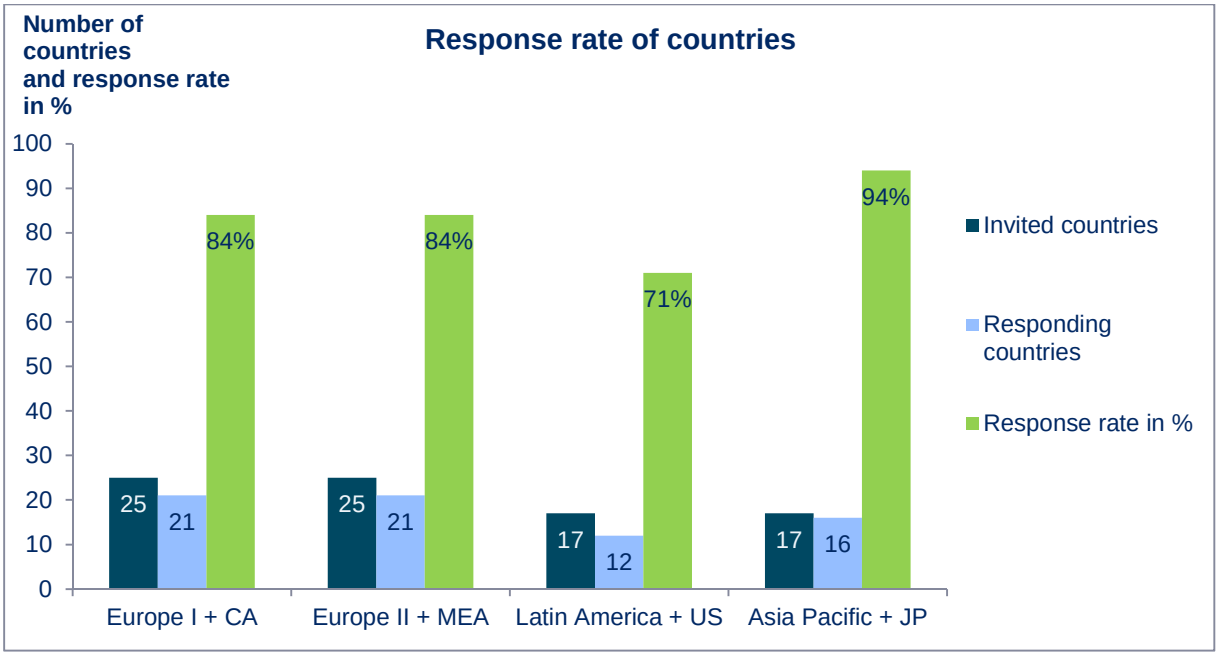

Figure 43: Response rate of countries

Besides the major interest in the topic, which is represented by the high participation, the survey results also reveal a high quality regarding the received answers. The majority of the questionnaires were completely filled out, with the participants giving valuable feedback instead of selecting "unknown" for numerous questions. Thus, the results show that the questions were well understood.

5.1.2.1 Question 1

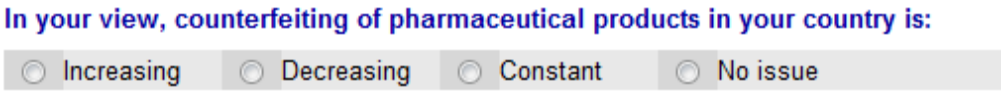

Figure 44: Question 1 of the affiliate survey, snap shot of the web-based questionnaire

The majority (75%) of the 149 respondents estimate the problem of counterfeiting of medicines as increasing or constant in their country. Only 26% state that the problem is decreasing or even no issue in their country. The results reflect the facts - known from literature - that the counterfeit problem is huge and further expanding.

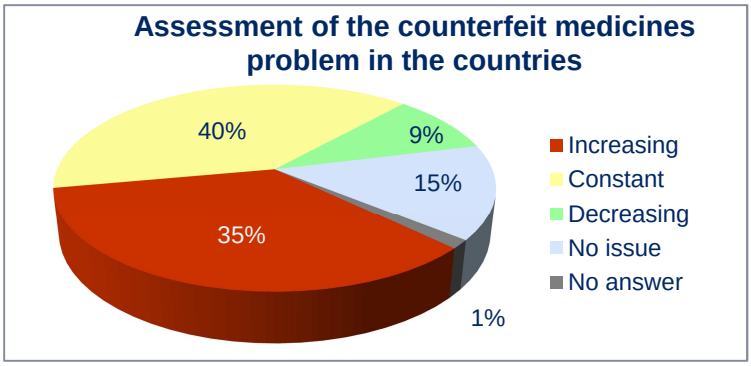

Figure 45: Assessment of the counterfeit medicines problem in the countries

Regarding the results by regions it was expected that - in comparison across the regions – more respondents from the western countries would estimate the problem of counterfeit medicines as no issue in their country. The results confirmed this expectation. However, even in these regions the number of respondents who estimate the problem as increasing exceeds the number of respondents who have the opinion that their country is not affected by counterfeiting of medicinal products. According to the respondents the most affected region is the region of Latin America + the United States, where almost one half of the respondents from this region estimates the problem as increasing.

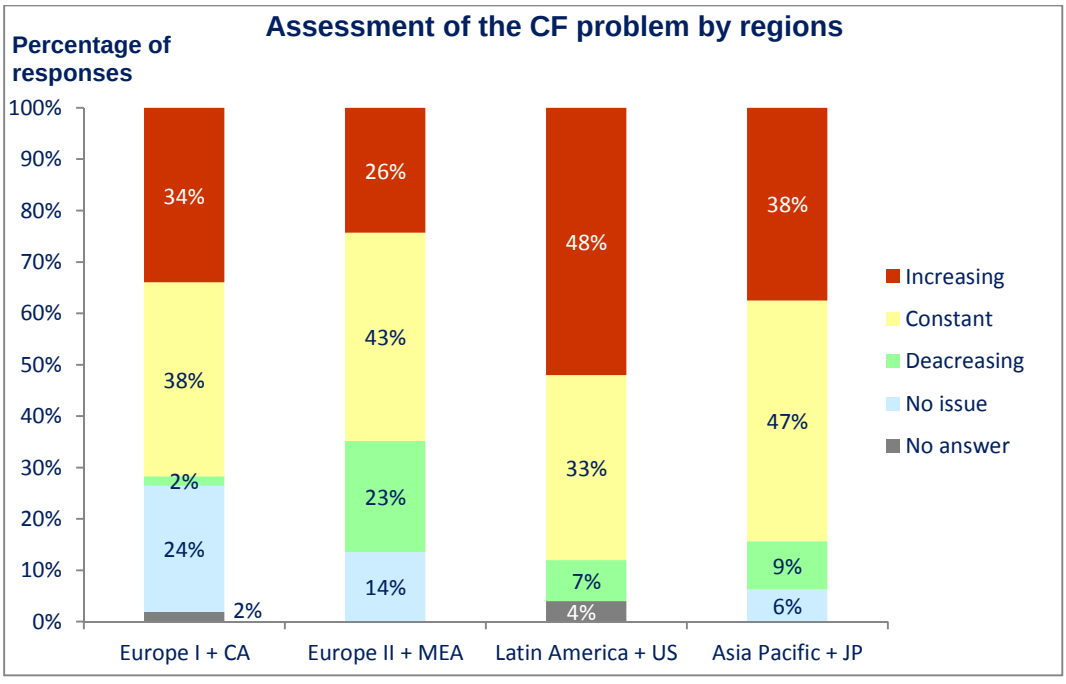

Figure 46: Assessment of the CF problem by regions

Furthermore, it is to mention that a variance in the responses across and even within countries was identified. The region showing the most heterogeneous responses across its countries is Europe II + Middle East & Africa. The dispersion of the different opinions does not present geographical patterns that would point to areas within the region where the

counterfeit problem is rather increasing and others where it is rather decreasing. The region with the most heterogeneous responses within its countries is Europe I + Canada. The heterogeneous responses within the countries could present a hint at a possible lack of communication between the different functions within a country.

5.1.2.2 Question 2

Figure 47: Question 2 of the affiliate survey, snap shot of the web-based questionnaire

More than one half (58%) of the respondents are aware of counterfeits with respect to the company's portfolio. In the regions Europe II + Middle East & Africa and Latin America + the United States the amount of respondents being aware of such counterfeits prevail. In Europe I + Canada and in Asia Pacific + Japan the numbers of respondents being aware and the ones being not aware of such counterfeit products are almost even. Again, an inconsistency of responses across and within the countries could be identified. The heterogeneous responses within the countries could again hint at a possible lack of communication between the local functions.

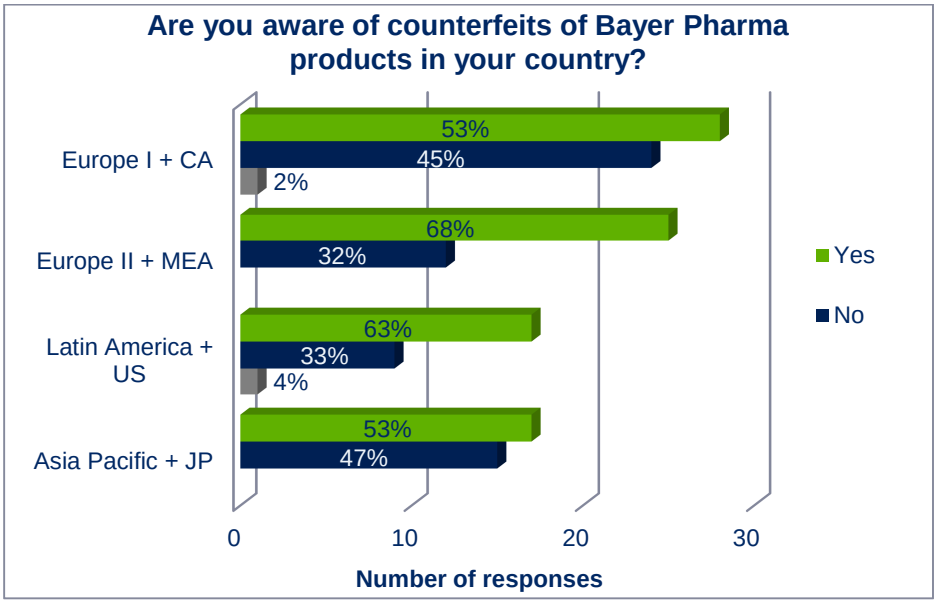

Figure 48: Responses to question 2

In the following bubble chart all responding countries (except the Netherlands and Cambodia from which no answers were received for this question) are displayed with respect to the consistency of the answers the respondents from the respective country gave. The used

country codes are in accordance with ISO 3166 and UN/LOCODE. [120][217] The heterogeneity of the responses across the countries of one region is also shown. Each bubble represents one country. The size of the bubbles corresponds with the number of respondents from the respective country. The color of the bubbles indicates if the answers of the respondents from the respective country are consistent (green) or not (red). Based on the position of the bubbles the answer of the respondents can be read out. The received answers mainly are homogenous within the countries, except within the countries of the region Europe I + Canada. There, in 65% of the responding countries the answers are inconsistent (considering the countries with more than one respondent). It is assumed that the awareness of counterfeit medicinal products depends on how much the respective respondent is involved in the topic. The respondents who are not involved in the topic would share the opinion that the western countries are not affected by counterfeiting of medicines. An enhanced communication between functions would establish clarity. Heterogeneity in the awareness of counterfeits of the company's products across the responding countries can be identified for all regions. Again, no geographical patterns regarding the countries within one region were identified.

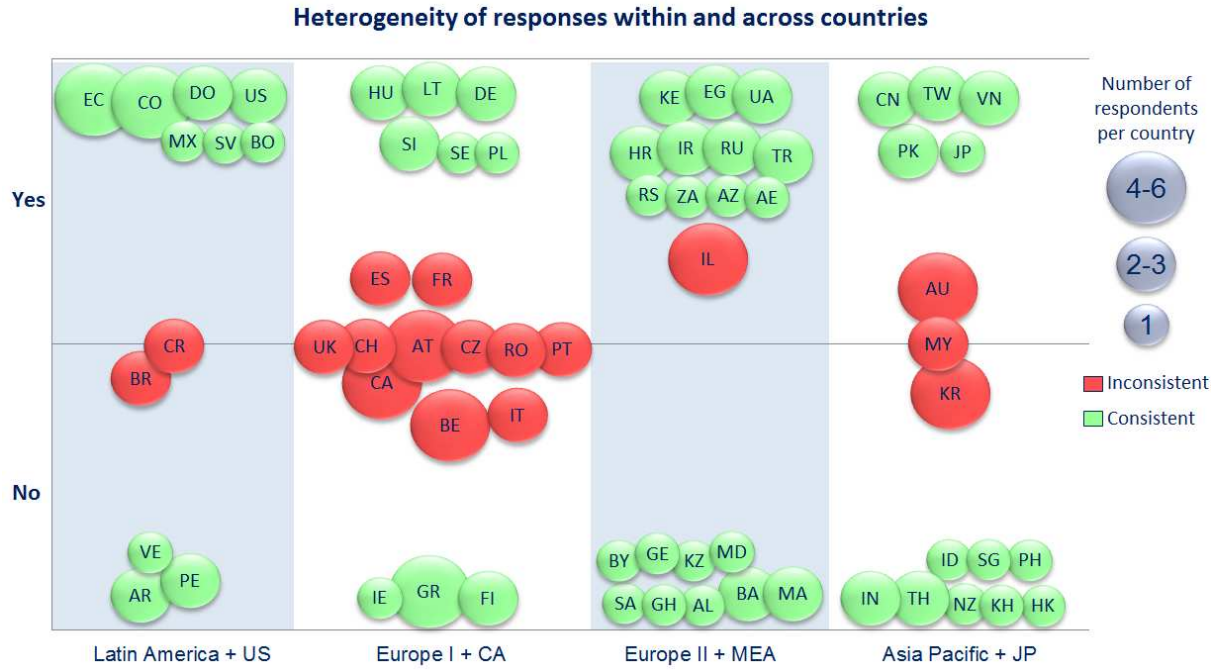

Figure 49: Heterogeneity of responses within and across countries

[217] United Nations Economic Commission for Europe, "United Nations Code for Trade and Transport Locations (UN/LOCODE)," July 2013. [Online]. Available: http://www.unece.org/cefact/locode/service/location.html. [Accessed 3 January 2014].

5.1.2.3 Question 3

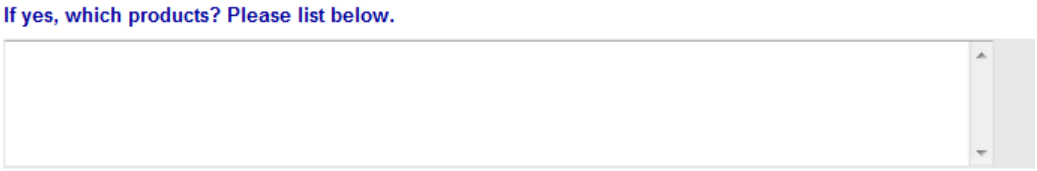

Figure 50: Question 3 of the affiliate survey, snap shot of the web-based questionnaire

Question 3 is related to question 2. With regard to the affected products listed by the respondents, medicinal products for the indication of erectile dysfunction (ED) were named most often followed by pharmaceuticals for hormonal contraception (of any kind of application) and steroids (that can be misused for their anabolic affects or to treat side effects of anabolic drugs). The respondents also listed “over-the-counter” (OTC, non-prescription) medicines and pharmaceutical products of the animal health division, despite the question referred to “Pharma” products that only include prescription-only medicines (POM) for human use. So, these results reveal that counterfeiting of medicines is not only a multi-regional but also a multi-divisional issue. The results also show that the counterfeit medicines problem is not limited to live style drugs but that medicines indicated for live-threatening diseases are affected, as well.

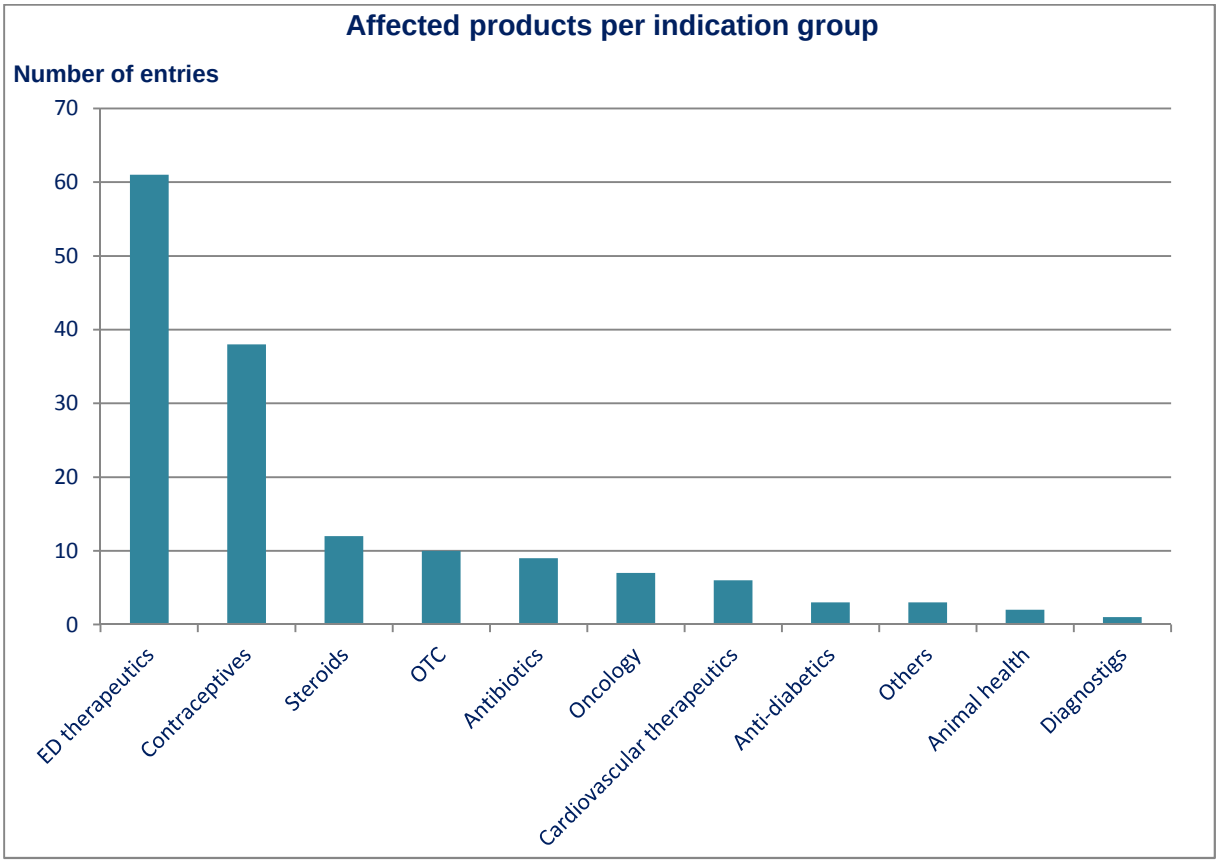

Figure 51: Affected products per indication group

5.1.2.4 Question 4

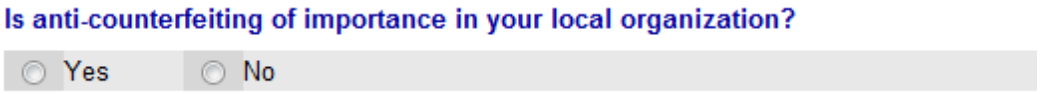

Figure 52: Question 4 of the affiliate survey, snap shot of the web-based questionnaire

More than three out of four (84%) of the respondents state that anti-counterfeiting is of importance in their local organization. This result reflects the major impact of the counterfeit medicines issue across the local affiliates. The respondents of the regions Europe II + Middle East & Africa and Latin America + the US clearly expressed that anti-counterfeiting is an important topic in their local organization. In Europe I + Canada 25% and in Asia Pacific + Japan 19% of the respondents do not share this opinion. With respect to the dispersion of the received answers, it is to say that the responses are mainly homogenous within the countries of all regions, except of region Europe I + CA. There, in 53% of the responding countries the answers are inconsistent (considering the countries with more than one respondent). This country-internal inconsistency in the respondents' attitude is very likely based on the differences regarding the respondents' knowledge and awareness of the issue in the countries of that region as already outlined in the results of questions 1 and 2.

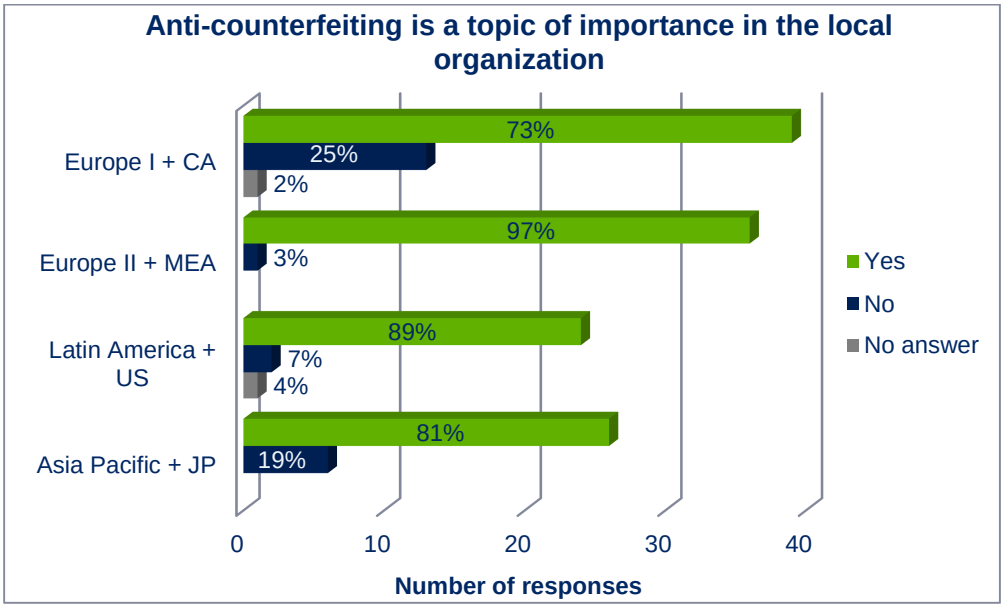

Figure 53: Anti-counterfeiting is a topic of importance in the local organization

5.1.2.5 Question 5

Figure 54: Question 5 of the affiliate survey, snap shot of the web-based questionnaire

In 76% of the responding countries a public anti-counterfeiting campaign was conducted at some point. This high result is not limited to one or two regions. The situation is similar across all regions. As it is displayed in figure 55 the values exceed 70% in all regions. However, it has to be mentioned that the high results are partly biased by the way the respondents understood the term “public campaign”. The details the respondents provided with respect to the campaigns reveal that the respondents defined the term “public campaign” rather broadly. Thus, the responses comprise several anti-counterfeiting activities that would rather meet the term “collaboration with and between authorities and associations” e.g. conferences and collaborative meetings between authorities, government, associations and pharmaceutical companies, presentations and trainings directed to pharmaceutical companies about ACF technologies (features) or about initiatives done by the authorities, information and alerting procedures between authorities and the pharmaceutical industry and investigative activities done by the police and the customs.

However, the provided information also includes activities under the term “public campaigns”, i.e. activities directed at the population with the purpose to inform and educate them. These activities include providing information and warnings about the risks of counterfeit medicines via the internet (e.g. at authorities’ websites), via press and broadcast media (e.g. TV and radio) and via healthcare professionals (e.g. pharmacies). So, it can be concluded that a lot of activities to combat counterfeiting of medicinal products are done in the countries across all regions. But the population is only in some extent involved in these activities.

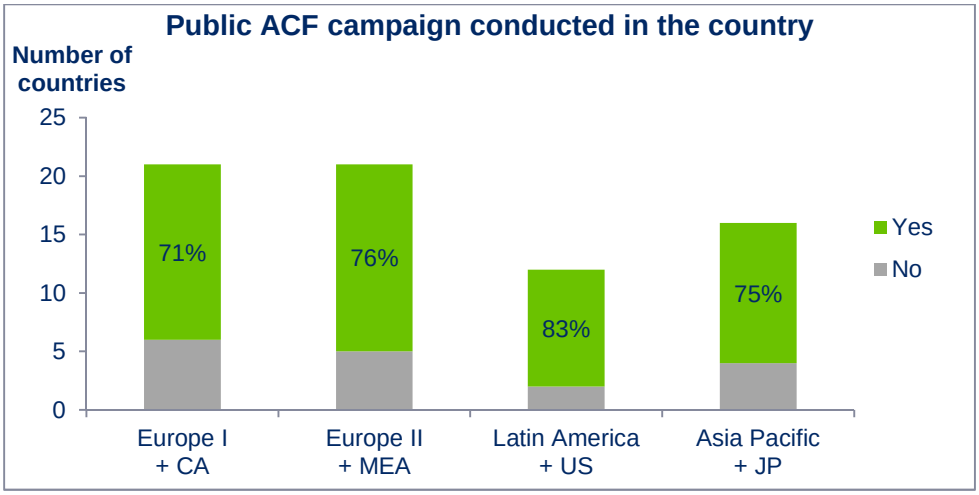

Figure 55: Public ACF campaign conducted in the country

5.1.2.6 Question 6

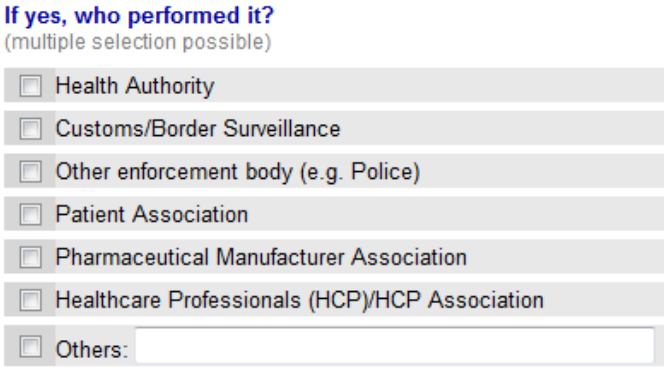

Figure 56: Question 6 of the affiliate survey, snap shot of the web-based questionnaire

Question 6 is related to the question 5 and refers to the public campaigns. The evaluation of the responses to question 6 is based on the number of countries in which a campaign was performed by one of the stakeholders at choice. One country can relate to more than one stakeholder because of the multiple choice option. Most of the campaigns or activities (for details, see evaluation of question 5) were performed by health authorities. In 66% of the responding countries this stakeholder was selected. In 36% of the responding countries the campaigns were performed by pharmaceutical manufacturer associations, in 33% by other enforcement bodies, in 26% by customs and border surveillance, in 13% by HCPs and healthcare professional associations, in 4% by patient associations and in 13% by others (e.g. competitors and press).

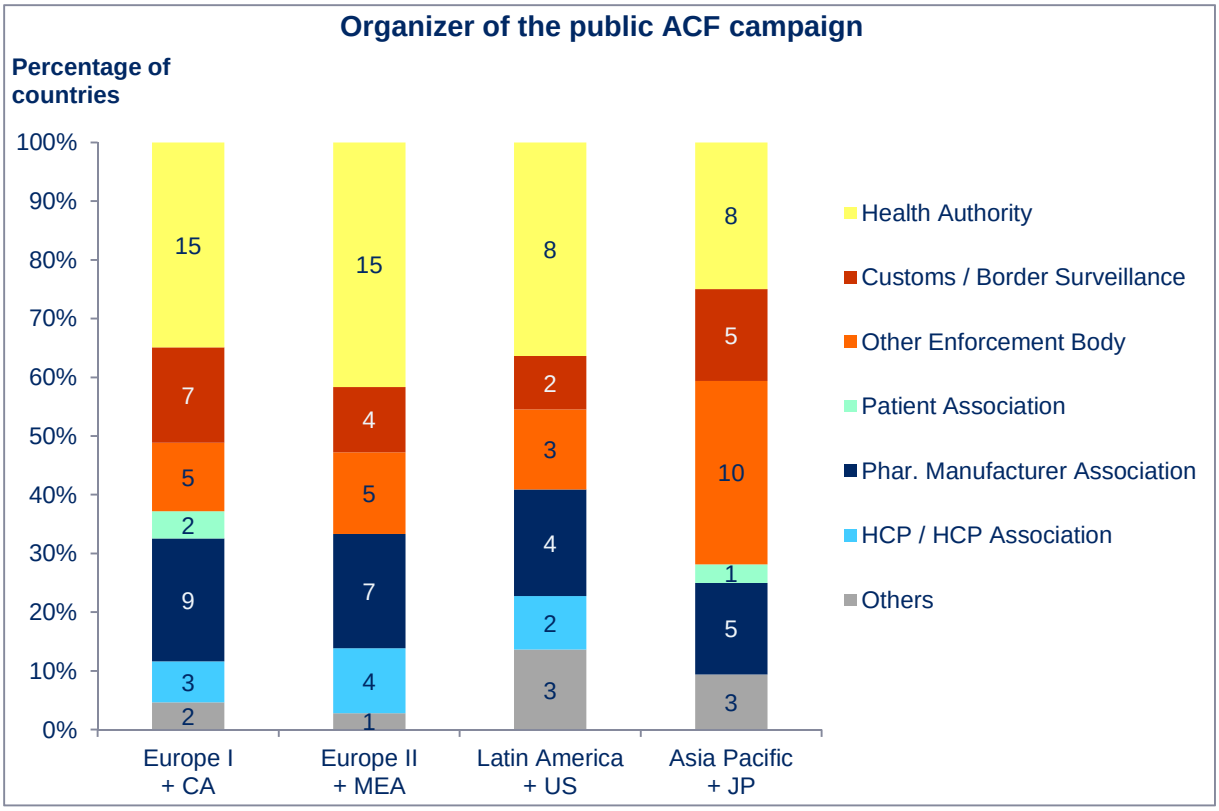

Figure 57: Organizer of the public ACF campaign

5.1.2.7 Question 7

Figure 58: Question 7 of the affiliate survey, snap shot of the web-based questionnaire

In 47% of all responding countries the local affiliate was involved in the campaigns or activities. The percentages displayed in figure 59 are based on the total number of responding countries in each region. If the percentages are considered based only on the number of countries where a public campaign actually has been done, the results are: EU I + CA (73%), EU II + MEA (56%), LA + US (70%) and AP + JP (50%). Hence, the participation and commitment of the local affiliates in anti-counterfeiting campaigns and activities is huge.

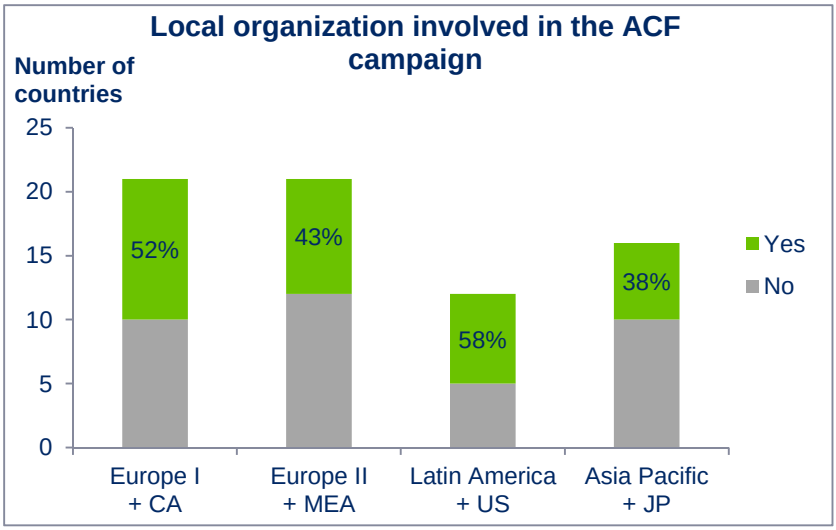

Figure 59: Local organization involved in the ACF campaign

5.1.2.8 Question 8

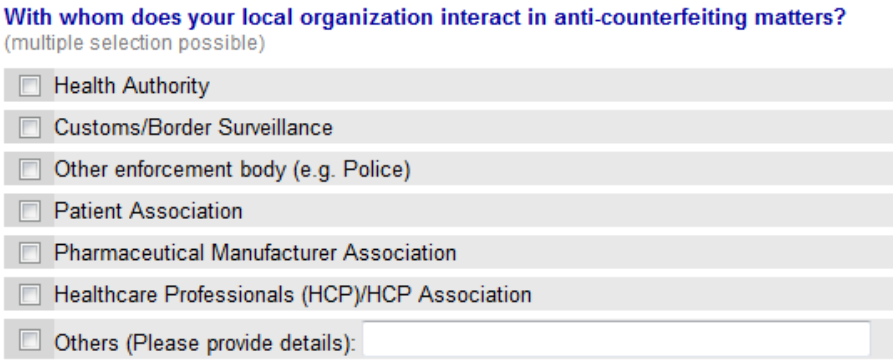

Figure 60: Question 8 of the affiliate survey, snap shot of the web-based questionnaire

The percentages of the responses to question 8, displayed in figure 61, are based on the number of countries collaborating with the different stakeholders at choice. One country can relate to more than one stakeholder because of the multiple choice option. With respect to anti-counterfeiting matters the affiliates of 94% of all responding countries collaborate with health authorities, 59% collaborate with pharmaceutical manufacturer associations, 54% with other enforcement bodies, 46% with customs & border surveillance, 37% with HCPs and healthcare professional associations, 7% with patient associations and 17% with others (e.g. press). The results show that there is already a broad network established in the countries to face the problem of counterfeit medicinal products. Nevertheless, the collaboration with healthcare professionals and patient organizations with respect to the issue of counterfeit medicinal products still offers some room for expansion.

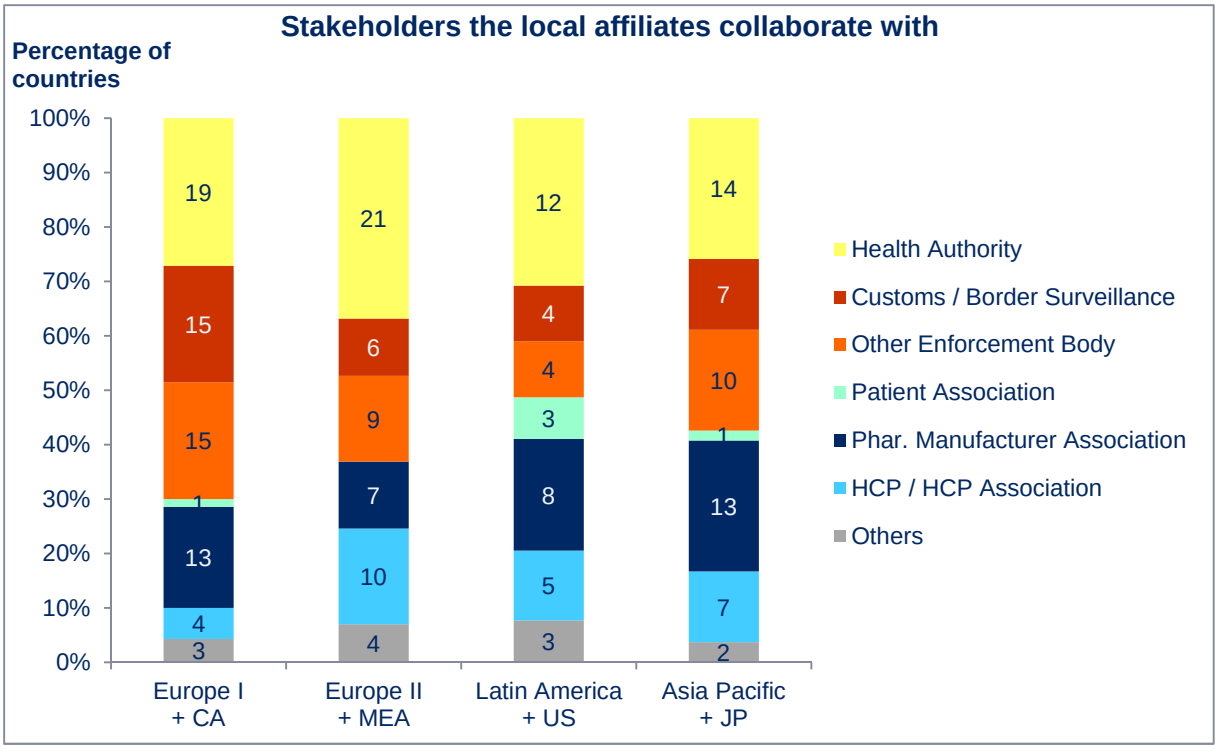

Figure 61: Stakeholders the local affiliates collaborate with

5.1.2.9 Question 9

Figure 62: Question 9 of the affiliate survey, snap shot of the web-based questionnaire

In some countries pharmaceutical companies may not be allowed to publish counterfeit-relevant information via the internet. However, as more and more people, especially patients use the internet to inform themselves about health-related matters, the internet should be used by pharmaceutical companies as a tool for reaching out to the population to provide helpful information and advice in the countries where it is legally permitted. Yet, only 20% of all responding countries state that they have a local anti-counterfeiting website established or at least some counterfeit-relevant information and warnings on their general local company website. The heterogeneous responses hint again to a lack of communication between the local functions since not every respondent was aware of the anti-counterfeiting website or counterfeit-relevant information even if it is established in the country.

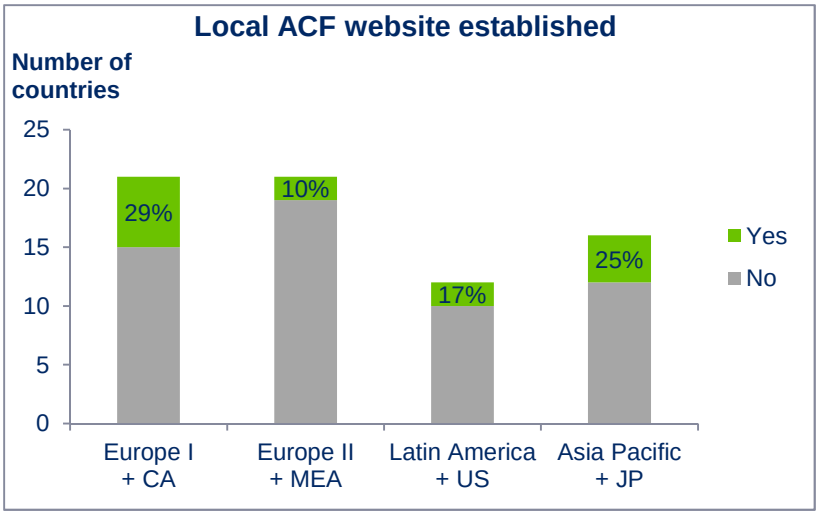

Figure 63: Local ACF website established

5.1.2.10 Question 10

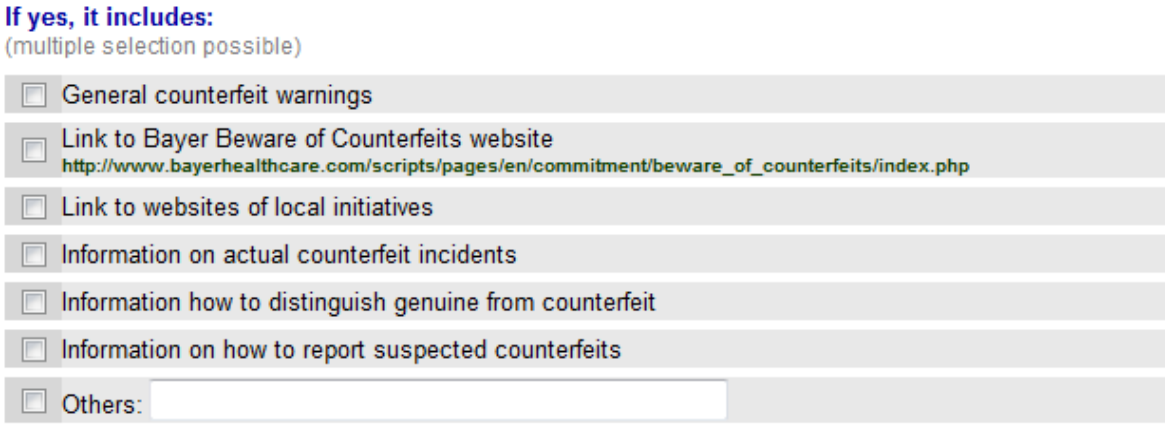

Figure 64: Question 10 of the affiliate survey, snap shot of the web-based questionnaire

Question 10 is related to question 9 and refers to the ACF websites. Regarding the contents of the established local anti-counterfeiting websites the most relevant information is provided. Out of the 14 affiliates that have a local anti-counterfeiting website in place 71% say that the website contains general warnings with regard to the counterfeit problem, 64% state that information on how to distinguish counterfeits from original products is provided on their website and 57% of the affiliates have information on how to report suspected counterfeit incidents included on their local website. Less than one half responds that their website contains information about current counterfeit incidents or links to the company's global anti-counterfeiting website or to websites of other initiatives against counterfeiting of medicines. Only 29% state that their local websites include additional information, e.g. about public media campaigns or on results of studies or surveys conducted with respect to the counterfeit issue.

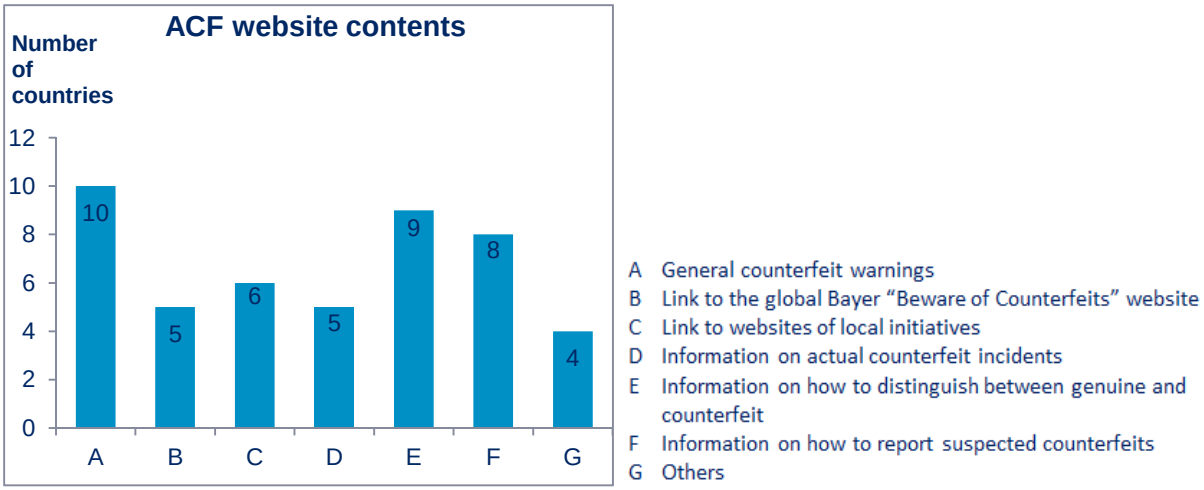

Figure 65: ACF website contents

5.1.2.11 Question 11

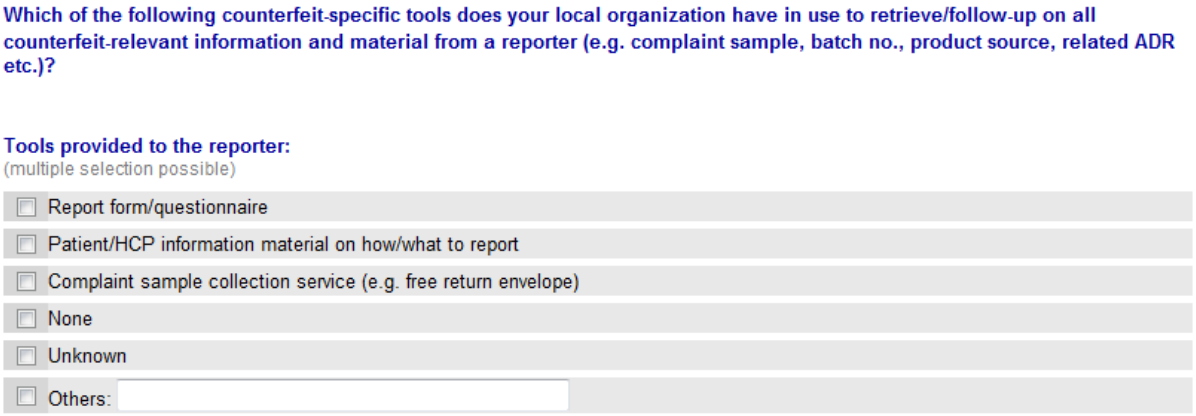

Figure 66: Question 11 of the affiliate survey, snap shot of the web-based questionnaire

Making topic-specific, supportive means available to reporters eases the reporting of suspected counterfeit incidents as the reporter has an orientation at hands about what kind of information is required by the recipient (in this case the MAH). Therefore, the respondents were asked what means their local affiliate provides to reporters. 31% of the respondents state that a report form or a questionnaire is available in their country to be filled out by the reporter. Another 23% say that a complaint sample collection service is provided by their local affiliate to support the reporters in terms of sending in the complaint sample for investigation. And 13% of the respondents reveal that they have informative literature on how to report suspected counterfeit incidents to be provided to patients and healthcare professionals in place in their country. Only 4% of the respondents state that there is none of such means available to reporters in their country. So, the majority of the local affiliates provides one or multiple supportive means to the reporters. Further options to report a suspected counterfeit incident mentioned under "others" by two respondents are the use of the company hotline or e-mail contact.

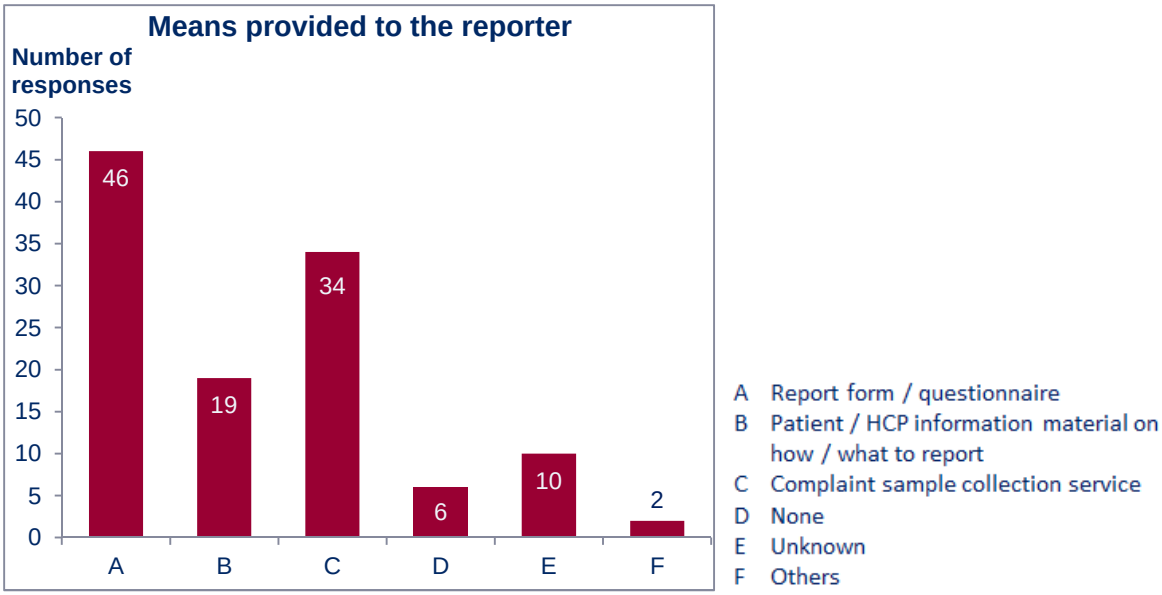

Figure 67: Means provided to the reporter

5.1.2.12 Question 12

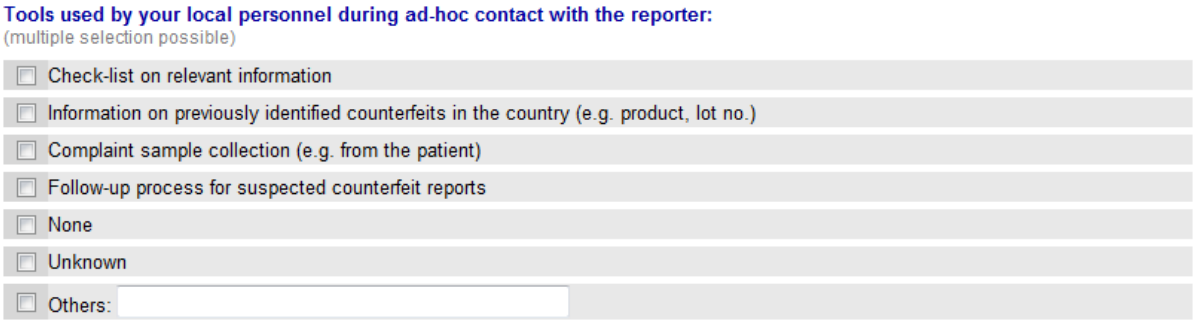

Figure 68: Question 12 of the affiliate survey, snap shot of the web-based questionnaire

Question 12 is related to question 11. To ensure that the collection of all relevant data is as complete as possible during the first contact with a reporter, it is helpful to provide the responsible personnel with some topic-specific, supportive means. Hence, the respondents were asked to select the means which are in use in their local affiliate. Both, the complaint sample collection process and the follow-up process for suspected counterfeit incidents are selected by more than 30% of the respondents, each, being in use in their local affiliate. So, the responsible employees can refer to the established processes. 26% of the respondents state that a check-list on relevant information is provided to the responsible personnel in their local affiliate. And 23% of the respondents say that the responsible employees are provided with information on previously identified counterfeits in their country. Thereby, the employees can orient themselves by this information to ask respective questions regarding the complaint sample characteristics during the ad-hoc contact with a reporter. Again, only 4% of the respondents say that there is none of such means provided to the responsible personnel in their local organization.

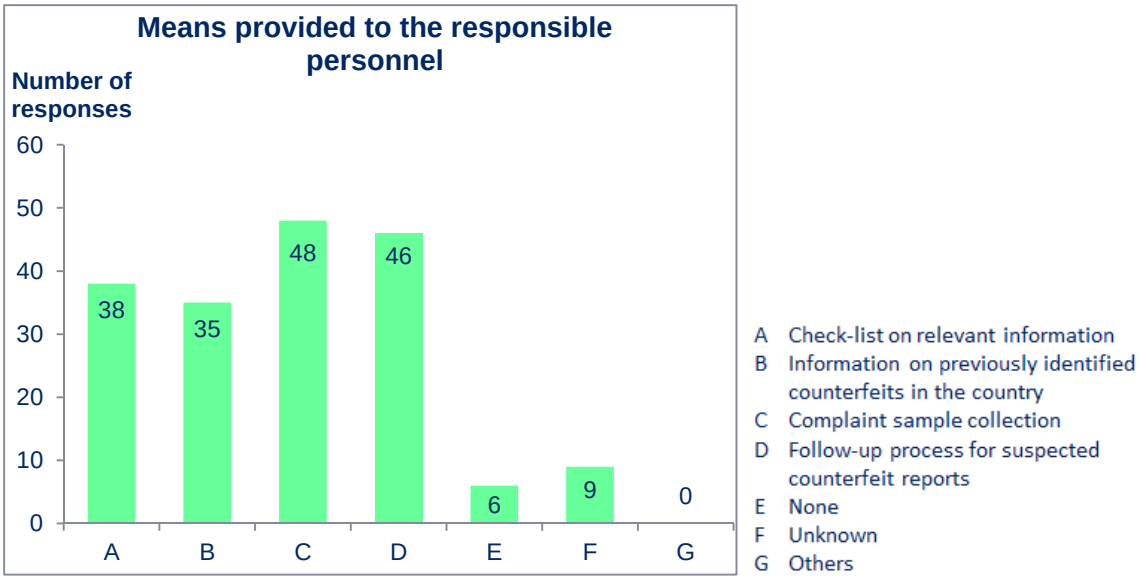

Figure 69: Means provided to the responsible personnel

5.1.2.13 Question 13

Which function/role within your local organization is actively involved in counterfeit-related matters towards the following external stakeholders?
(multiple selection possible)

	Health Authority	Customs	Other Enforcement Body	Public Media/Press	Associations	Not Applicable/None
CDH (Country Division Head)	☐	☐	☐	☐	☐	☐
Medical Affairs/CMD (Country Medical Director)	☐	☐	☐	☐	☐	☐
Pharmacovigilance/PVCH (Pharmacovigilance Country Head)	☐	☐	☐	☐	☐	☐
Quality Affairs/LQR (Local Quality Representative)	☐	☐	☐	☐	☐	☐
LSC (Local Security Coordinator)	☐	☐	☐	☐	☐	☐
Legal/LACM (Local Anti-Counterfeiting Manager)	☐	☐	☐	☐	☐	☐
Security/LSR (Local Security Representative)	☐	☐	☐	☐	☐	☐
Communication	☐	☐	☐	☐	☐	☐
Regulatory Affairs/LRAM (Local Regulatory Affairs Manager)	☐	☐	☐	☐	☐	☐
Business/Marketing	☐	☐	☐	☐	☐	☐
Customer Service	☐	☐	☐	☐	☐	☐
Medical Information	☐	☐	☐	☐	☐	☐
Others:	☐	☐	☐	☐	☐	☐

Please specify "Others".

Figure 70: Question 13 of the affiliate survey, snap shot of the web-based questionnaire

The results of question 13 show very clearly that the responsible contact persons towards different stakeholders with respect to counterfeit-related matters are not limited to only one or just a few functions. Several and somehow rather different functions within the company are involved in the anti-counterfeiting topic towards multiple stakeholders. The variety of functions includes Medical Affairs and Medical Information, Pharmacovigilance, Quality Assurance, Legal and Regulatory, and even Marketing and Communications functions.

Hence, anti-counterfeiting is definitely a multifunctional topic. Therefore, all employees of the involved functions should be provided with topic-specific training to make sure they have the required knowledge to handle counterfeit-related matters properly. Furthermore, the respective functions should remain in communication with regard to current counterfeit incidents or anti-counterfeiting activities and the respective decisions which need to be made.

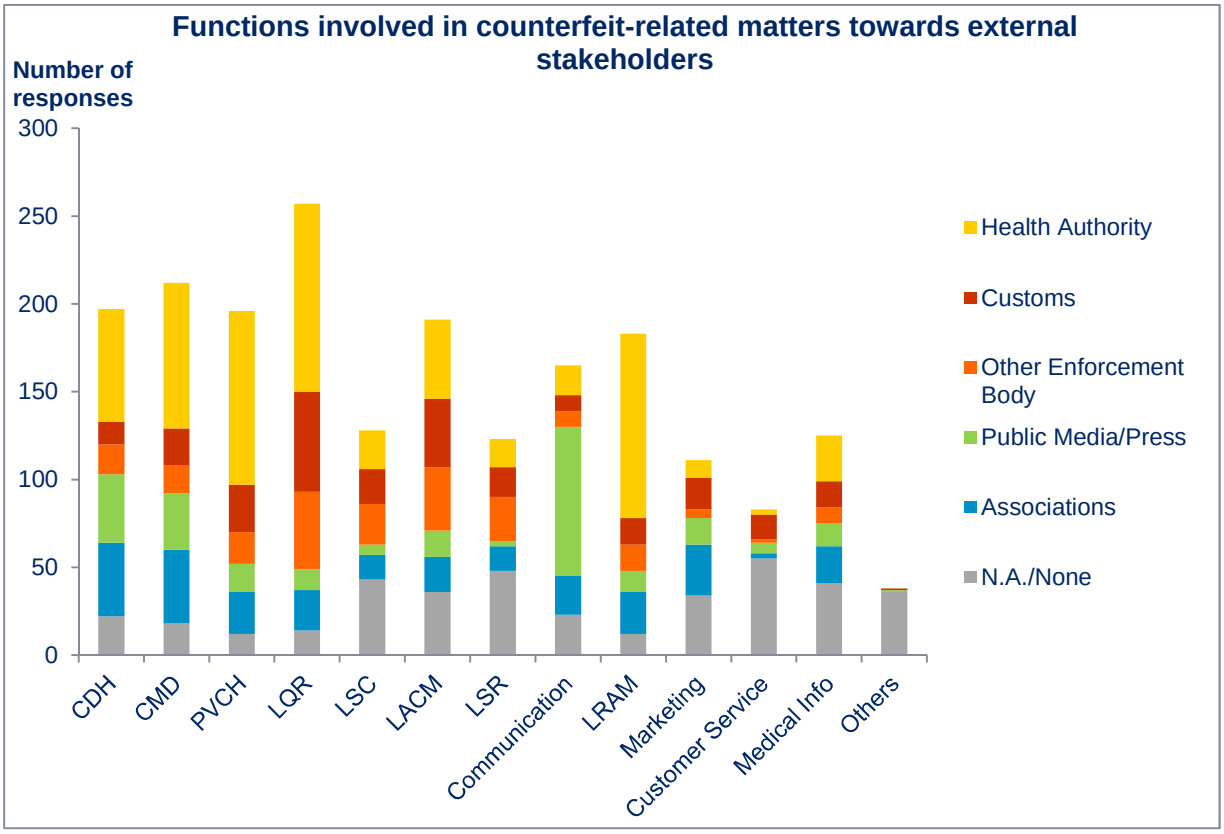

Figure 71: Functions involved in counterfeit-related matters towards external stakeholders

5.1.2.14 Question 14

Which of the following functions/responsible persons within your local organization are responsible for internal processing of counterfeit-related matters?
(multiple selection possible)

	Counterfeit Reports	Theft Reports	Agency Support (e.g. Information Material, Raids)	Media Support (e.g. Press Statements)	Patient/HCP Education	Not Applicable/None
CDH (Country Division Head)	☐	☐	☐	☐	☐	☐
Medical Affairs/CMD (Country Medical Director)	☐	☐	☐	☐	☐	☐
Pharmacovigilance/PVCH (Pharmacovigilance Country Head)	☐	☐	☐	☐	☐	☐
Quality Affairs/LQR (Local Quality Representative)	☐	☐	☐	☐	☐	☐
LSC (Local Security Coordinator)	☐	☐	☐	☐	☐	☐
Legal/LACM (Local Anti-Counterfeiting Manager)	☐	☐	☐	☐	☐	☐
Security/LSR (Local Security Representative)	☐	☐	☐	☐	☐	☐
Communication	☐	☐	☐	☐	☐	☐
Regulatory Affairs/LRAM (Local Regulatory Affairs Manager)	☐	☐	☐	☐	☐	☐
Business/Marketing	☐	☐	☐	☐	☐	☐
Customer Service	☐	☐	☐	☐	☐	☐
Medical Information	☐	☐	☐	☐	☐	☐
Others:	☐	☐	☐	☐	☐	☐

Please specify "Others".

Figure 72: Question 14 of the affiliate survey, snap shot of the web-based questionnaire

Also with regard to the internal handling of counterfeit-related matters the variety of the involved functions is broad. Again, respective topic-specific knowledge is required to ensure the consistent processing of the counterfeit-related matters within and across the involved functions of the respective local organization.

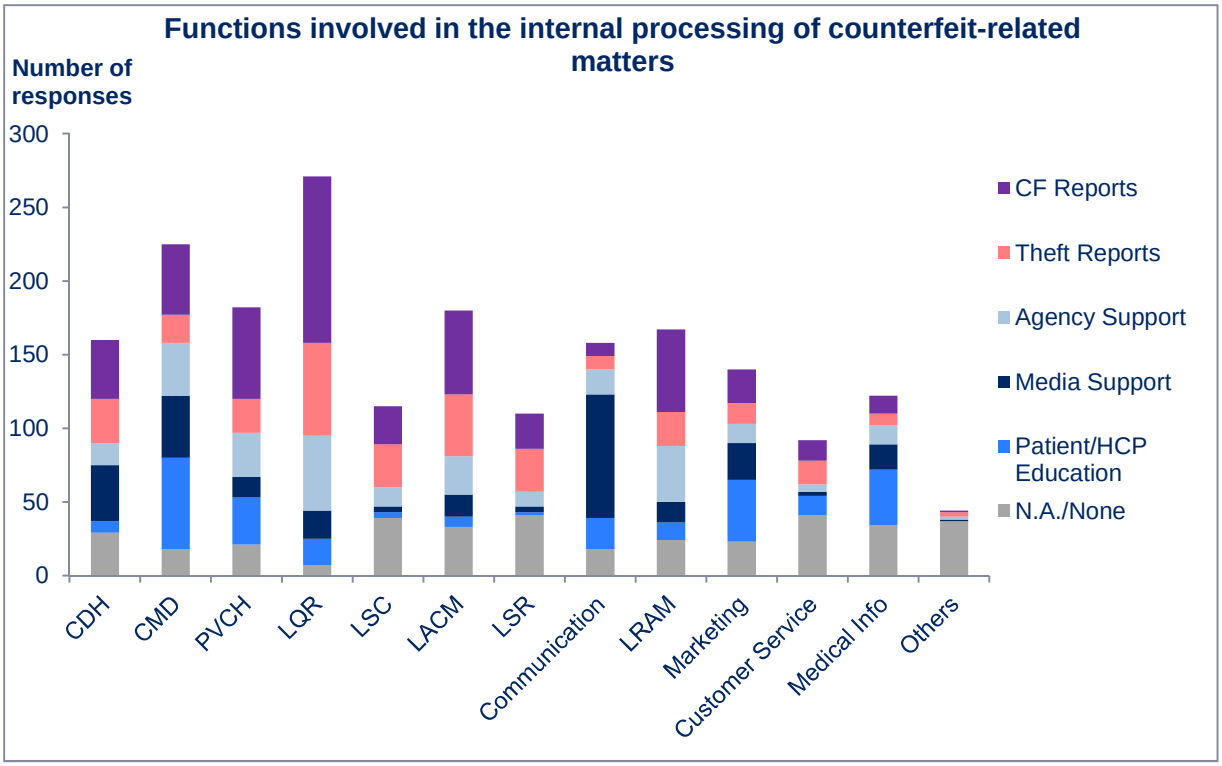

Figure 73: Functions involved in the internal processing of counterfeit-related matters

5.1.2.15 Question 15

Are you familiar with the following terms and their meaning/definition in the context of counterfeit and product security-related issues?

	Yes	No	Not sure
Imitation	○	○	○
Mix up of genuine/counterfeit	○	○	○
Adulteration (Tampering)	○	○	○
Smuggling	○	○	○
Theft	○	○	○
Fraudulent generic	○	○	○
Manipulation	○	○	○

Figure 74: Question 15 of the affiliate survey, snap shot of the web-based questionnaire

The evaluation of the responses to question 15 is based on the number of respondents who are familiar with all 7 of the given terms, with 4 to 6 of the given terms, with less than 4 terms and with none of the terms. The percentages of the number of respondents per group are calculated considering the total number of respondents (149) as 100%. Less than one half (44%) of all respondents are familiar with all of the given terms. Altogether, 81% of the respondents are familiar with at least 4 of the counterfeit-relevant terms. 14% of the respondents are familiar with less than 4 of the given terms and 5% do not know any of the terms.

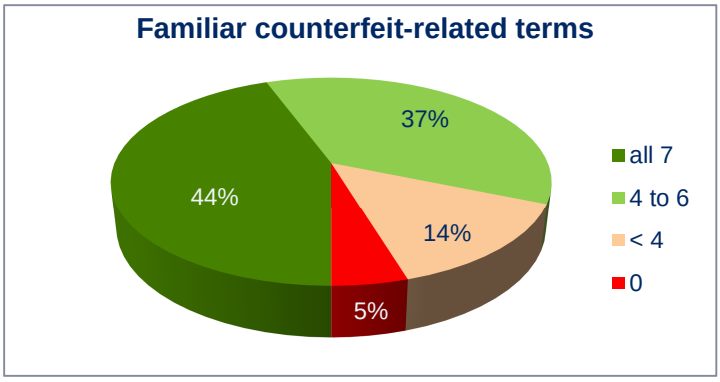

Figure 75: Familiar counterfeit-related terms

Comparing the regions, Latin America + the United States is the region with the best result of knowledge regarding the given counterfeit-related terms. 74% of the respondents of that region are familiar with all of the given terms and at the same time there are no respondents who know less than 4 or even none of the terms. In all other regions the percentage of respondents knowing less than 4 or even none of the given terms altogether is higher than 20%.

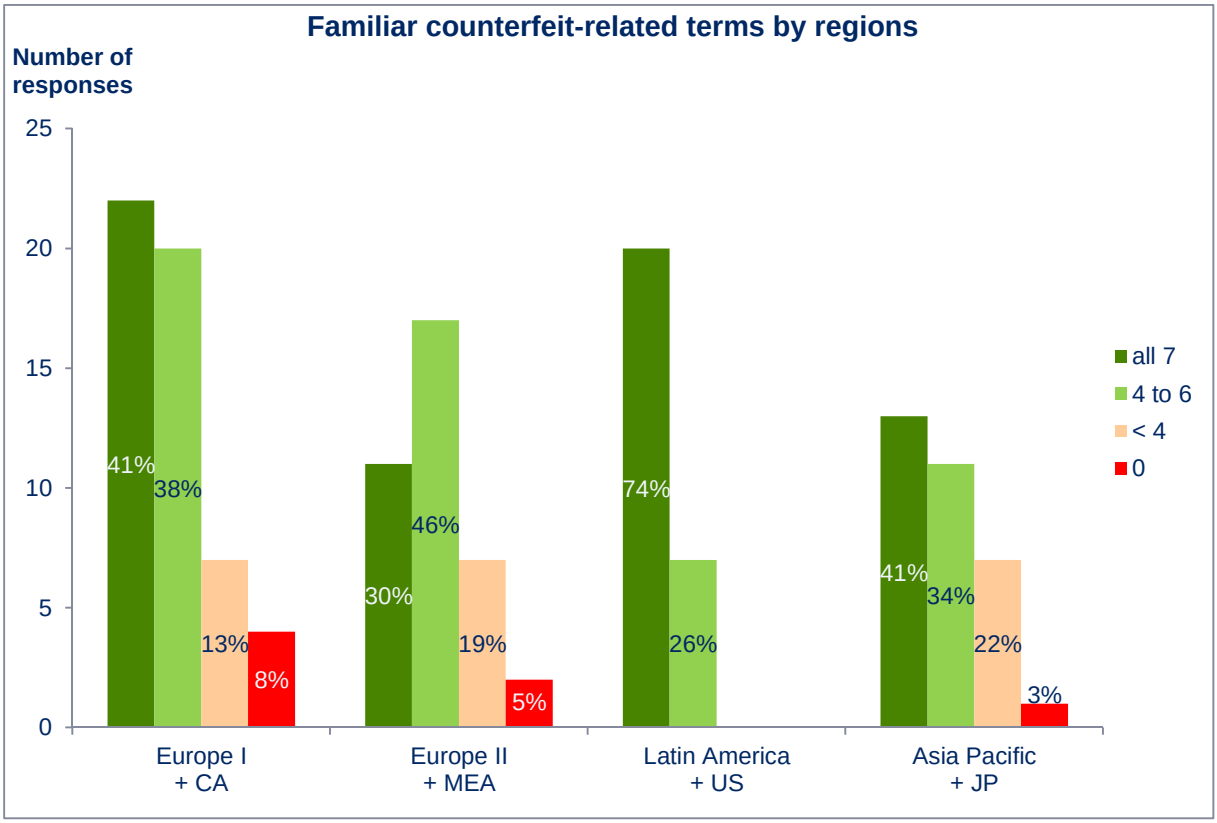

Figure 76: Familiar counterfeit-related terms by regions

5.1.2.16 Question 16

Figure 77: Question 16 of the affiliate survey, snap shot of the web-based questionnaire

When a suspected counterfeit incident or any other counterfeit-related matter is brought to the attention of an employee, he / she should know whom to contact or to whom to forward the received information or matter. Therefore, it is necessary to know the responsible colleagues. Less than one half of the respondents actually knew the responsible contact persons (and their role). With regard to a well-established collaboration between functions it should be ensured that the information about the responsible employees is communicated to all functions potentially involved in the topic.

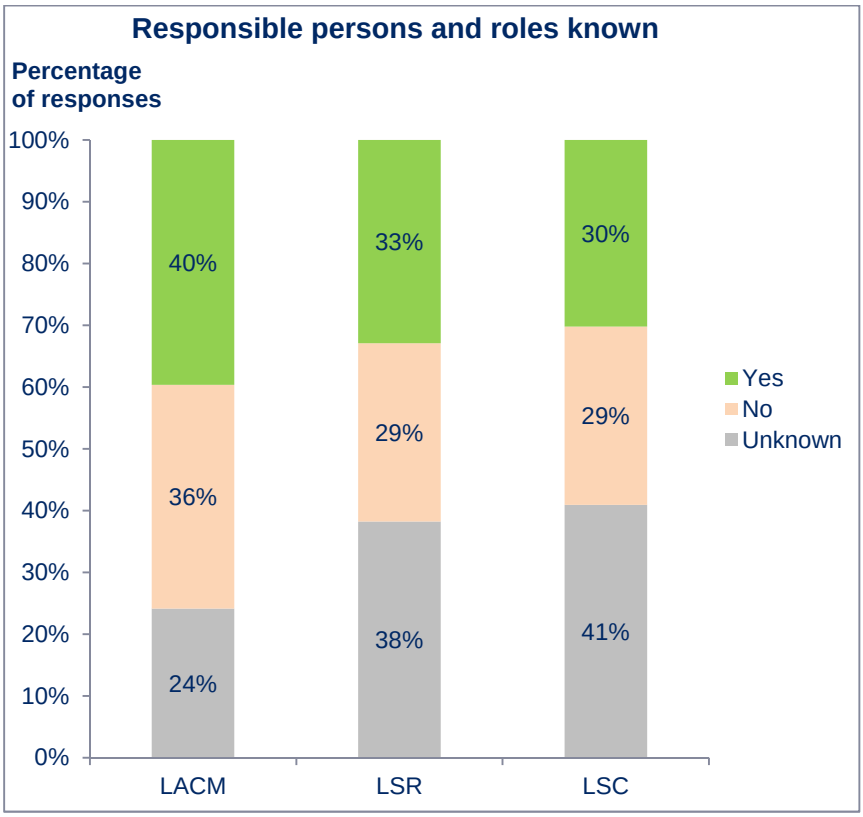

Figure 78: Responsible persons and roles known

5.1.2.17 Question 17

Are any of the following functions provided with counterfeit-specific training?

	Yes	No	Unknown
Customer Service/Hotline	○	○	○
Sales Representatives	○	○	○
Medical Scientific Liaisons	○	○	○
Medical Advisors	○	○	○
Local Pharmacovigilance	○	○	○
Local Complaint Management	○	○	○
Product Managers (Marketing)	○	○	○
Security	○	○	○

Figure 79: Question 17 of the affiliate survey, snap shot of the web-based questionnaire

Based on the number of functions which receive counterfeit-specific training in the affiliates, the responding countries are clustered in countries where all of the given functions are provided with such training, where at least 4 of the given functions receive such training, where less than 4 of the given functions receive counterfeit-specific training and countries where none of the given functions is provided with respective training. The percentages are calculated based on the total number of responding countries (70) as 100%. In only 14% of the responding countries all given functions are provided with counterfeit-specific training. In 40% of the countries at least 4 of the functions receive such training. Less than 4 of the given functions are provided with counterfeit-specific training in 29% of the responding countries and in 17% of the countries no counterfeit-related training is provided, at all, to the given functions.

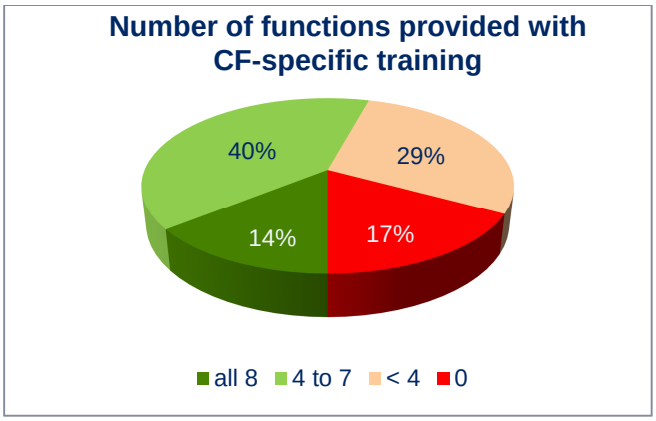

Figure 80: Number of functions provided with CF-specific training

The regional comparison reveals a huge need for counterfeit-relevant training, especially in the countries of Asia Pacific + Japan. In 38% of the countries from this region none of the given functions receive counterfeit-specific training.

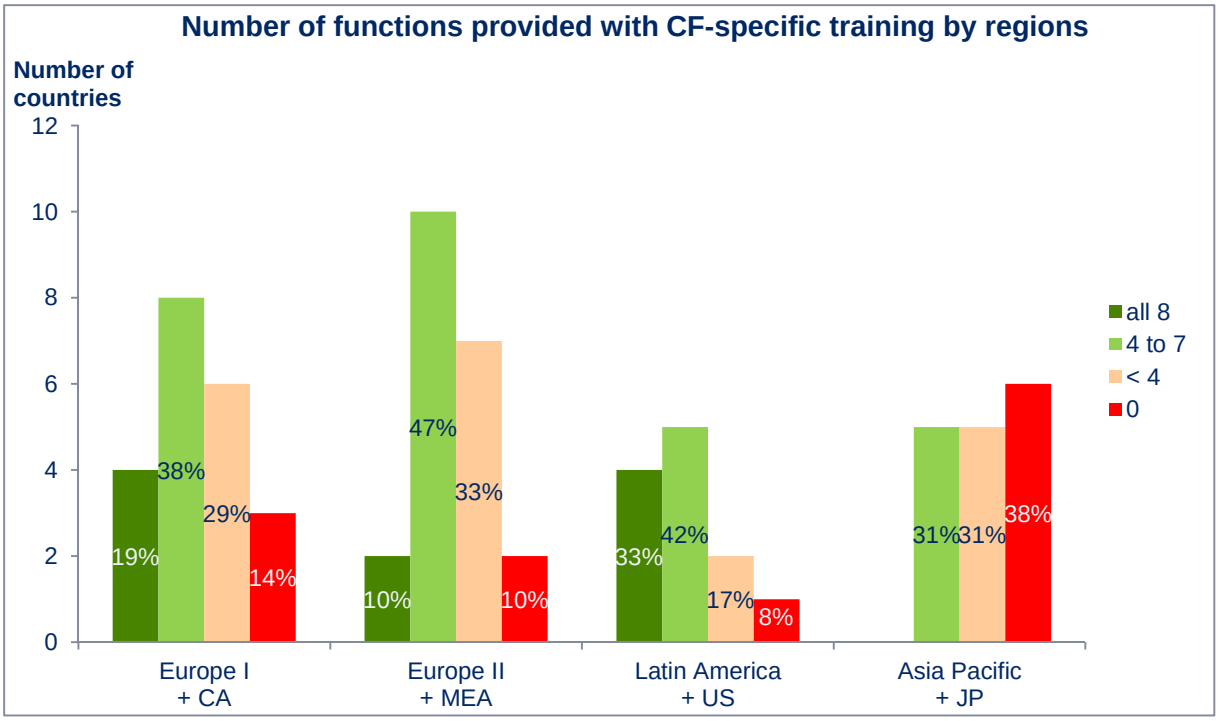

Figure 81: Number of functions provided with CF-specific training by regions

The function which is provided with counterfeit-specific training in most of the countries (95%) is the local pharmacovigilance function followed by the local complaint management, a Quality Assurance function, which receives counterfeit-related training in 69% of the responding countries, which provide such training. The two Marketing functions, sales representatives and product managers, are ranked third in the listing. The personnel insufficiently trained with respect to the counterfeit topic in many of the responding countries belong to Medical Affairs, Security and the customer service. The customer service employees, in particular, should at least receive a basic counterfeit-related training so that they are able to ask relevant questions during the ad-hoc contact with a reporter and know whom to contact with regard to counterfeit-related matters in the local organization.

Functions	Number of countries where functions receive counterfeit-specific training (total = 58)	Percentage of respondents
Local pharmacovigilance	55	95%
Local complaint management	40	69%
Sales representatives	37	64%
Products managers	37	64%
Medical advisors	31	53%
Medical scientific liaisons	23	40%
Security	23	40%
Customer service / hotline	21	36%

Table 12: Ranking of functions which receive CF-specific training

5.1.2.18 Question 18

Does the training contain the following?
(multiple selection possible)

- ☐ Current counterfeit situation in general/global
- ☐ Current counterfeit situation in your country
- ☐ Specific Bayer Pharma products with respect to counterfeit protection
- ☐ Visible anti-counterfeiting security features applied on the Bayer Pharma products in your country
- ☐ How to identify counterfeit Bayer Pharma products by means of known characteristics of previously identified counterfeit Bayer Pharma products
- ☐ Whom to contact when a counterfeit/product security-relevant information is received
- ☐ Others:

Figure 82: Question 18 of the affiliate survey, snap shot of the web-based questionnaire

The responses to question 18 are clustered based on the number of contents included in the counterfeit-specific training in the respective countries. The percentages are calculated based on the total number of responding countries where such a training is provided (58) as 100%. The 12 responding countries where no counterfeit-related training is provided are excluded from the calculation. In 31% of the countries where counterfeit-related training is provided, the training contains all 6 of the listed suggestions of training contents, i.e. the trainings are broad. In 39% of the countries the counterfeit-specific training contains at least 3 of the suggested training contents. In 30% of the countries less than 3 of the given contents are comprised in the provided training.

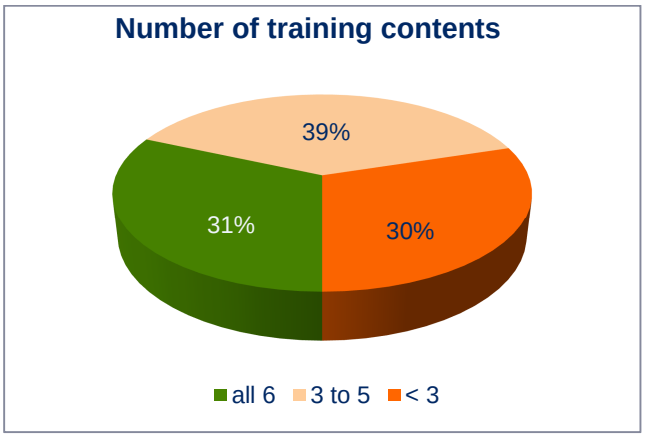

Figure 83: Number of training contents

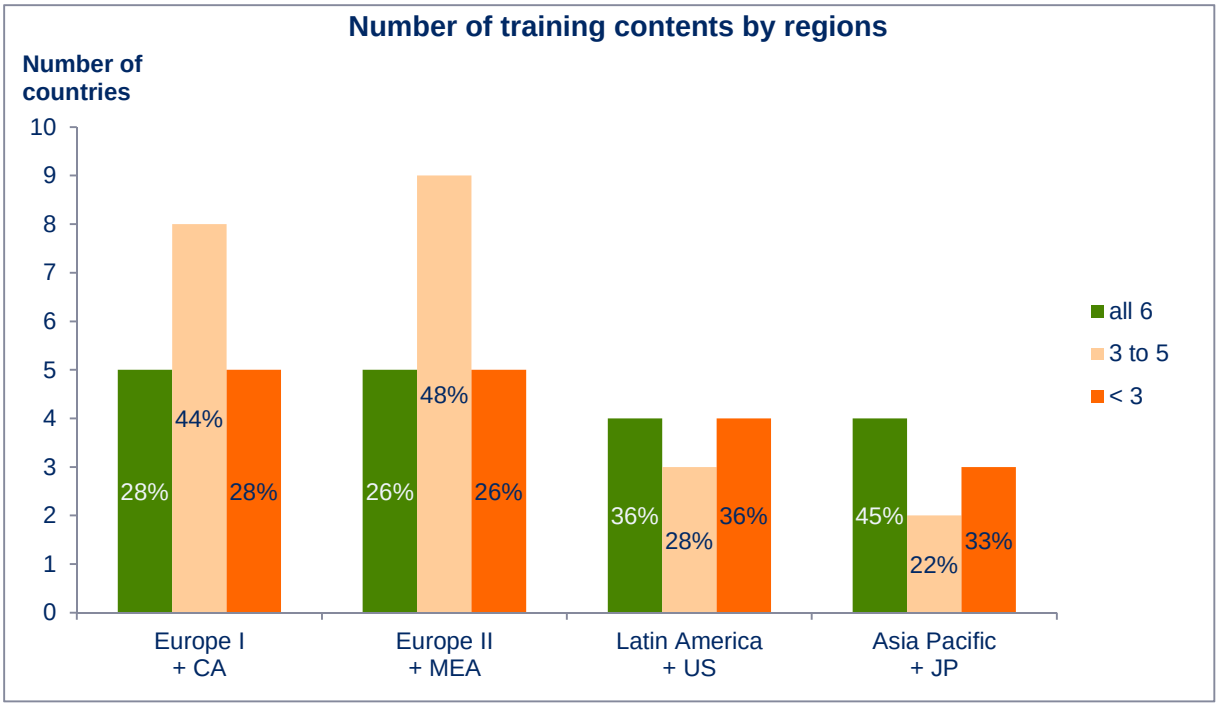

Figure 84: Number of training contents by regions

In the majority (88%) of the countries where counterfeit-specific training is provided the training contains information about the responsible contact person(s) to whom counterfeit-related matters should be forwarded. In more than one half of the countries information about the current counterfeit situation in general and in particular regarding the local situation is provided. This information refers also to the company's product portfolio, if applicable. In some countries the topic-specific training even comprises detailed information on the characteristics of already identified counterfeit products and on overt anti-counterfeiting security features applied to the company's products.

Training contents	Number of countries (total = 58)	Percentage of respondents
Whom to contact when a counterfeit- / product security-relevant information is received	51	88%
Current counterfeit situation in general / global	36	62%
Current counterfeit situation in your country	36	62%
Specific Bayer Pharma products with respect to protection against counterfeiting	36	62%
How to identify counterfeits of BPH products by means of known characteristics of previously identified counterfeits of BPH products	34	59%
Visible ACF security features applied on the BPH products in your country	28	48%

Table 13: Ranking of CF-specific training contents

5.1.2.19 Question 19

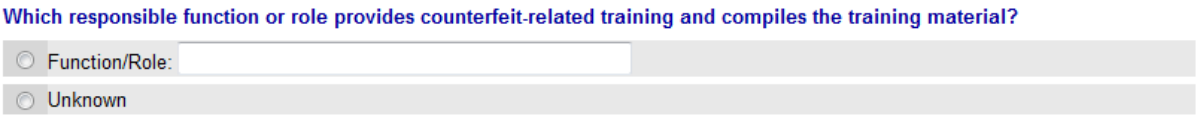

Figure 85: Question 19 of the affiliate survey, snap shot of the web-based questionnaire

The responses to question 19 reveal that the responsibility of compiling and providing counterfeit-specific training material is not limited to one and the same function in the different affiliates. Still, there is a distinct tendency to the Quality Assurance function to take care of the required topic-specific trainings and training materials. 46% of the 110 respondents who stated that counterfeit-relevant training is provided in their country say that the responsible function for the respective training is the Quality Assurance function. The remaining 54% of the respondents named 5 other functions as responsible for this task or said that they do not know which function is responsible.

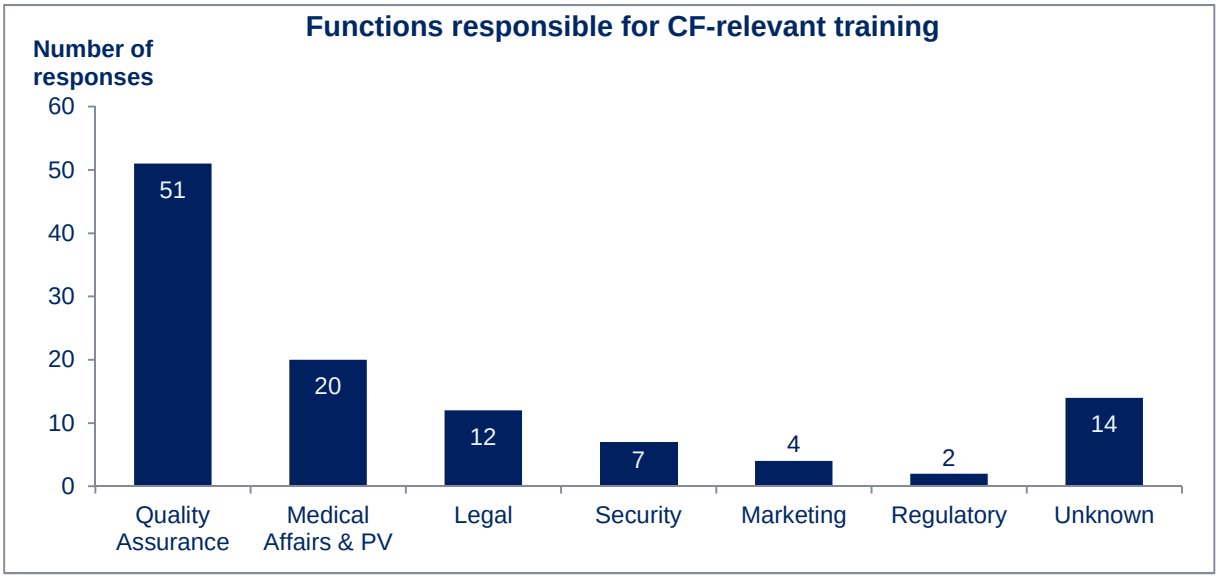

Figure 86: Functions responsible for CF-specific training

5.1.2.20 Question 20

Figure 87: Question 20 of the affiliate survey, snap shot of the web-based questionnaire

For the central functions it is valuable to know how to support the personnel of the local affiliates. For that reason, the respondents were asked to select supportive means which they would be interested in.

All in all, the result evaluation reveals that the majority of the respondents is very interested in support to be received from the central functions with respect to the counterfeit topic. In total, 73% of the respondents selected more than half of the supportive means as “of interest”. Even 29% of the respondents selected all of the supportive means as “of interest”.

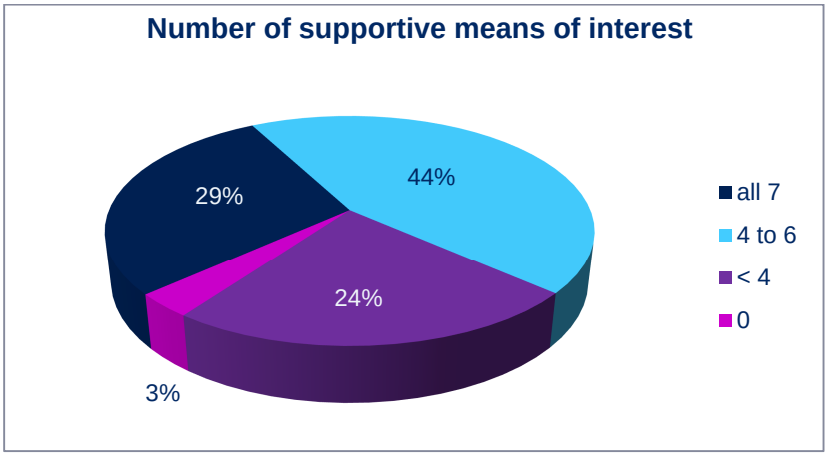

Figure 88: Number of supportive means of interest

Across the regions the picture is similar. In all regions the majority shows great interest in support with respect to the counterfeit topic.

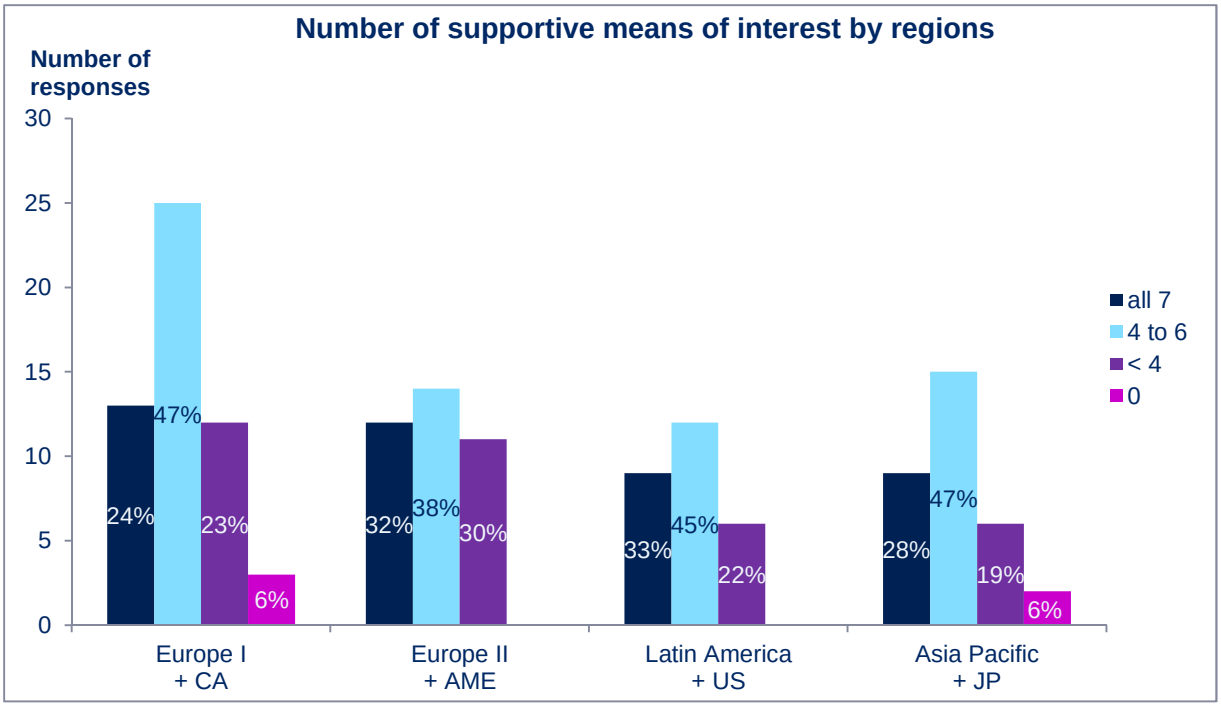

Figure 89: Number of supportive means of interest by regions

Regarding the rate of the selected supportive means the counterfeit-specific training material was selected by 87% of the respondents and is therefore on rank 1 of the most required supportive means followed by best practice material and information about overt (visible) ACF security features with 74% of the respondents, each.

Supportive means	Number of respondents (total = 149)	Percentage of respondents
Counterfeit-specific training material	130	87%
Best practice material	110	74%
Information on overt (visible) ACF security features	110	74%
BHC strategy on counterfeit protection	103	69%
News on internal ACF activities in other countries / regions	96	64%
Counterfeit-specific questionnaires / check-lists for use in call centers	85	57%
Global or regional news on external ACF initiatives	83	56%

Table 14: Ranking of supportive means with respect to the counterfeit topic

5.1.3 Response actions

In the context of this dissertation the survey results were compiled in a presentation and were presented to the heads of the different functions that were involved in the survey. The results were also presented to the company's Global Anti-counterfeiting Working Group and the Global Product Security Working Group which are in charge to initiate required response actions according to the identified needs of the local affiliates.

5.2 Country-specific interviews

The results of the affiliate survey reveal that the interest in and the impact of the counterfeit medicines topic is very high in many of the responding countries. Also the willingness to discuss the topic and to contribute to further anti-counterfeiting activities is rather high. The experiences gained during the preparation and the conduct of the product-specific education campaign revealed the necessity of considering country-specific circumstances when planning a public education campaign. In this context, the importance of collaborating and net-working between several involved functions additionally became clear. For that reason, a follow-up activity with respect to the affiliate survey was planned, in the context of this thesis, to gain more detailed information regarding country-specific circumstances of e.g. the licit use of media with respect to health-related topics. In addition, experiences and personal assessment of the local employees regarding anti-counterfeiting measures should be collected. Hence, another questionnaire comprising 12 questions regarding 7 topics was developed, within the frame of this dissertation, to be discussed in interviews with the local employees of 10 selected affiliates. The conduct of the interviews is explained below.

5.2.1 Contents and conduct of the survey follow-up interviews

The 10 selected countries - representative for all regions - that showed huge commitment in the affiliate survey are:

Region	Countries
Europe I + Canada	Germany, United Kingdom
Europe II + Middle East & Africa	Kenya, Israel
Asia Pacific + Japan	Australia, Korea, Japan
Latin America + United States	Brazil, Colombia, USA

Table 15: Participant countries of the interviews

All respondents of the selected countries who had been invited to the affiliate survey were invited again to the interviews. Yet this time, every invitee of the respective affiliates was allowed to forward the invitation to further employees within his / her affiliate who, from the invitee's point of view, should also participate in the interview. For each country a telephone conference (TC) of 1h duration was scheduled and the questionnaire was sent out in form of a Microsoft® Word file to the participants one week prior to the TC meeting for better preparation. In the context of this thesis all questions were discussed during the interviews, which were conducted in English and the interview results were evaluated in detail, as presented in the following paragraphs.

5.2.2 Interview results

5.2.2.1 Topic 1: Media and tools to reach out to the public

Q #1: Which media is considered suitable to publish health-related matters in your country?

Reaching out to the public, especially to patients and healthcare professionals, in order to raise awareness of health-related issues including the risks that counterfeit medicines pose to patients' health and safety requires the use of suitable media to approach the public of different countries effectively. The majority of the interviewed respondents consider a combination of different kinds of media as most effective. Print media, including newspapers, professional journals, brochures and posters is considered to be the most reliable and therefore the most suitable media with respect to health-related issues. The preferred distribution points of brochures and posters are pharmacies, hospitals and international travel points e.g. airports according to the respondents. In 80% of the responding countries the internet is also seen as a suitable media to publish health-related information. In this context, the respondents favor the use of websites rather than social media. Moreover, the option to collaborate with search engine providers was mentioned to refer to specific websites (in this case the topic-specific information / warning website) after the input of defined search terms. In 50% of the countries the respondents rated broadcast media, including TV and radio, as appropriate to provide respective information. However, it was also mentioned that this kind of media is very cost-intensive, which is an aspect that should be considered when selecting media for an education campaign.

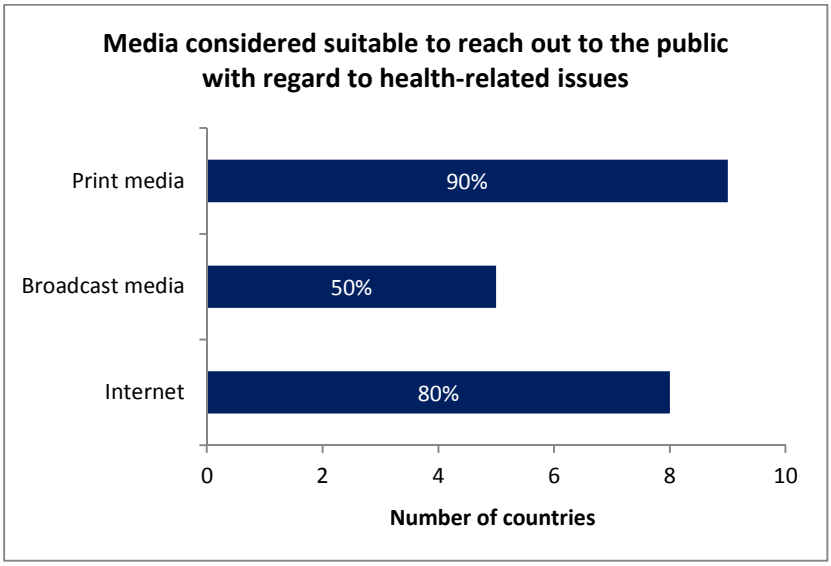

Figure 90: Media considered suitable to reach out to the public with regard to health-related issues

Q #2: What are the national regulatory restrictions with respect to the publishing of health-related matters in your country?

If health-related issues shall be published in a country, national regulations have to be followed. It is required to know if the health-related information can be provided with reference to medicinal products, in particular to prescription-only medicines (POM), and if yes, to whom. In most of the countries only general (non-product-specific) information with respect to health-related matters is permitted to be communicated to patients. In the countries, where pharmaceutical companies are allowed to publish POM-specific information, it must be communicated to healthcare professionals only. However, some respondents e.g. from Australia assumed that their health authorities might give permission to pharmaceutical companies to publish also POM-specific information if it is communicated in the context of warning patients against counterfeits of the respective medicinal product and referring to the anti-counterfeiting security features applied to it. In the minority of the responding countries pharmaceutical companies have permission to publish POM-specific information to patients, under limitations. In most of the countries the information to be published has to be in accordance with the competent authorities. Therefore, the respective information has to be communicated to the competent authorities and their approval received before the information can be published. In some countries the pharmaceutical companies are not allowed to communicate POM-specific information directly to patients but they are permitted to provide such information via the internet (via the company website), so that patients can access it, if they want to.

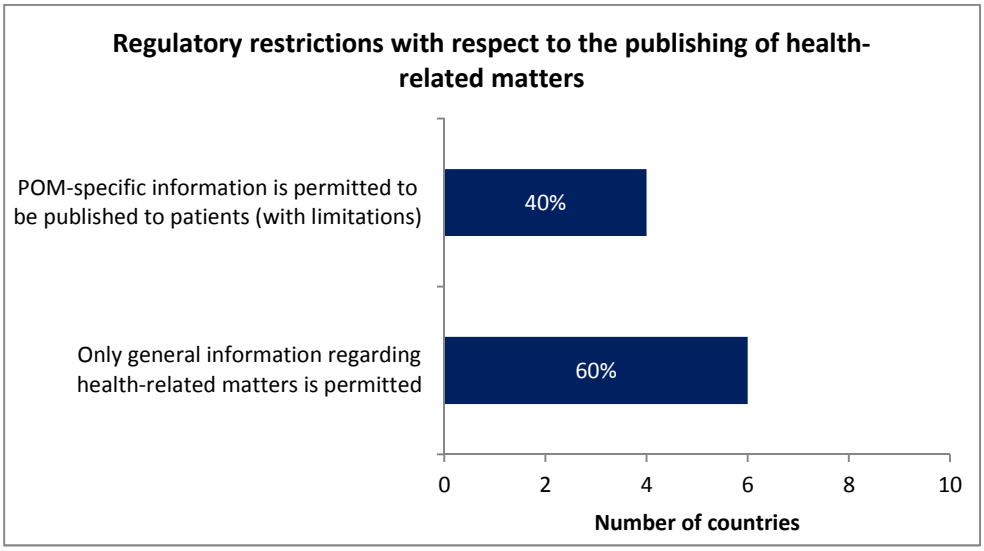

Figure 91: Regulatory restrictions with respect to the publishing of health-related matters

Q #3: Are patient assistant programs / patient support programs considered suitable to reach out to patients in order to inform them about the risks of counterfeit medicinal products and would that be permitted?

The respondents of 5 countries considered PAPs as an appropriate way to approach patients in order to educate them about the risks counterfeit medicines pose and to inform them about specific product characteristics that serve as identification features for the respective product. However, the condition mentioned by the respondents is that the respective PAP refers to a medicinal product for which counterfeits are actually already known or which are at high risk to be counterfeited. Otherwise, the patients of the PAP would be alarmed unnecessarily. The countries which argument against the use of PAP for the education of patients about the counterfeit issue share the opinion that patients of PAPs are not the main target group for the education about counterfeit medicines and that only a limited number of patients would be reached. In some countries there are no PAPs in use hence, such programs are no possible access point to educate patients, there.

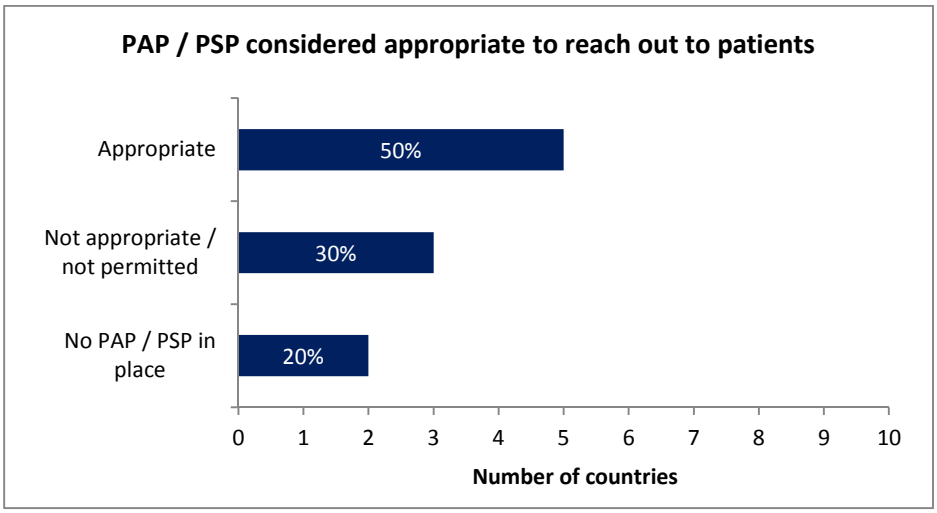

Figure 92: PAP / PSP considered appropriate to reach out to patients

5.2.2.2 Topic 2: Patient perception

Q #4: In your view, would the population in your country be interested in / appreciate to be provided with counterfeit-relevant information and what kind of approach would you consider suitable?

The respondents of only one country considered the communication of counterfeit-relevant information as counterproductive. In this country the presence of counterfeit medicinal products is extremely minor and the purchase of medicines via the internet is prohibited. Therefore, the risk for patients to purchase counterfeit drugs is assessed to be rather small. It is assumed that the warnings about counterfeit medicines would rather be misperceived as

an indication for the existence of counterfeit medicines in the national market leading to mistrust in the medicinal products.

The majority of the respondents assumed that the population in their country would appreciate to be provided with information about counterfeit medicines and how to protect themselves against these. Nevertheless, the respondents stated that the patients' perception very much depends on how the relevant information is provided to them. In most of the countries the respondents assumed that the population would perceive an anti-counterfeiting education campaign carried out under the name of a pharmaceutical company as a means of personal promotion. Thus, the conduct of an ACF education campaign under the name of a "neutral" entity, e.g. a health authority (or at least an association of several pharmaceutical companies) would be preferred and is considered to be more effective.

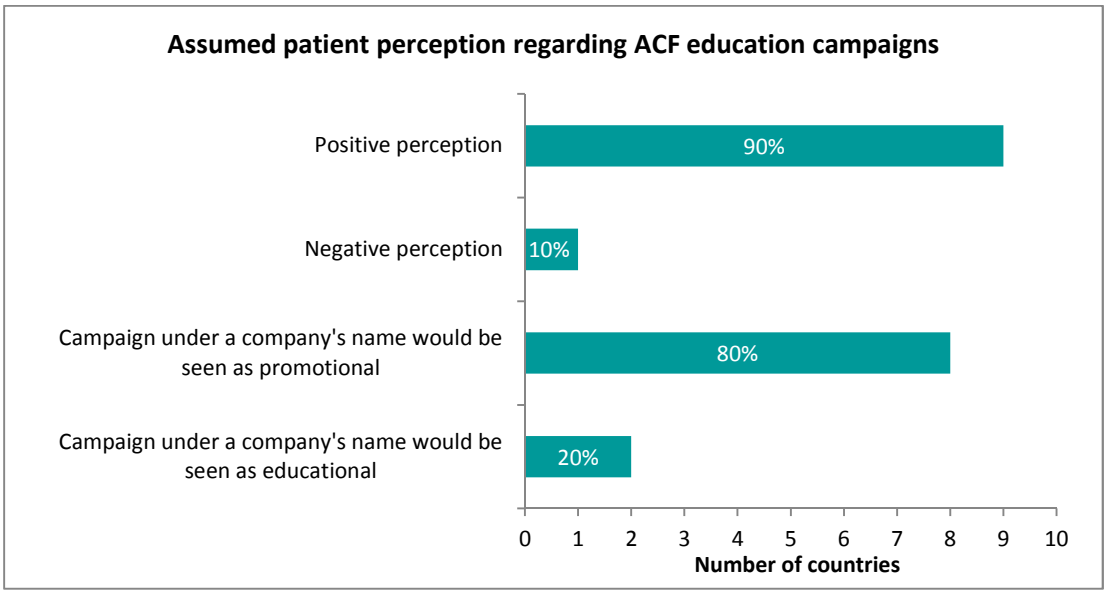

Figure 93: Assumed patient perception regarding ACF education campaigns

5.2.2.3 Topic 3: Patient purchase behavior

Q #5: To what extend do patients in your country purchase medicinal products via the internet? What do you estimate?

The half of the responding countries, where the purchase rate of medicines via the internet is rather high, is almost completely limited to high developed countries. The respondents of these countries stated that the purchase of medicines via the internet is mainly related to OTC medicines and despite the rather high online purchase rate the "traditional" distribution way is still used more often. The other half of the responding countries mentioned several reasons for the low online purchase rate with respect to medicines, including the total

regulatory restriction of purchasing medicinal products via the internet, the limited access to the internet and the resentment of the population to purchase medicinal products online.

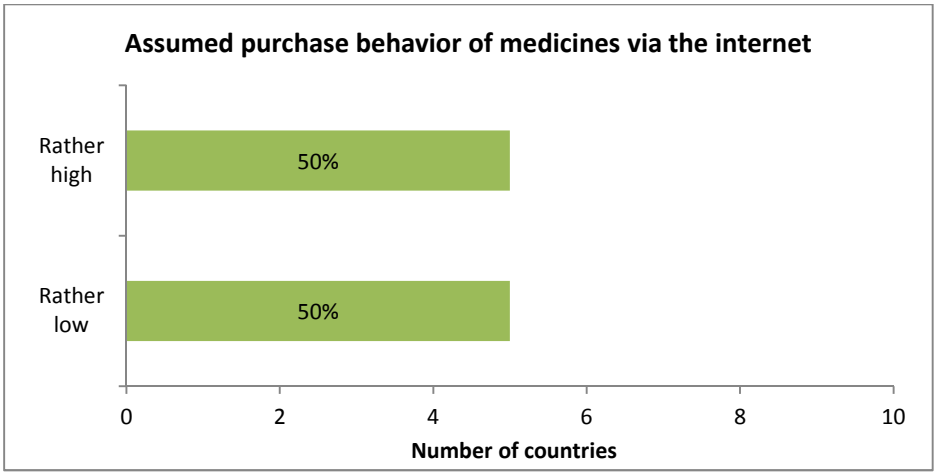

Figure 94: Assumed purchase behavior of medicines via the internet

5.2.2.4 Topic 4: Communication strategy

Q #6: What kind of approach with regard to a public anti-counterfeiting education campaign would you consider as more effective in your country?

In each case, the respondents had to select the more effective option out of 4 pairs of approaches or select both options in case they are considered equally effective. Regarding the first pair, the result is very clear. In 100% of the responding countries the option of an education campaign conducted under the name of a neutral organization (a health authority or an association) was selected as more effective than an education campaign conducted under the name of one pharmaceutical company. Even if an education campaign run under the name of a pharmaceutical company would not be ineffective in some countries (see results of question 4), the neutral approach is still considered more effective in all of the responding countries. The respondents of 50% of the interviewed counties considered a generalized (i.e. non-product-specific) campaign as more effective than a product-specific campaign. This opinion is also related to the fact that the national legislation in many countries does not permit a product-specific education campaign. The respondents of the remaining half of the countries considered the product-specific education campaign as more effective or regarded both options as equally effective. If an anti-counterfeiting education campaign should refer to security features or other specific characteristics, which should be used to distinguish between the genuine and the counterfeit product, it is mandatory to refer to specific products unless the characteristics or security features are applied to all products of a company's portfolio (or all medicinal products in a country). Regarding the media, the majority of the respondents (70% of the responding countries) considered the use of multiple

media as more effective than using only one media. In the view of the respondents a broader spectrum of people can be reached by using different kinds of media. In 30% of the countries both options are seen as equally effective. The fourth and last pair to decide about refers to the time frame of an anti-counterfeiting education campaign. The respondents stated that the timely manner in which such a campaign should be conducted very much depends on the media in use. As in most of the countries the use of different media is considered more effective and the internet is one of the suitable media in 80% of the countries (see results of question 1), the respondents of 80% of the countries would prefer to provide the counterfeit-related information continuously on the local website. In 20% of the countries both options are considered equally effective also depending on the used media. Counterfeit-related information and warnings published via print and broadcast media would be preferred to be provided in a short-term way and the respective information published via the internet (websites) would be preferred to be provided and updated continuously.

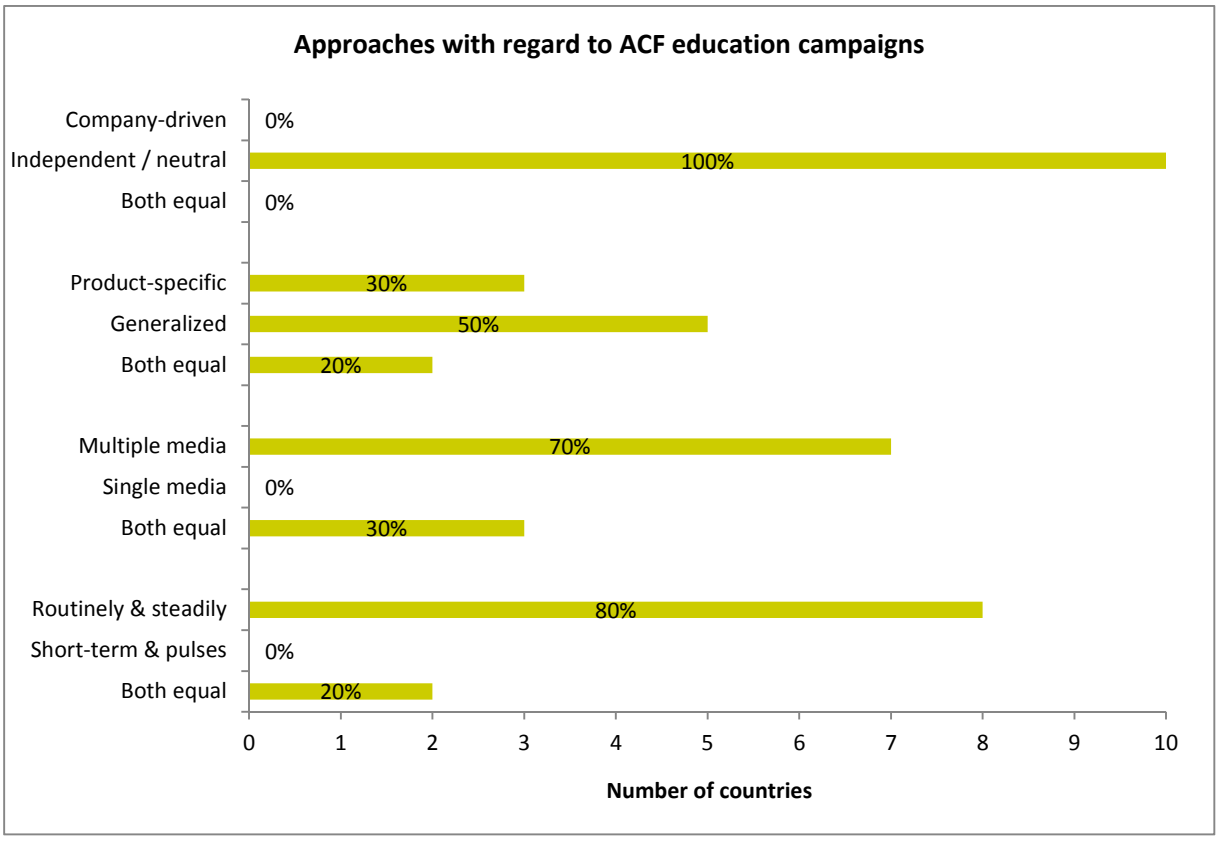

Figure 95: Approach options with regard to ACF education campaigns

5.2.2.5 Topic 5: Collaboration with and support by external stakeholders

Q #7: How was the collaboration with external stakeholders with regard to the counterfeit issue established?

The respondents from each country were allowed to give multiple answers, if applicable. So, in the majority of the countries (70%) the contact between the local affiliate and the local external stakeholders regarding the counterfeit medicines topic was established during topic-specific meetings, conferences and information days. In 50% of the responding countries a contact person was already known due to an established collaboration regarding other matters. In this case the contact person was approached directly (e.g. via phone or e-mail) with respect to counterfeit-related matters. In 30% of the countries the respondents said that the company or the external stakeholder was approached using the official contact (hotline) asking for the responsible person with respect to the counterfeit medicines topic. In 30% of the countries the local affiliate is member of the local pharmaceutical manufacturers association which established contact with other external stakeholders.

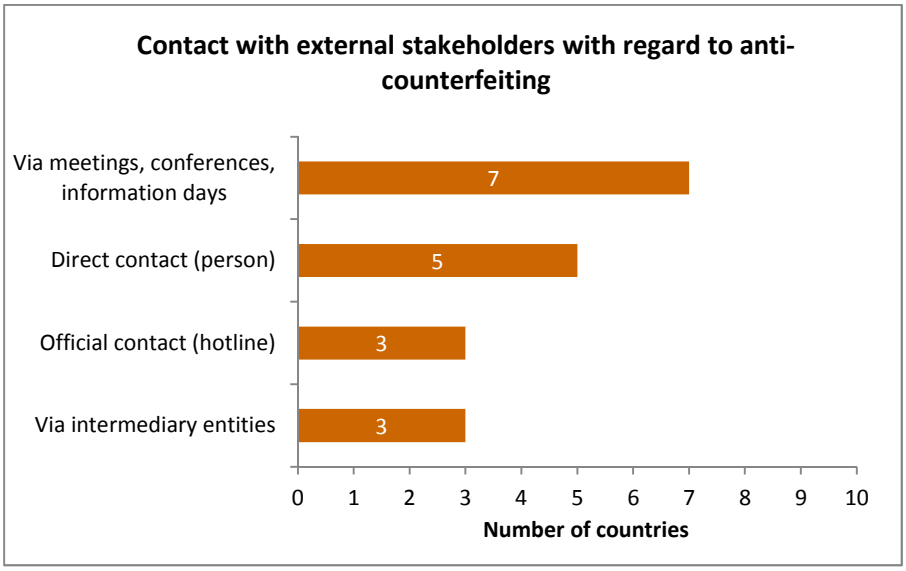

Figure 96: Contact with external stakeholders with regard to the counterfeit issue

Q #8: Do your local authorities and associations consider anti-counterfeiting as an important issue and offer support?

The attitude of the local authorities and associations towards the counterfeit medicines issue and the resulting support that can be expected from them are of interest for a pharmaceutical company that plans to carry out anti-counterfeiting activities and wants to collaborate with the respective stakeholders. In more than half of the responding countries the local authorities and associations consider counterfeiting of medicinal products as a major issue and are willing to offer support in countermeasures. The countries where the topic is of interest but

the resulting support in terms of anti-counterfeiting activities is rather limited and the countries where the support by authorities and associations is little, since the counterfeit topic is assumed to be a minor issue, count 20% each.

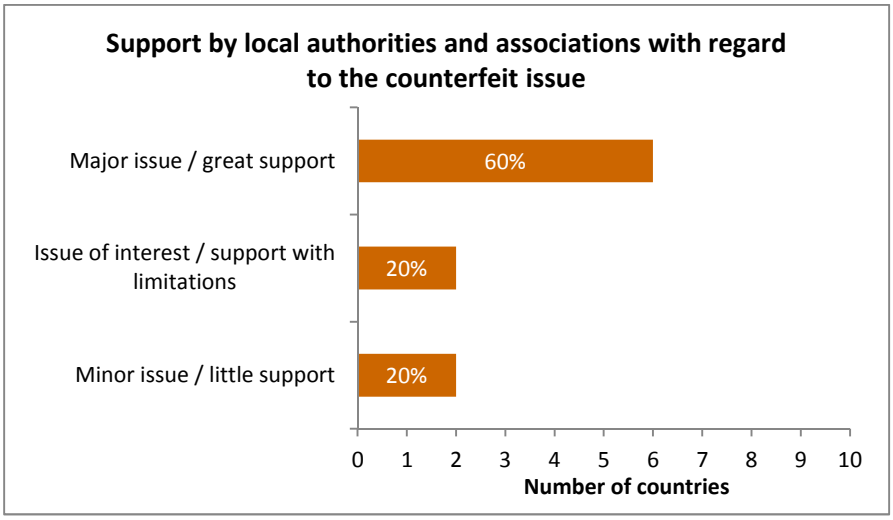

Figure 97: Support by local authorities and associations with regard to anti-counterfeiting

Q #9: Do local authorities (or associations) provide information about legal / licit online pharmacies to the public?

Such information is only provided in Germany (by the DIMDI) and in the USA (by the NABP). Japan and the UK stated that such a service is under discussion but not yet established. In the remaining 60% of the responding countries such information is not provided or it is not applicable as the purchase of medicinal products via the internet is not permitted.

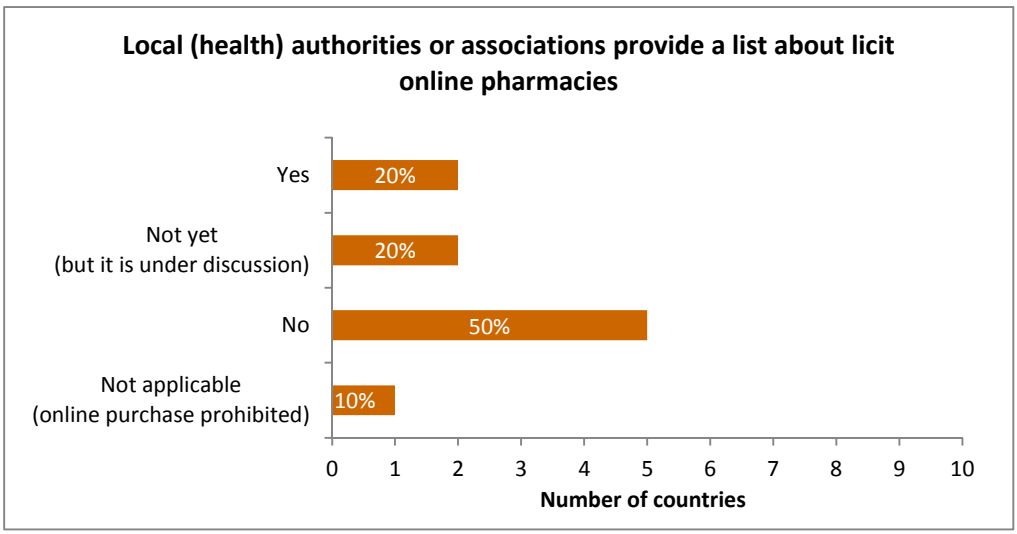

Figure 98: Local (health) authorities or associations provide a list about licit online pharmacies

5.2.2.6 Topic 6: Local processes

Q #10: How is the main responsibility regarding anti-counterfeiting handled in your local organization?

60% of the responding countries state that the responsibility with respect to the counterfeit topic is assigned to several functions which collaborate. However, none of the involved functions is in a leading position. In 40% of the responding countries also multiple functions are involved in the topic and have different tasks assigned but there is one function that is in a leading position and coordinates the different tasks.

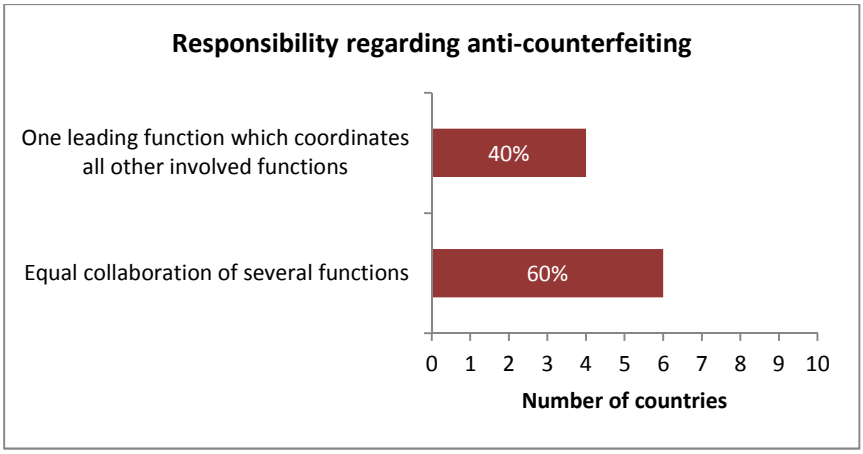

Figure 99: Responsibility regarding anti-counterfeiting

Q #11: How would you assess the collaboration between these functions with respect to anti-counterfeiting matters?

More than one half of the responding countries assess the inter-functional collaboration as rather good. 40% of the responding countries state that there is still room for improvement since the collaboration between some of the involved functions is very good. However, often not all affected functions, involved in the counterfeit topic, are involved in the collaboration or some functions elude themselves from the collaboration.

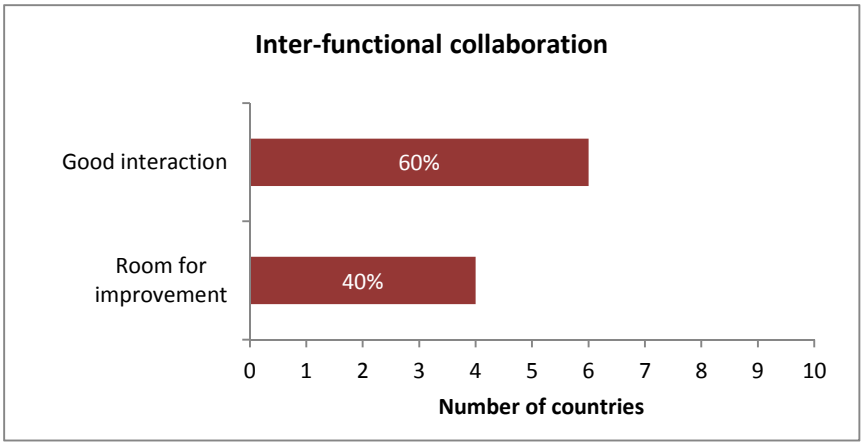

Figure 100: Assessment of the inter-functional collaboration

5.2.2.7 Topic 7: Net-working

Q #12: What would you consider as desirable / required to enhance net-working between functions and across countries?

To explore what the employees of the different local organizations would like to have implemented to enhance the net-working regarding the counterfeit topic, the respondents were asked to make suggestions and to address their remarks. The respective desirable measures can be differentiated into 4 subject areas as shown in the figure below. The respondents would value very much to be provided with a company-internal website or tool where the most relevant information regarding the counterfeit topic is available for every company employee, including the company's global anti-counterfeiting concept, affected products of the company's portfolio and overt anti-counterfeiting security features that are applied to the company's products. Moreover, anti-counterfeiting activities initiated by the company, the related experiences and results would be highly appreciated information. In addition, information on anti-counterfeiting initiatives, organized by external entities but in which the company is involved, could be given. Furthermore, the company-internal dialogue about anti-counterfeiting measures and activities between functions, especially across countries, would be appreciated to be enhanced to a routine basis to keep all involved functions updated and broadly informed. Thereby, feedback from the local organizations could be given to the central functions on a routine basis. The regular conduct of topic-specific trainings would strengthen the responsible employees' confidence in handling their tasks and all their required procedures. Consequently, the local affiliates would highly appreciate to be provided with respective topic-specific training and informative literature to support their local personnel.

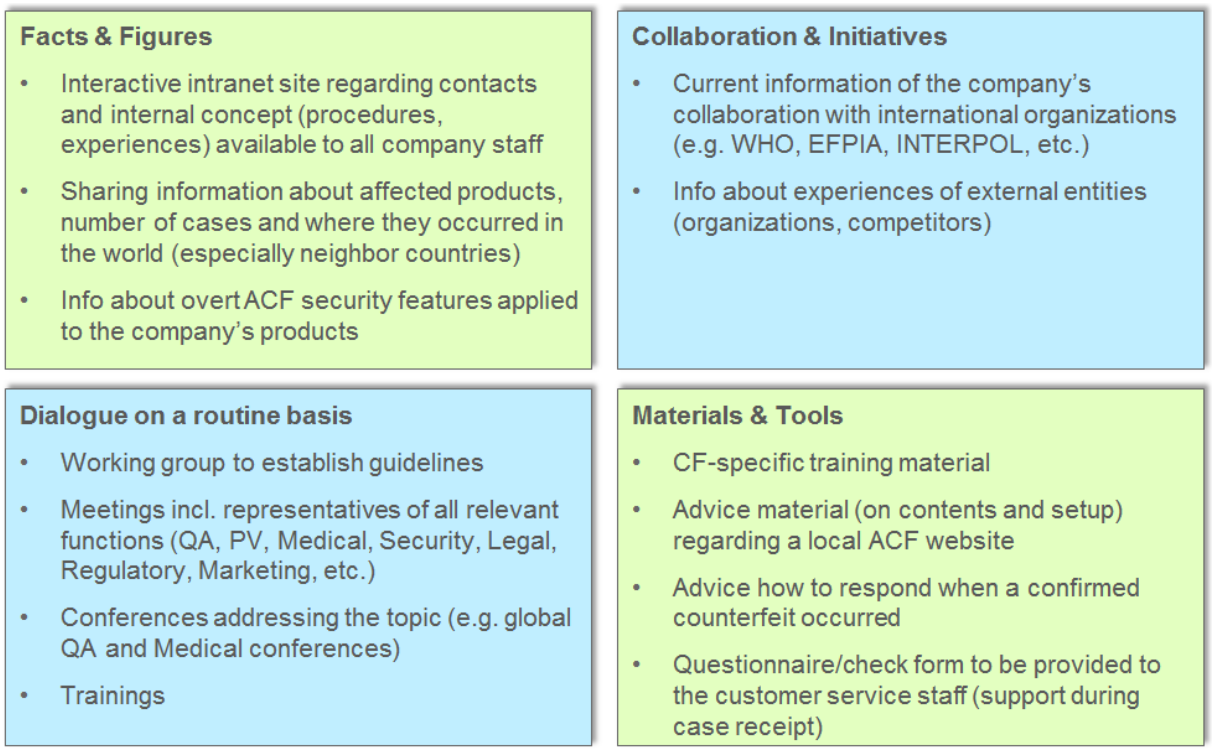

Figure 101: Overview on desirable measures to enhance net-working with regard to the counterfeit topic

5.3 Training and communication concept

Based on the information, gained within the frame of the affiliate survey and the interviews, the following training and communication concept was developed the context of this dissertation and is recommended to meet the identified internal education needs. A company-internal topic-specific communication platform should be established to enhance the net-working and the exchange of information with respect to the counterfeit topic between the central and the local functions and also the affiliates among themselves. By means of such a tool topic-specific information about basic counterfeit-relevant facts, established concepts and procedures, responsible contact persons and implemented or planned anti-counterfeiting activities should be provided to all affected functions within the company. According to the status of confidentiality of the provided information restricted access rights have to be created so that confidential information can only be accessed by authorized personnel. For instance, a Microsoft® SharePoint can be a suitable tool for this purpose. The tool should also be used to allocate topic-specific training materials for the access by employees who are involved in the counterfeit topic. The training materials should be segmented into modules in order to provide the required information according to the employees' responsibilities and tasks with respect to the counterfeit topic, e.g. a basic module, an advanced module and an expert module. According to the module type the contents range from basic information over detailed information to confidential information. The basic module should at least contain general information about the problem of

counterfeit medicines and the risks they pose to patients, the company's policy regarding the topic and responsible contact persons who can be approached in case of questions or for support. The advanced module should comprise more detailed information regarding the company's anti-counterfeiting concept, procedures, activities, counterfeit-specific terms and definitions and supportive material, e.g. for counterfeit-relevant data handling. One example for such supportive material was developed in the context of the thesis and is presented in figure 102. The expert module should contain product-specific information, including anti-counterfeiting security features which are applied to the products as far as confidentiality permits.

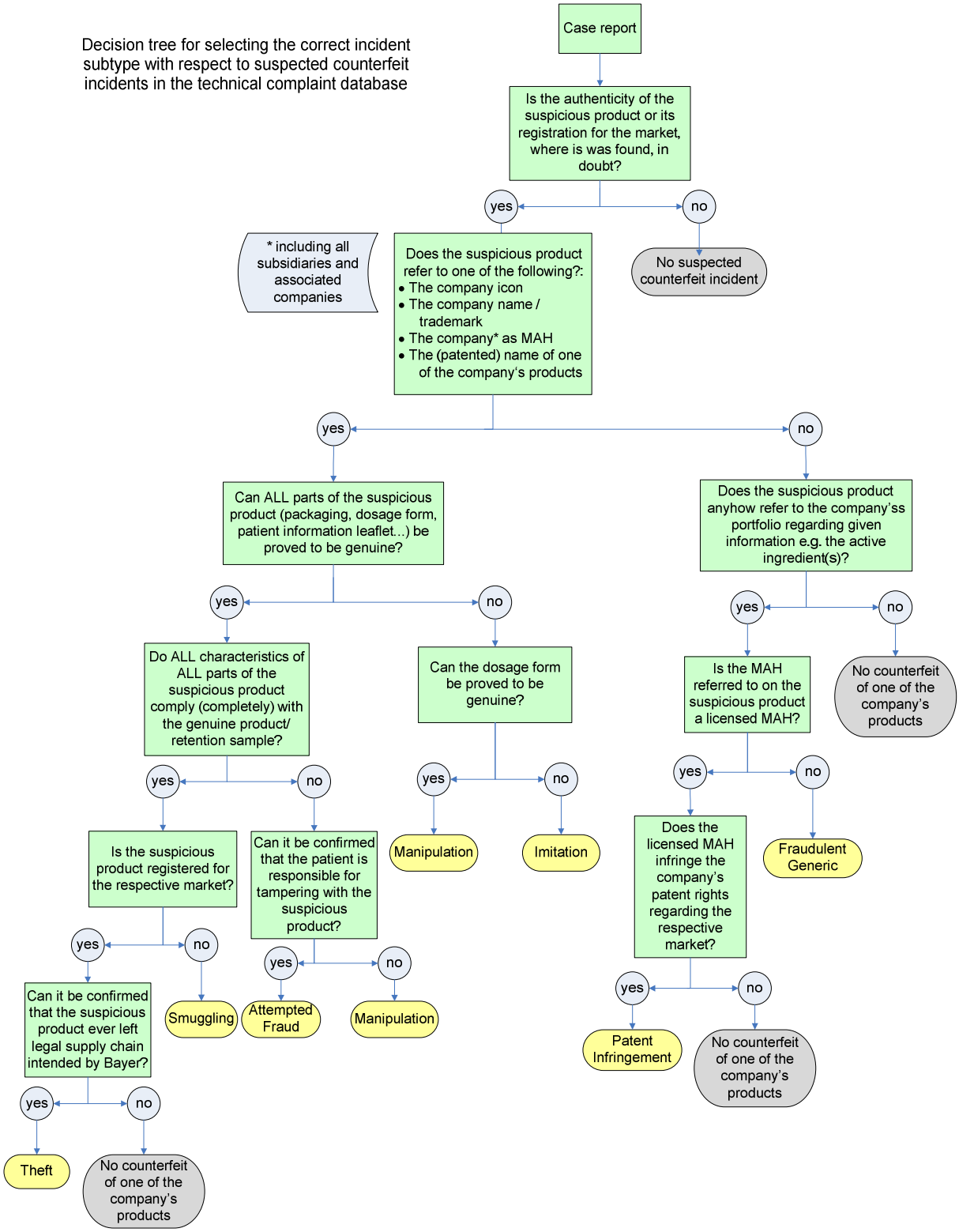

Figure 102: Decision tree on the counterfeit incidents classification

CHAPTER SIX - CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion and recommendations

Counterfeit products present a huge problem due to their great number on the market all over the world. In contrast to counterfeit luxury goods, which mainly harm the economy, counterfeit medicinal products pose a serious risk to health and safety. As indicated in this dissertation these products can cause serious or even fatal health outcomes. In fact, the flooding of the market with counterfeit drugs increased over the previous decade. For this reason, the combat against counterfeit medicines should be of particular interest by the stakeholders of the health sector to safeguard patients' welfare.

Concerning the issue of counterfeit medicinal products existing statutory provisions are presented in this dissertation with a special focus on the obligations of the pharmaceutical industry. The objective of this thesis is to reveal what kind of anti-counterfeiting measures can be and should be adopted by the pharmaceutical industry exceeding the legal provisions. In this context, special focus is laid on the opportunities and limitations of such anti-counterfeiting measures. Thereby, three measures were examined and presented in detail, which are: Monitoring, education and procedural review of anti-counterfeiting activities.

Monitoring

A marketing authorization holder is obliged to verify the quality, safety and efficacy of its products in order to protect patient safety, e.g. by means of pharmacovigilance activities as described in this dissertation. Today, it is no longer sufficient for a marketing authorization holder to implement control and surveillance measures in order to exclude and prevent potential risks only with respect to its genuine medicinal products. Instead, the MAH is also required to take action with regard to counterfeits of its genuine products.

One of the anti-counterfeiting measures analyzed in particular within the frame of this thesis is data monitoring and evaluation. A marketing authorization holder is obliged to collect, process and evaluate counterfeit incident reports (as well as adverse event reports) and to report the respective cases to the competent authorities, as per local regulations. The collected data represents the basis for further counterfeit evaluation and root cause analysis. Moreover, the confirmed counterfeit incidents provide information on the company's affected products and the affected countries, so that appropriate anti-counterfeiting activities can be initiated based on this information. Counterfeit medicines are often difficult to detect due to their visual similarity to the genuine products. Hence, it is reasonable to expect that a

marketing authorization holder receives reports about adverse events that are actually not related to the MAH's original medicinal products, but rather to their counterfeits. For that reason, monitoring and evaluation of suspected counterfeit incident reports is not sufficient. The results of the performed data analysis show that more options with respect to data monitoring should be taken into consideration.

The company's adverse event data was investigated to ascertain if it could serve as a basis for an extended monitoring with respect to potential counterfeit signals. Based on the assumed correlation between the number of reported adverse events and a counterfeit presence on the respective market, the adverse event data and the counterfeit incident data of 6 example products was analyzed with regard to a potential correlation.

The results show that with respect to 3 example products a correlation between particularly defined adverse event data and counterfeit incident data could be identified. Hence, peaks in the number of adverse event reports can hint at a potential counterfeit presence on the market. Such peaks should be monitored and evaluated considering this aspect. As discussed in the respective chapter (chapter three), the criteria for data used as the monitoring basis must be product-specific and should be monitored country-specifically over a broad time period to narrow influencing factors, as much as possible. The consideration of potential influencing factors, which cannot be excluded by the use of specific data criteria, should always be included in the result assessment for validity. Such factors are mainly of the kind that has an impact on the reporting behavior of patients, healthcare professionals and authorities in the different countries.

The results of the data analysis show that counterfeit monitoring activities can be extended using adverse event data to identify potential signals of a possible counterfeit presence. Hence, more valuable data is available to be used as a basis for further investigations to detect counterfeit products on the market. Therefore, the extended monitoring can contribute to minimize the risk of an undetected counterfeit presence causing harm to patients and negatively influencing the benefit-risk profile of the original medicinal products.

Education

The suspected counterfeit incident data, investigated in this dissertation, moreover show an underreporting in many regions and countries, which possibly points to a need of education and awareness regarding patients and healthcare professionals. Their reporting behavior, with respect to suspected counterfeit incidents, very much depends on their awareness of counterfeit medicines. For that reason, an education campaign pilot project with the purpose

to raise awareness of the counterfeit issue was initiated within the frame of this thesis. The campaign was planned and carried out in a product-specific way in one country. Thereby, its perception by and effect on the target group and its applicability to serve as an example for further education campaigns were examined.

As highlighted in the thesis, measures with the purpose to raise awareness of the issue of counterfeit medicines require much effort regarding their preparation and organization. However, as revealed in this dissertation, they can be tremendously effective and thus, are worth the effort. The different options of conducting measures with the purpose to raise awareness should be considered very carefully and probably should be based on preceding activities. The points to be considered regarding the preparation and implementation of such awareness-raising measures and possible preceding activities are explained in detail in the respective chapter (chapter four).

The results of the conducted pilot project show that a product-specific education campaign performed under the name of its MAH using different kinds of media is a very effective measure to raise awareness. Using both, the internet to provide counterfeit-relevant information on the company's websites and print media, including posters and brochures being distributed via selected drug distribution points, e.g. hospitals and pharmacies, located all over the country, guarantees a broad outreach to patients in a rather short period of time. Thus, patients are provided with valuable information to be able to better protect themselves against the risks posed by counterfeit medicines, which is a great contribution to the protection of their safety.

Another important aspect regarding the realization of such an anti-counterfeiting measure is the collaboration between multiple stakeholders, including several central and local, internal functions of the respective marketing authorization holder and external stakeholders, e.g. health authorities. The experiences gained during the education campaign pilot project revealed that it is imperative to involve multiple functions of different areas within a pharmaceutical company to successfully initiate and implement such a project. The following figure, created in the context of this thesis, presents an overview of functions within a pharmaceutical company which should be involved in such an anti-counterfeiting project. Moreover, it presents external stakeholders which can and possibly have to be involved when a marketing authorization holder plans to carry out a public education campaign or other ACF activities.

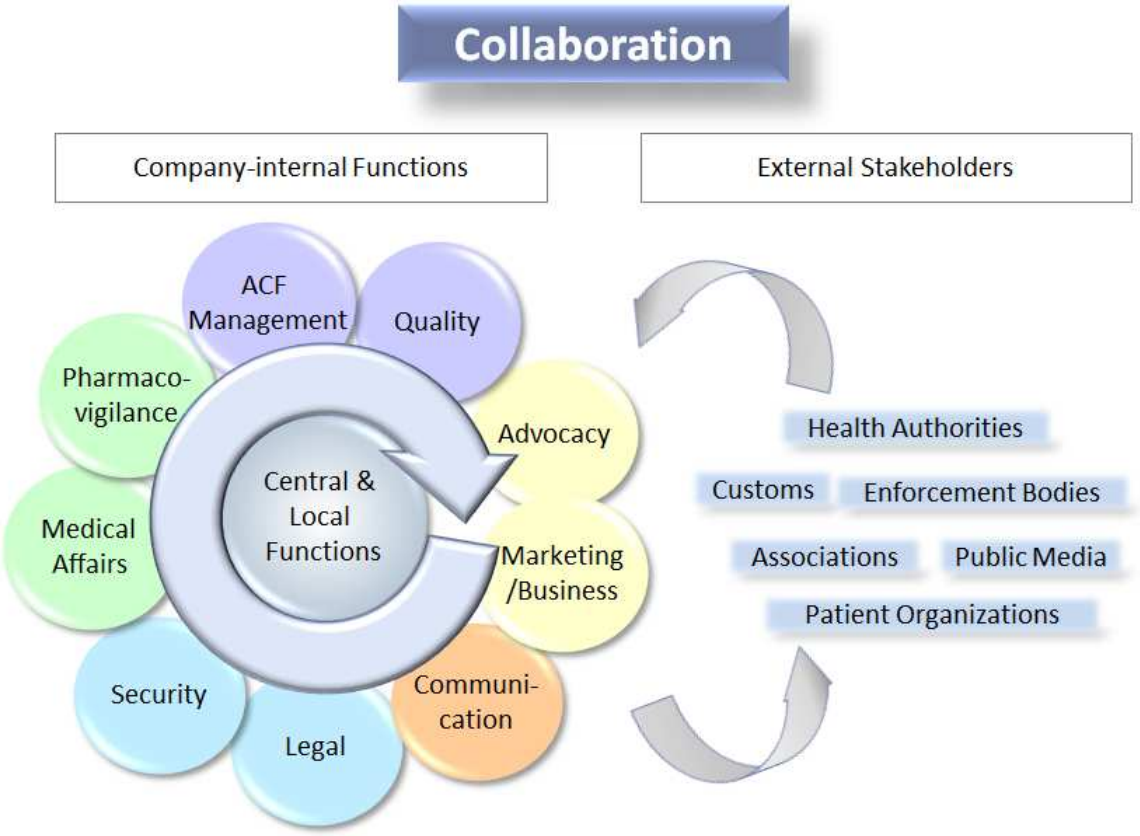

Figure 103: Collaboration between several stakeholders on ACF activities

The initiated pilot project is only one option to conduct a public education campaign with regard to the problem of counterfeit medicines. The variety of means and conduct strategies is huge. The results of the interviews, conducted with 10 selected countries, show for example that a neutral education campaign, which provides general information about the risks of counterfeit medicines, is also considered a successful option to raise awareness among the public. Preparing and implementing a public education campaign, the MAH always has to take national circumstances into account and should adapt the campaign accordingly to make sure the campaign does not conflict with national legislation. However, all available options with regard to suitable media and potential collaborative stakeholders should be considered in order to carry out a campaign of maximum success.

The education campaign, initiated in the context of this thesis, revealed that education about the risks counterfeit medicines pose to patients' health and how to minimize the risk of exposure to counterfeit medicines helps patients to protect themselves against the threat. Hence, it is highly recommended that the pharmaceutical industry adopts measures to contribute to the education of the public about the counterfeit medicines problem.

Review of anti-counterfeiting activities and procedures

All over the world, many different functions within a global pharmaceutical company are involved in the topic of anti-counterfeiting. To guarantee consistent procedures according to the company's anti-counterfeiting concept the different functions have to be provided with required information about the counterfeit topic, as well as anti-counterfeiting activities and procedures. Therefore, a global survey including all relevant functions of the local affiliates was initiated and carried out within the frame of this thesis to review the current state of implemented anti-counterfeiting activities and procedures and the required topic-specific expertise. Afterwards, the affiliates of 10 countries were selected as interview partners to gain further and more detailed information.

The results of the conducted global company-internal affiliate survey and the interviews demonstrate the huge interest of the affiliates in the counterfeit topic as a whole. The results also confirm the necessity of a broad internal collaboration and the net-working between multiple functions of different areas within a global pharmaceutical company and the importance of the collaboration with external stakeholders with respect to the counterfeit topic. Furthermore, the results reveal a need for improvement regarding the counterfeit-specific knowledge and consequently the counterfeit-specific training of the employees of multiple functions. Thus, a coordinated support with regard to counterfeit-relevant company-internal education and training would meet the employees' needs and thereby lead to a more consist and confident handling of counterfeit-relevant data and procedures. A respective training and communication concept was developed within the frame of this dissertation and is presented in chapter five.

The general procedure that is recommended in the context of this thesis provides that the pharmaceutical company's central functions, involved in the counterfeit topic, should develop an anti-counterfeiting concept which is applicable for the whole company. In addition, an overview of anti-counterfeiting measures, which are already implemented in some countries or which the central functions would support, should be provided as an orientation for all affiliates of the company. The local affiliates which decide or are asked by the central functions to implement one or more of the suggested measures would check if the measures comply with their national legislation or if any adaptations are required. This would be discussed with the central functions. Furthermore, the overview should include examples of the successful collaboration of company-internal functions and external stakeholders. The overview should describe how the collaboration was established in order to encourage further local affiliates to likewise establish or extend the collaboration with local external stakeholders (e.g. health authorities, customs, police or associations). In doing so, the

exchange of information and the mutual support with regard to anti-counterfeiting activities between the pharmaceutical industry and the external stakeholders can be extended.

In conclusion, this dissertation presents multiple measures to combat counterfeiting of medicines including data monitoring and evaluation, collaboration with authorities, investigative, legal and technological measures, awareness-raising and the review of anti-counterfeiting activities and procedures within a pharmaceutical company. The presented measures should serve as an orientation for the pharmaceutical industry on what can be done in order to counteract the counterfeiting of medicinal products. Three of these measures have been analyzed and are presented in more detail using practical examples. Thereby, important aspects to be considered with regard to anti-counterfeiting activities and procedures were revealed to serve also as an orientation for the implementation of such measures. Furthermore, the effectiveness of the available anti-counterfeiting measures and their importance is outlined in the dissertation.

The insights of this thesis show that an enhanced awareness of the counterfeit issue and the related risks among the public can contribute to the reduction of incidents where patients experience adverse events from counterfeit medicines. Moreover, it can lead to an extended cognition and reporting of potential counterfeit medicinal products leading to an increase in valuable counterfeit-related data. This information, in turn, can be used for the targeted implementation of investigative and legal measures against counterfeiters. In order to take action in anti-counterfeiting pharmaceutical companies should implement an anti-counterfeiting concept, if not yet established. The concept including all implemented anti-counterfeiting activities and procedures should be reviewed considering the presented aspects and adapted accordingly, if required. Furthermore, they should foster the collaboration with external stakeholders with respect to the counterfeit issue. Thereby, the smooth operation and the efficacy of all internal anti-counterfeiting procedures and external anti-counterfeiting activities are optimized to achieve maximum effects.

By means of this thesis pharmaceutical companies shall be encouraged to adopt anti-counterfeiting measures. It is very unlikely that the problem of counterfeiting medicinal products will ever be solved completely. Thus, it is imperative that the pharmaceutical industry actively contributes to the combat against counterfeit medicines by adopting appropriate anti-counterfeiting measures in order to protect patient safety and to safeguard patients' welfare.

CHAPTER SEVEN - REFERENCES

7.1 List of figures

7.2 List of tables

7.3 Annexes

Annex 1: Education campaign regarding Nexavar® in China; hand-out page 1 – English

Figure 104: Education campaign hand-out, page 1 - English

Annex 2: Education campaign regarding Nexavar in China; hand-out page 2 – English

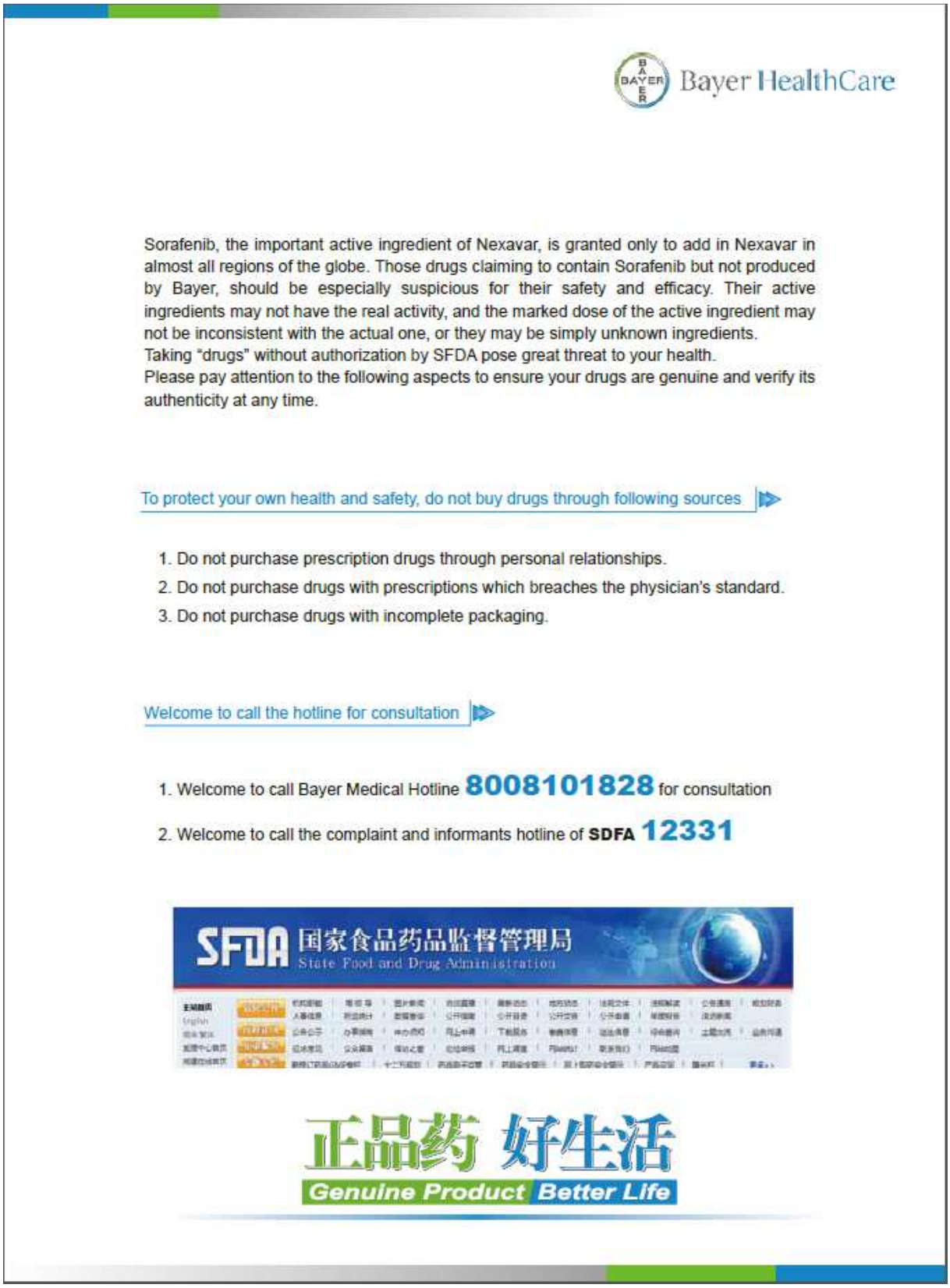

Figure 105: Education campaign hand-out, page 2 - English

Annex 3: Education campaign regarding Nexavar in China; poster – English

Figure 106: Education campaign poster - English

Annex 4: Questionnaire, including landing page, developed for the global affiliate survey which presented the framework for the digital questionnaire

Welcome to the Survey
"Anti-Counterfeiting and Product Security"
(BHC Pharma)

Please answer the following **20 multiple choice questions**.

The survey should not take more than **15 minutes** of your time. Your responses are anonymous and will be kept strictly confidential. They will not be used for any purpose other than the compilation of the survey results.

The term "counterfeit" is being used in the questionnaire as a synonym for all counterfeit, falsified medicine, and product security-related issues, including imitation, adulteration (tampering), mix-up of genuine and counterfeit product, smuggling, theft, fraudulent generics, and manipulation.

Your participation is highly appreciated.

Please enter your

Country: _drop down_

1) In your view, counterfeiting of pharmaceutical products in your country is:

□ Increasing □ Decreasing □ Constant □ No issue

2) Are you aware of counterfeits of Bayer Healthcare Pharma products in your country?

□ Yes □ No

3) If yes, which products? Please list below.

Free text

4) Is anti-counterfeiting of importance in your local organization?

□ Yes □ No

5) Has there ever been a public campaign to combat counterfeit medicinal products in your country?

□ Yes □ No

6) If yes, who performed it? (multiple selections possible)

□ Health Authority

□ Customs / Border Surveillance

□ Other enforcement body (e.g. Police)

□ Patient Association

□ Pharmaceutical Manufacturer Association

□ Healthcare Professionals (HCP) / HCP Association

□ Others:

Free text

Please provide details / references, if possible:

Free text

_____

7) Has your local organization ever been involved in such a campaign?

□ Yes □ No

8) With whom does your local organization interact in anti-counterfeiting matters? (multiple selection possible)

□ Health Authority

□ Customs / Border Surveillance

□ Other enforcement body (e.g. Police)

□ Patient Association

□ Pharmaceutical Manufacturer Association

□ Healthcare Professionals (HCP) / HCP Association

□ Others (Please provide details):

Free text

9) Does your local organization have a website or a section on your website established that contains counterfeit-specific information for patients and healthcare professionals?

□ Yes □ No

10) If yes, it includes (multiple selection possible):

□ General counterfeit warnings

□ Link to Bayer Beware of Counterfeits website

http://www.bayerhealthcare.com/scripts/pages/en/commitment/beware_of_counterfeits/index.php

□ Link to websites of local initiatives

□ Information on actual counterfeit incidents

□ Information how to distinguish between genuine and counterfeit

□ Information on how to report suspected counterfeits

□ Others:

Free text

Please provide the link to your local anti-counterfeit webpage:

Free text

11) Which of the following counterfeit-specific tools does your local organization have in use to retrieve / follow-up on all counterfeit-relevant information and material from a reporter (e.g. complaint sample, batch no., product source, related ADR etc.)?

Tools provided to the reporter:

□ Report form / questionnaire

□ Patient / HCP information material on how / what to report

□ Complaint sample collection service (e.g. free return envelope)

□ None

□ Unknown

□ Others:

Free text

12) Tools used by your local personnel during ad-hoc contact with the reporter:

□ Check-list on relevant information

□ Information on previously identified counterfeits in the country (e.g. product, lot no.)

□ Complaint sample collection (e.g. from the patient)

□ Follow-up process for suspected counterfeit reports

□ None

□ Unknown

□ Others:

Free text

13) Which function / role within your local organization is actively involved in counterfeit-related matters towards the following external stakeholders? (multiple selection possible)

	Health Authority	Customs	Other Enforcement Body	Public Media / Press	Associations	Not Applicable / None
CDH (Country Division Head)	☐	☐	☐	☐	☐	☐
Medical Affairs / CMD (Country Medical Director)	☐	☐	☐	☐	☐	☐
Pharmacovigilance / PVCH (Pharmacovigilance Country Head)	☐	☐	☐	☐	☐	☐
Quality Affairs / LQR (Local Quality Representativ)	☐	☐	☐	☐	☐	☐
LSC (Local Security Coordinator)	☐	☐	☐	☐	☐	☐
Legal / LACM (Local Anti-Counterfeiting Manager)	☐	☐	☐	☐	☐	☐
Security / LSR (Local Security Representative)	☐	☐	☐	☐	☐	☐
Communication	☐	☐	☐	☐	☐	☐
Regulatory Affairs / LRAM (Local Regulatory Affairs Manager)	☐	☐	☐	☐	☐	☐
Business / Marketing	☐	☐	☐	☐	☐	☐
Customer Service	☐	☐	☐	☐	☐	☐
Medical Information	☐	☐	☐	☐	☐	☐
Others: *Freetext*	☐	☐	☐	☐	☐	☐

14) Which of the following functions / responsible persons within your local organization are responsible for internal processing of counterfeit-related matters? (multiple selection possible)

	Counterfeit Reports	Theft Reports	Agency Support (e.g. Information Material, Raids)	Media Support (e.g. Press Statements)	Patient / HCP Education	Not Applicable / None
CDH (Country Division Head)	☐	☐	☐	☐	☐	☐
Medical Affairs / CMD (Country Medical Director)	☐	☐	☐	☐	☐	☐
Pharmacovigilance / PVCH (Pharmacovigilance Country Head)	☐	☐	☐	☐	☐	☐
Quality Affairs / LQR (Local Quality Representativ)	☐	☐	☐	☐	☐	☐
LSC (Local Security Coordinator)	☐	☐	☐	☐	☐	☐
Legal / LACM (Local Anti-Counterfeiting Manager)	☐	☐	☐	☐	☐	☐
Security / LSR (Local Security Representative)	☐	☐	☐	☐	☐	☐
Communication	☐	☐	☐	☐	☐	☐
Regulatory Affairs / LRAM (Local Regulatory Affairs Manager)	☐	☐	☐	☐	☐	☐
Business / Marketing	☐	☐	☐	☐	☐	☐
Customer Service	☐	☐	☐	☐	☐	☐
Medical Information	☐	☐	☐	☐	☐	☐
Others: *Freetext*	☐	☐	☐	☐	☐	☐

15) Are you familiar with the following terms and their meaning / definition in the context of counterfeit and product security-related issues?

	Yes	No	Not sure
Imitation	☐	☐	☐
Mix-up of genuine / counterfeit	☐	☐	☐
Adulteration (Tampering)	☐	☐	☐
Smuggling	☐	☐	☐
Theft	☐	☐	☐
Fraudulent generic	☐	☐	☐
Manipulation	☐	☐	☐

16) Do you have the following responsible persons appointed and communicated in your country?

	Yes	No	Unknown
LACM (Local Anti-Counterfeiting Manager)	☐	☐	☐
LSR (Local Security Representative)	☐	☐	☐
LSC (Local Security Coordinator)	☐	☐	☐

17) Are any of the following functions provided with counterfeit-specific training?

	Yes	No	Unknown
Customer Service / Hotline	☐	☐	☐
Sales Representatives	☐	☐	☐
Medical Scientific Liaisons	☐	☐	☐
Medical Advisors	☐	☐	☐
Local Pharmacovigilance	☐	☐	☐
Local Complaint Management	☐	☐	☐
Product Managers (Marketing)	☐	☐	☐
Security	☐	☐	☐

If you answered none of the above with “Yes” then please move on to question #20.

18) Does the training contain the following? (multiple selection possible)

□ Current counterfeit situation in general / global

□ Current counterfeit situation in your country

□ Specific Bayer Pharma products with respect to counterfeit protection

□ Visible anti-counterfeiting security features applied on the Bayer Pharma products in your country

□ How to identify counterfeit Bayer Pharma products by means of known characteristics of previously identified counterfeit Bayer Pharma products

□ Whom to contact when a counterfeit / product security-relevant information is received

□ Others:

Free text

19) Which responsible function or role provides counterfeit-related training and compiles the training material?

Function / Role: | *Free text* | □ Unknown

20) Which of the following support with regard to counterfeit protection of Bayer Pharma products would be of interest to you / your local organization? (multiple selection possible)

□ Counterfeit-specific questionnaires / check-lists for use in Call Centers

□ Counterfeit-specific training material

□ Best Practice material (e.g. tools)

□ Information about overt (visible) anti-counterfeiting security features applied on the Bayer Pharma products in your country

□ Bayer Pharma strategy on counterfeit protection

□ News on internal anti-counterfeiting activities in other countries / regions

□ Global or regional news on external anti-counterfeiting initiatives e.g. WHO, FDA, 2D matrix code, etc.

□ Others:

Free text

Annex 5: Questionnaire developed for the interviews

Interview Questions: The questions are only related to the circumstances in your country.

1) MEDIA AND TOOLS

There are many conceivable tools used in the communication with patients e.g. the internet including websites and social media; public media including newspaper publications, radio and TV and information media including posters and brochures.

1.1 Which media would you consider suitable to publish health-related matters?

Free text

1.2 What are the national regulatory restrictions with respect to the publishing of health-related matters?

Free text

1.3 Would you consider Patient Assistant Programs (PAPs) or Patient Support Programs (PSPs) as suitable to reach out to patients in order to inform them about the risks of counterfeit medicinal products and would that be permitted?

Free text

2) PATIENT PERCEPTION

Anti-counterfeiting activities could be perceived positively as a company responsibility in order to protect patient safety and build trust in the company's product portfolio. On the other hand, they could be misperceived as an indication of counterfeit existence leading to mistrust in the company's product portfolio.

2.1 In your view, would the population in your country be interested in / appreciate to be provided with counterfeit-relevant information and what kind of approach would you consider suitable?

Free text

3) PATIENT PURCHASE BEHAVIOR

3.1 To what extend do patients in your country purchase medicinal products via the internet? What do you estimate?

Free text

4) COMMUNICATION STRATEGY

A targeted communication concept is one of the key elements in anti-counterfeiting. In order to be effective the strategy has to be adapted according to local needs (e.g. consumer behavior, regulatory restrictions).

4.1 What kind of approach with regard to a public anti-counterfeiting education campaign would you consider as more effective in your country?
(With regard to the given 4 pairs please mark the approach you consider "more effective" with an "x" or select "both equal" if you consider them equally effective)

	More effective	Both equally effective
a1) company-driven *initiative is conducted under the name of the enforcing company / companies*		
a2) independent / neutral *initiative in collaboration with e.g. associations under the name of the respective association*		
b1) product-specific *initiative is related to one product or a product group*		
b2) generalized *not product-specific*		
c1) using multiple media *one initiative comprises the use of multiple media*		
c2) using only one media *one initiative relates to the use of only one media*		
d1) routinely and steadily *activities are carried out continuously over a longer period of time*		
d2) short-term and pulses *activities are carried out in a short repeated manner*		

5) COLLABORATION

Collaboration with external stakeholders is another key element in an effective ACF strategy and the survey results revealed that many affiliates maintain a broad collaboration with external parties.

5.1 How was contact with the external stakeholders with regard to the counterfeit issue established in your organization?
(please mark the applicable row(s) with an "x")

	Please select *(multiple selection possible)*
meetings, conferences, information day	
direct contact via e-mail or phone *(contact person was known / publicly accessible)*	
official contact via e-mail or phone *(general institution contact address)*	
via intermediary entities *(e.g. associations)*	

5.2 Do your local authorities and associations consider anti-counterfeiting as an important issue and offer support?

Free text

5.3 Do local authorities (or associations) provide information about legal / licit online pharmacies to the public?

Free text

6) LOCAL PROCESSES

6.1 How is the main responsibility regarding anti-counterfeiting handled in your local organization?

Free text

6.2 How would you assess the collaboration between these functions with respect to anti-counterfeiting matters?

Free text

7) NETWORKING

Based on the ACF survey results a great need for knowledge-sharing and networking was identified.

7.1 What would you consider as desirable / required to enhance net-working between functions and across countries?

Free text

7.4 Bibliography

[1] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001," (OJ L 311, 28.11.2001, p. 67). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [Accessed 16 January 2015].

[2] "The 1906 Food and Drugs Act and Its Enforcement," [Online]. Available: http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054819.htm. [Accessed 11 November 2013].

[3] "PSI - Counterfeits - Trend Data," [Online]. Available: http://www.psi-inc.org/incidentTrends.cfm. [Accessed 31 January 2015].

[4] IMPACT, "Counterfeit Drugs Kill!," May 2008. [Online]. Available: http://www.who.int/impact/FinalBrochureWHA2008a.pdf. [Accessed 7 November 2013].

[5] "WHO Fact sheet N° 275," May 2012. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs275/en/index.html. [Accessed 29 October 2013].

[6] "WHO - Counterfeit medicines: General information," [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/. [Accessed 25 October 2013].

[7] "PSI - Counterfeits - Definitions," [Online]. Available: http://www.psi-inc.org/counterfeitSituation.cfm. [Accessed 5 November 2013].

[8] "European Commission - Medicinal Products for Human Use," [Online]. Available: http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm. [Accessed 5 November 2013].

[9] "Oxford Dictionaries - Fraud," [Online]. Available: http://www.oxforddictionaries.com/definition/american_english/fraud. [Accessed 5 November 2013].

[10] "The Importance of Pharmacovigilance - Safety Monitoring of medicinal products, WHO 2002," [Online]. Available: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. [Accessed 29 October 2013].

[11] "Report on EU customs enforcment of intellectual property rights - Results at the EU borders - 2010," 2011. [Online]. Available: http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/statistics_2010.pdf. [Accessed 13 November 2013].

[12] "Report on EU customs enforcment of intellectual property rights - Results at the EU borders - 2011," 2012. [Online]. Available: http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/2012_ipr_statistics_en.pdf. [Accessed 13 November 2013].

[13] H. G. Schweim, "Arzneimittelkauf im Ausland - das kann gefährlich sein!," *Deutsche Apotheker Zeitung,* no. 21, pp. 48-51, 2010.

[14] B. Moran, "Cracking Down on Counterfeit Drugs," 20 August 2013. [Online]. Available: http://www.pbs.org/wgbh/nova/next/body/uncovering-counterfeit-medicines/. [Accessed 19 November 2013].

[15] S. Kannan, "BBC News: Counterfeit drugs targeted by technology in India," 11 October 2011. [Online]. Available: http://www.bbc.co.uk/news/business-15208595. [Accessed 19 November 2013].

[16] "GPHF homepage," [Online]. Available: http://www.gphf.org/web/en/minilab/hintergrund_arzneimittelfaelschungen.htm. [Accessed 29 October 2013].

[17] K. Monson and A. Schoenstadt, "MedTV homepage - Lipitor Recall," 6 January 2009. [Online]. Available: http://cholesterol.emedtv.com/lipitor/lipitor-recall.html. [Accessed 29 October 2013].

[18] H. G. Schweim, "DAZ Online Arzneimittelfälschungen global und in," 11 August 2005. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/daz-ausgabe/artikel/articlesingle/2005/32/14414.html. [Accessed 29 October 2013].

[19] H. Korzilius, "Deutsches Ärzteblatt Gefälschte HIV-Medikamente: Schäbiges Geschäft," 4 March 2011. [Online]. Available: http://www.aerzteblatt.de/archiv/81141. [Accessed 29 October 2013].

[20] K. Bachmann, "Vorsicht, Fälschung!," *GEO,* no. 11, pp. 56-64, 2012.

[21] "FDA sends letters to 19 medical practices about counterfeit product and other unapproved cancer medicines," 14 February 2012. [Online]. Available: http://www.fda.gov/drugs/drugsafety/ucm291960.htm. [Accessed 21 November 2013].

[22] "SafeMedicines.org - Counterfeit Cancer Drugs Are A Big Money Maker for Fake Drug Criminals," [Online]. Available: http://www.safemedicines.org/counterfeit-cancer-drugs-are-a-big-money-maker-for-fake-drug-criminals.html. [Accessed 6 January 2015].

[23] "PSI - Counterfeits - Therapeutic Categories," [Online]. Available: http://www.psi-inc.org/therapeuticCategories.cfm. [Accessed 31 January 2015].

[24] ABDA, Pfizer and Bayer, "03 Warning Fake – What exactly is in counterfeit medicines? EN,"

2013. [Online]. Available: http://vimeo.com/74366006. [Accessed 19 November 2013].

[25] World Health Organization, "General information on counterfeit medicines: Factors encouraging counterfeiting of drugs," 2014. [Online]. Available: http://www.who.int/medicines/services/counterfeit/overview/en/index1.html. [Accessed 29 October 2013].

[26] United Nations Office on Drugs and Crime, "New UNODC campaign highlights transnational organized crime as a US$870 billion a year business," 16 July 2012. [Online]. Available: http://www.unodc.org/unodc/en/frontpage/2012/July/new-unodc-campaign-highlights-transnational-organized-crime-as-an-us-870-billion-a-year-business.html. [Accessed 9 March 2014].

[27] ABDA, "Factsheet Counterfeit Medicines," October 2013. [Online]. Available: http://www.abda.de/fileadmin/assets/Faktenblaetter/Faktenblatt_Arzneimittelfaelschungen_Oktober_2013_final.pdf. [Accessed 20 November 2013].

[28] C. Jung and J. McCue, "Protecting Patients from Counterfeit and Other Substandard Drugs/Supply Chain Threats; FDA 2nd Annual Health Professional Organizations Conference," 4 October 2012. [Online]. Available: http://www.fda.gov/downloads/ForHealthProfessionals/UCM330640.pdf. [Accessed 20 November 2013].

[29] P. H. Group, "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," 12 July 2011. [Online]. Available: http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Reports/Health/Pew_Heparin_Final_HR.pdf. [Accessed 20 November 2013].

[30] European Commission, "Quality of medicines and Good Manufacturing Practices," 31 January 2015. [Online]. Available: http://ec.europa.eu/health/human-use/quality/index_en.htm. [Accessed 31 January 2015].

[31] European Alliance for Access to Safe Medicines, "Packaging Patient Protection - Recommendations for new legislation to combat counterfeit medicines," 2009. [Online]. Available: http://www.eaasm.eu/cache/downloads/5dhbepyu124ggkoc4kgsw48os/PPP%20to%20print%20FINAL.pdf. [Accessed 28 November 2013].

[32] C. J. Shaw, "Combating Pharmaceutical Counterfeiting; Second Global Congress for Combating Counterfeiting, Lyon, France," 14-15 November 2005. [Online]. Available: http://www.ccapcongress.net/archives/Lyon/files/CJShaw.pdf. [Accessed 20 November 2013].

[33] "WTO Fact sheet: TRIPS and PHarmaceutical Patents," September 2006. [Online]. Available: http://www.wto.org/english/tratop_e/trips_e/factsheet_pharm02_e.htm. [Accessed 25

November 2013].

[34] P. Kanavos, J. Costa-i-Font, S. Merkur and M. Gemmill, "The Economic Impact of Pharmaceutical Parallel Trade in European Union Member States: A Stakeholder Analysis," January 2004. [Online]. Available: http://archives.who.int/prioritymeds/report/append/829paper.pdf. [Accessed 21 November 2013].

[35] "WHO - Access to medicines," [Online]. Available: http://www.who.int/trade/glossary/story002/en/index.html. [Accessed 25 November 2013].

[36] "WHO - Trade-related aspects of intellectual property rights (TRIPS)," [Online]. Available: http://www.who.int/trade/glossary/story091/en/index.html. [Accessed 25 November 2013].

[37] BfArM, "Parallelimport von Arzneimitteln," 2013. [Online]. Available: http://www.bfarm.de/DE/Arzneimittel/zul/zulassungsverfahren/parimp/_node.html. [Accessed 15 January 2015].

[38] "PZ online Bedenken bei Parallel- und Importware?," 2011. [Online]. Available: http://www.pharmazeutische-zeitung.de/index.php?id=39580. [Accessed 15 January 2015].

[39] European Medicines Agency, "Parallel distribution," 2015. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000067.jsp&mid=WC0b01ac0580024594. [Accessed 15 January 2015].

[40] EFPIA Position Paper, "International Exaustion of Trade Mark Rights - Protecting Patients - The Importance of Trade Mark Rights for Medicines," April 2001. [Online]. Available: http://efpia.org/Objects/1/Files/protecpatients.pdf. [Accessed 25 November 2013].

[41] K. Sucker-Sket, "DAZ Online Spektrum Gefälschte Import-Ware landet vor allem in Deutschland," 28 August 2014. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/spektrum/news/2014/08/28/gefaelschte-import-ware-landet-vor-allem-in-deutschland/13680.html. [Accessed 15 January 2015].

[42] Italian Medicines Agency, "Rapid Alert - August 8, 2014," 11 August 2014. [Online]. Available: http://www.agenziafarmaco.gov.it/en/content/rapid-alert-august-8-2014. [Accessed 15 January 2015].

[43] J. Pradel, "apotheke adhoc BMG lässt Parallelhandel überprüfen," 2 October 2014. [Online]. Available: http://www.apotheke-adhoc.de/nachrichten/nachricht-detail/arzneimittelfaelschungen-bundesgesundheitsministerium-eu-kommission-soll-rechtsrahmen-fuer-parallelh/. [Accessed 15 January 2015].

[44] The National Center on Addiction and Substance Abuse at Colombia University , "You've Got Drugs! V: Prescription Drug Pushers on the Internet," July 2008. [Online]. Available: http://www.casacolumbia.org/articlefiles/531-

2008%20You%27ve%20Got%20Drugs%20V.pdf. [Accessed 29 October 2013].

[45] OpSec Security, Inc., "Risk Assessment: Counterfeit Pharmaceuticals in the Online Marketplace," 15 November 2010. [Online]. Available: http://info.opsecsecurity.com/assessing-the-risk-of-counterfeit-pharmaceuticals-in-the-online-marketplace. [Accessed 25 November 2013].

[46] European Alliance for Access to Safe Medicines, "The Counterfeiting Superhighway," June 2008. [Online]. Available: http://www.eaasm.eu/cache/downloads/dqqt3sge9hwssgcgcos440g40/455_EAASM_counterfeiting%20report_020608%281%29.pdf. [Accessed 29 November 2013].

[47] Pfizer, "Cracking Counterfeit Europe," February 2010. [Online]. Available: http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=6&ved=0CF4QFjAF&url=http%3A%2F%2Fwww.ots.at%2Fanhang%2FOTS_20100218_OTS0066.pdf&ei=gGyTUparI8f2ygOAr4Bo&usg=AFQjCNGZ642DdFk0dPLC0Z3MeLn0C2KMxQ&bvm=bv.56988011,d.bGQ. [Accessed 25 November 2013].

[48] "Gesundheitsrisiko Arzneimittelfälschungen - Zwischen Kavaliersdelikt und Lebensgefahr," *Deutsche Apotheker Zeitung,* no. 11, pp. 30-32, 2011.

[49] S. Schersch, "Arzneimittelfälschungen - Aufklärung als höchstes Ziel," *Pharmazeutische Zeitung,* no. 9, pp. 10-11, 2010.

[50] H. G. Schweim and J. Fuchs, "Arzneimittelfälschungen und Scheinsicherheit - Wie effektiv ist das Sicherheitslogo für Versandapotheken?," *Deutsche Apotheker Zeitung,* no. 10, pp. 52-55, 2011.

[51] H. G. Schweim, "DAZ Online Arzneimittel im Internet-Versandhandel - sicher!?," 2007, 27. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/daz-ausgabe/artikel/articlesingle/2007/27/24083.html. [Accessed 30 October 2013].

[52] "Der Kardinalfehler," *Deutsche Apotheker Zeitung,* no. 27, p. 3, 2007.

[53] "German Medicinal Products Act; Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG)," as announced on 12 December 2005 (Federal Law Gazette I p. 3394); last amended on 10 October 2013 (Federal Law Gazette I p. 3813). [Online]. Available: http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf. [Accessed 26 November 2013].

[54] "German Pharmacies Act; Gesetz über das Apothekenwesen (Apothekengesetz - ApoG)," as announced on 15 October 1980 (Federal Law Gazette I p. 1993); last ammended on 15 July 2013. [Online]. Available: http://www.gesetze-im-internet.de/bundesrecht/apog/gesamt.pdf. [Accessed 26 November 2013].

[55] "DIMDI - Licensed Online Pharmacies," 23 September 2013. [Online]. Available: http://www.dimdi.de/static/de/amg/var/index.htm. [Accessed 27 November 2013].

[56] National Association of Boards of Pharmacy, "VIPPS information and verification site," 13 January 2011. [Online]. Available: http://vipps.nabp.net/. [Accessed 27 November 2013].

[57] "NABP - VIPPS," 2013. [Online]. Available: http://www.nabp.net/programs/accreditation/vipps. [Accessed 27 November 2013].

[58] European Commission, "Concept paper for public consultation on the implementing act on a common logo for legally-operating online pharmacies/retailers offering medicinal products for human use for sale at a distance to the public," 17 October 2012. [Online]. Available: http://ec.europa.eu/health/files/falsified_medicines/commonlogo_consult.pdf. [Accessed 5 January 2015].

[59] European Commission, "EU logo for online sale of medicines," 27 June 2014. [Online]. Available: http://ec.europa.eu/health/human-use/eu-logo/index_en.htm. [Accessed 6 January 2015].

[60] European Commission, "Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014," (OJ L 184, 25.06.2014, p. 5). [Online]. Available: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_184_R_0004&from=EN. [Accessed 6 January 2015].

[61] European Alliance for Access to Safe Medicines, "Counterfeiting the Counterfeiter," 2012. [Online]. Available: http://www.eaasm.eu/cache/downloads/av3r9l87z4wg4ocs8w84gogs0/CtC%20report%202012.pdf. [Accessed 29 November 2013].

[62] "IMPACT homepage," [Online]. Available: http://www.who.int/impact/about/en/. [Accessed 30 October 2013].

[63] "INTERPOL - Operation Pangea," 2015. [Online]. Available: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea. [Accessed 2 January 2015].

[64] K. Sucker-Sket, "DAZ Online Spektrum Operation Pangea II - Weltweite Razzia gegen illegale Internet-"Apotheken"," 20 November 2009. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/spektrum/news/2009/11/20/weltweite-razzia-gegen-illegale-internet-apotheken.html. [Accessed 30 October 2013].

[65] K. Sucker-Sket, "DAZ Online Spektrum Operation Pangea III - Aktion gegen illegale Internet-Anbieter von Arzneimitteln," 14 October 2010. [Online]. Available: http://www.deutsche-apotheker-zeitung.de/spektrum/news/2010/10/14/aktion-gegen-illegale-internet-anbieter-von-arzneimitteln.html. [Accessed 30 October 2013].

[66] European Federation of Pharmaceutical Industries and Associations, "INTERPOL and pharmaceutical industry join forces in new global initiative to protect patients from

counterfeit medicines," 12 March 2013. [Online]. Available: http://www.efpia.eu/mediaroom/13/85/INTERPOL-and-pharmaceutical-industry-join-forces-in-new-global-initiative-to-protect-patients-from-counterfeit-medicines. [Accessed 27 November 2013].

[67] INTERPOL, "Pharmaceutical Industry Initiative to Combat Crime," 2015. [Online]. Available: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Pharmaceutical-Industry-Initiative-to-Combat-Crime. [Accessed 8 January 2015].

[68] European Federation of Pharmaceutical Industries and Associations, "Stamping out Falsified Medicines," 2015. [Online]. Available: http://www.efpia.eu/topics/industry-economy/falsified-medicines. [Accessed 8 January 2015].

[69] "Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011," (OJ L 174, 1.7.2011, p. 74). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf. [Accessed 31 January 2015].

[70] European Federation of Pharmaceutical Industries and Associations, "Progress towards a European Medicines Verification System: the European Stakeholder Model and securPharm link-up," 4 March 2014. [Online]. Available: http://www.efpia.eu/mediaroom/147/21/Progress-towards-a-European-Medicines-Verification-System-the-European-Stakeholder-Model-and-securPharm-link-up. [Accessed 8 January 2015].

[71] "securPharm – the German shield against counterfeit medicines," 2015. [Online]. Available: http://www.securpharm.de/international-sites/english.html. [Accessed 8 January 2015].

[72] "securPharm - Mitglieder der Initiative," 2015. [Online]. Available: http://www.securpharm.de/securpharm-initiative/mitglieder.html. [Accessed 13 January 2015].

[73] "securPharm - Status Report 1. 2014," 18 March 2014. [Online]. Available: http://www.securpharm.de/fileadmin/pdf/englisch/Statusbericht_Druckbogen_engl._1.2014_final.pdf. [Accessed 13 January 2015].

[74] "European Commission - Pharmaceutical package," 2013. [Online]. Available: http://ec.europa.eu/health/human-use/package_en.htm. [Accessed 29 November 2013].

[75] European Medicines Agency, "EudraVigilance homepage," 9 April 2013. [Online]. Available: https://eudravigilance.ema.europa.eu/human/index.asp. [Accessed 3 December 2013].

[76] European Medicines Agency, "EudraVigilance - Background," 2013. [Online]. Available: http://www.adrreports.eu/EN/background.html. [Accessed 3 December 2013].

[77] R. Eicher, "European Compliance Acadamy - GMP News," 16 February 2011. [Online]. Available: http://www.gmp-compliance.org/eca_news_2439_6748,6737,6762,6892.html.

[Accessed 31 October 2013].

[78] European Medicines Agency, "EudraGDMP database," 2013. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000159.jsp. [Accessed 3 December 2013].

[79] GMP Navigator, "EU-Kommission veröffentlicht erweitertes Frage-Antwort Dokument zur Written Confirmation," 4 February 2013. [Online]. Available: http://www.gmp-navigator.com/nav_news_3547_7675,7817.html. [Accessed 3 January 2015].

[80] European Commission, "Template for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC Version 2.0," 28 January 2013. [Online]. Available: http://ec.europa.eu/health/files/gmp/2013_01_28_template.pdf. [Accessed 3 January 2015].

[81] "Commission Implementing Decision of 23 January 2013," (OJ L 21, 24.01.2013, p. 36). [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-1/dec_2013_51/dec_2013_51_en.pdf. [Accessed 7 January 2015].

[82] E. Podpetschnig-Fopp, "Wirkstoffimport aus Drittländern - Notfallplan der MHRA zur Sicherstellung der Arzneimittelversorgung," Pharm. Ind. 75, no. 7, pp. 1188-1190, 2013. [Online]. Available: http://www.ecv.de/download/download/Zeitschriften//pharmind/volltext/PI-2013-07-1188_PI7507_0579_podpetschnig-fopp_umbr2-web.pdf. [Accessed 16 January 2015].

[83] G. Macdonald, "EC Wants Info on API Import Law-Related Shortages," 1 July 2013. [Online]. Available: http://www.in-pharmatechnologist.com/Regulatory-Safety/EC-Wants-Info-on-API-Import-Law-Related-Shortages. [Accessed 16 January 2015].

[84] European Commission, "Concept paper for public consultation on the delegated act on the detailed rules for the unique identifier for medicinal products for human use and its verification," 18 November 2011. [Online]. Available: http://ec.europa.eu/health/files/counterf_par_trade/safety_2011-11.pdf. [Accessed 7 January 2015].

[85] G. Jones, "The Pharmaceutical Journal - The Falsified Medicines Directive: time to get is right," 16 October 2014. [Online]. Available: http://www.pharmaceutical-journal.com/opinion/comment/the-falsified-medicines-directive-time-to-get-it-right/20066783.article. [Accessed 7 January 2015].

[86] "European Stakeholder Model," 2012. [Online]. Available: http://www.esm-system.eu/about-us/what-we-do.html. [Accessed 3 December 2013].

[87] H. Rahalkar, "Historical Overview of Pharmaceutical Industry and Drug Regulatory," 29 September 2012. [Online]. Available: http://www.omicsgroup.org/journals/historical-

overview-of-pharmaceutical-industry-and-drug-regulatory-affairs-2167-7689.S11-002.pdf. [Accessed 11 November 2013].

[88] "Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products," (OJ L 22, 9.2.1965, p. 369). [Online]. Available: http://www.echamp.eu/fileadmin/user_upload/Regulation/Directive_65-65-EEC__-__Consolidated_Version.pdf. [Accessed 11 November 2013].

[89] "Volume 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use," September 2008. [Online]. Available: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. [Accessed 30 October 2013].

[90] J. H. Kim and A. R. Scialli, "Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease (Oxford Journals; Toxicological Sciences Volume 122, Issue 1, pp. 1-6)," 2 April 2011. [Online]. Available: http://toxsci.oxfordjournals.org/content/122/1/1.full. [Accessed 22 November 2013].

[91] "WHO-UMC homepage," [Online]. Available: http://www.who-umc.org/DynPage.aspx. [Accessed 30 October 2013].

[92] "WHO - Pharmacovigilance," [Online]. Available: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. [Accessed 30 October 2013].

[93] European Medicines Agency, "ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)," January 2013. [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500136402.pdf. [Accessed 27 January 2014].

[94] European Medicines Agency, "2010 Pharmacovigilance Legislation," 2013. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&mid=WC0b01ac058033e8ad. [Accessed 3 December 2013].

[95] European Medicines Agency, "Good Pharmacovigilance Practices," 2014. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp. [Accessed 31 January 2015].

[96] European Commission, "The EU Phamacovigilance System," 2013. [Online]. Available: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm. [Accessed 3 December 2013].

[97] International Medical Products Anti-Counterfeiting Taskforce, "Anti-counterfeit Technologies for the Protection of Medicines," [Online]. Available:

http://www.who.int/impact/events/IMPACT-ACTechnologiesv3LIS.pdf. [Accessed 9 January 2014].

[98] TGA - Therapeutic Goods Administration (Australia), "Code of Practice for Tamper-Evident Packaging (TEP) of Therapeutic Goods," June 2003. [Online]. Available: http://www.tga.gov.au/pdf/packaging-tamper-evident-cop.pdf. [Accessed 10 January 2014].

[99] US Food and Drug Administration, "Radio Frequency Identification (RFID)," 13 August 2013. [Online]. Available: http://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/ElectromagneticCompatibilityEMC/ucm116647.htm. [Accessed 13 January 2014].

[100] A. M. Thayer, "Chemical & Engineering News "Instrumentation Firms Develop Portable Technology To Detect Counterfeit Drugs" Volume 90, Issue 33, pp.11-15," 13 August 2012. [Online]. Available: http://cen.acs.org/articles/90/i33/Instrumentation-Firms-Develop-Portable-Technology.html. [Accessed 14 January 2014].

[101] World Health Organization, Uppsala Monitoring Center, "Glossary of terms used in Pharmacovigilance," January 2013. [Online]. Available: http://www.who-umc.org/graphics/27400.pdf. [Accessed 6 February 2014].

[102] International Conference on Harmonization, "Guidance for Industry E2C Clinical Data Safety Management: Periodic Safety Update Reports for Marketed Drugs," November 1996. [Online]. Available: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073102.pdf. [Accessed 12 February 2014].

[103] National Center for Biomedical Ontology, "Medical Dictionary for Regulatory Activities - Lack of efficacy," [Online]. Available: http://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMDR%2F20000032. [Accessed 6 February 2014].

[104] International Conference on Harmonization, "MedDRA Term Selection: Points to Consider," 1 October 2013. [Online]. Available: http://www.meddra.org/sites/default/files/guidance/file/9491-1610_termselptc_r4.6_sep2013.pdf. [Accessed 24 February 2014].

[105] "ICH MedDRA homepage - basics," [Online]. Available: http://www.meddra.org/how-to-use/support-documentation/english. [Accessed 05 August 2013].

[106] "ICH MedDRA homepage - structure," [Online]. Available: http://www.meddra.org/how-to-use/basics/hierarchy. [Accessed 21 August 2013].

[107] G. Buttler and K. Oeckler, "Zusammenhang von Rangmerkmalen," in *Einführung in die Statistik*, Rowohlt-Verlag GmbH, 2010, pp. 224-233.

[108] D. Rumsey, "Korrelationen mit dem Spearman'schen Rang bestimmen," in *Statistik II für Dummies*, Weinheim, WILEY-VCH Verlag GmbH & Co. KGaA, 2013, pp. 327-330.

[109] "Spearman's correlation," [Online]. Available: http://www.statstutor.ac.uk/resources/uploaded/spearmans.pdf. [Accessed 30 January 2014].

[110] Barcelona Field Studies Center, "Spearman's Rank Correlation Coefficient," 12 May 2013. [Online]. Available: http://geographyfieldwork.com/SpearmansRank.htm. [Accessed 30 January 2014].

[111] Barcelona Field Studies Center, "Significance of Spearman's Rank Correlation Coefficient," 11 May 2013. [Online]. Available: http://geographyfieldwork.com/SpearmansRankSignificance.htm. [Accessed 30 January 2014].

[112] Bayer AG, "Nexavar.com," October 2011. [Online]. Available: http://www.nexavar-international.com/home/index.php. [Accessed 19 February 2014].

[113] Bayer AG, "Nexavar zur Behandlung von differenziertem Schilddrüsenkrebs in den USA zugelassen," February 2014. [Online]. Available: http://www.nexavar.de/de/fachkreise/rcc/aktuelles/news/news.php/15303. [Accessed 19 February 2014].

[114] Bayer AG, "Bayer erhält EU-Zulassung für Nexavar zur Behandlung des differenzierten Schilddrüsenkarzinoms," 30 May 2014. [Online]. Available: http://www.nexavar.de/de/fachkreise/rcc/aktuelles/news/news.php/15517. [Accessed 13 June 2014].

[115] Bayer AG, "Bayer erhält in Japan die Zulassung für Nexavar® (Sorafenib) zur Behandlung von differenzierten Schilddrüsenkarzinomen," 20 June 2014. [Online]. Available: http://www.nexavar.de/de/fachkreise/rcc/aktuelles/news/news.php/15543. [Accessed 4 July 2014].

[116] Bayer AG, "Nexavar — Demonstrated a Statistically Significant Advantage in Overall Survival (OS) vs Placebo in HCC," [Online]. Available: http://www.nexavar-international.com/home/hcp_nexavar_hcc/index.php. [Accessed 19 February 2014].

[117] Bayer AG, "Nexavar — A Multikinase Inhibitor Approved for the Treatment of Patients With Advanced RCC," [Online]. Available: http://www.nexavar-international.com/home/nexavar_for_advanced_rcc/index.php. [Accessed 19 February 2014].

[118] Bayer AG, "Nexavar Approved for Liver Cancer in China," 28 July 2008. [Online]. Available: http://pharma.bayer.com/scripts/pages/en/news_room/news_room/news_room64.php.

[Accessed 19 February 2014].

[119] A. Gaffney, "RF Regulatory Focus," 25 March 2013. [Online]. Available: http://www.raps.org/focus-online/news/news-article-view/article/3073/chinas-sfda-becomes-cfda-amidst-consolidation-of-power-and-new-leadership.aspx. [Accessed 26 August 2013].

[120] United Nations Economic Commission for Europe, "United Nations Code for Trade and Transport Locations (UN/LOCODE)," July 2013. [Online]. Available: http://www.unece.org/cefact/locode/service/location.html. [Accessed 3 January 2014].