# The new Falsified Medicines Directive 2011/62/EU and its requirements for stakeholders

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# 1. List of Abbreviations

| | |
|---|---|
| ADHD | Attention deficit hyperactivity disorder |
| Aefi | Comisión de Normas de Correcta Fabricación |
| AFSSAPS | French Agency of Sanitary Safety and Health Products |
| ABDA | German Federal Association of Pharmacist |
| API | Active pharmaceutical ingredients |
| ASCII | American Standard Code for Information Interchange |
| BAH | German Medicines Manufacturers Association |
| BGMA | British Generic Manufacturers Association |
| BMA | British Medical Association |
| BMG | Federal Ministry of Health |
| BPI | German Pharmaceutical Industry Association |
| BRIDGE | Building Radio frequency IDentification for the Global Environment |
| CoA | Certificate of Authenticity |
| CoS | Certificate of Suitability |
| CEP | Certificate of suitability of Monographs of the European Pharmacopoeia |
| DG ENTR | Directorate-General for Enterprise and Industry |
| DIN | Deutsches Institut für Normung |
| DIMDI | German Institute of Medical Documentation and Information |
| DMF | Drug Master File |
| EAASM | European Alliance for Access to Safe Medicine |
| EAEPC | European Licensed Parallel Distribution Industry |
| EDI | Electronic receipt notice |
| EDQM | European Directorate for the Quality of Medicines and Healthcare |
| EEA | European Economic Area |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EGA | European Generic medicines Association |
| EIPG | European Industrial Pharmacists Group |
| EMA | European Medicines Agency |
| EMVO | European Medicines Verification Organisation |
| EMVS | European Medicines Verification System |
| ESM | European Stakeholder Model |
| EU | European Union |

| | |
|---|---|
| EUCOPE | European Confederation of Pharmaceutical Entrepreneurs |
| FDA | Food and Drug Administration |
| FP | Finished Medicinal Product |
| GDP | Good Distribution Practice |
| GIRP | The European Association of Pharmaceutical Full-line Wholesalers |
| GMP | Good Manufacturing Practice |
| GRG | Gesundheits-Reformgesetz |
| GS1 | Global Standards One |
| GTIN | Global Trade Item Number |
| ICH | International Conference on Harmonisation |
| IDRAC | Single-source global regulatory database from Thomson Reuters |
| IFA | Informationsstelle für Arzneimittelspezialitäten GmbH |
| IPR | Intellectual property rights |
| ISO | International Organisation for Standardization |
| IT | Information Technology |
| ITS | Turkish “Pharmaceutical Track and Trace System” |
| MAA | Marketing Authorisation Application |
| MAH | Marketing authorization holder |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MP | Medicinal Product |
| NHS | National Health Service |
| NTIN | National Trade Item Number |
| OTC | Over-the-counter |
| PGEU | The Pharmaceutical Group of the European Union |
| PHAGRO | Association of Pharmaceutical Wholesalers |
| Pharmexil | Pharmaceuticals Export Promotion Council of India |
| PPN | Pharmacy Product Number |
| PRA-Code | Product Registration Agency code |
| PSI | Pharmaceutical Security Institute |
| PZN | Pharmazentralnummer |
| QP | Qualified Person |
| R & D | Research and Development |
| RFID | Radio Frequency Identication |

| | |
|---|---|
| RX | Prescription only medicine |
| SF | Safety Features |
| SGB | Sozialgesetzbuch |
| SGK | Social Security Institution |
| TFEU | Treaty of the functioning of the EU |
| UMI | Unique medicine identifier |
| Vfa | Association of Research-Based Pharmaceutical Companies |
| WHO | World Health Organization |
| WuV | Werbe- und Vertriebsgesellschaft Deutscher Apotheker |

## 2. Introduction

Counterfeiting medicine pose an ever-increasing threat to public health. Although counterfeiters are especially attracted to those medicines which are used in high numbers and of high prices, the available data's indicate that all types of medicinal products have been targeted. The range of fake products includes, among others lifestyle medicine such as those for erectile dysfunction, hair loss or weight management but also anticancer medicine, antibiotics, cholesterol-lowering drugs, hormones, steroids, medicine for hypertension or generic version of pain killers and antihistamines.

The World Health Organization (WHO) defines a counterfeit drug [1] as "*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*."

The Pharmaceutical Security Institute (PSI) has published the figures for the year 2011 [2], in which 1986 incidents (counterfeit, illegally diverted drugs and pharmaceutical thefts) has been reported, containing the largest number of incidents in the genito-urinary, anti-infective and cardiovascular therapeutic categories. It is mentioned that the figures might be even higher as many of reports in the public media showed a lack of adequate details and could not be included in the analysis. Linked to pharmaceutical crime the top two regions were Asia (954 cases) and Latin America (381 cases) followed by Europe (351 cases), Eurasia (257 cases), North America (237 cases), Near East (128 cases) and Africa (64 cases). The PSI pointed out that it is important to highlight that all these figures should not be interpreted in such a way that regions with high incidents are those with weak enforcement and inspection programs and those with low incidents are unaffected by or at a lower risk of pharmaceutical crime. In fact, countries with high incidents of pharmaceutical crimes are highly efficient in identifying such cases through law enforcement activity and inspections by drug regulatory agencies whereas in certain regions of the world, counterfeit medicine remain undetected due to inadequate regulatory structures, lack of funding or competing law enforcement priorities.

Counterfeiting medicinal products is a very lucrative business with higher profit margins than addictive drugs. In many countries counterfeiters are facing only low risks to be punished or governments are unwilling to recognize the existence of the problem. Other factors that play a significant role are the ineffective cooperation and exchange of information between the stakeholders like health authorities, police, industry and trade and also the lack of awareness among consumers and health professionals.

The UK`s Medicine and Healthcare products Regulatory Agency (MHRA) belongs to one of the most active competent authorities in Europe in the supervision of the supply chain security. They have published in November 2007 the first MHRA "*Anti-Counterfeiting Strategy 2007-2010*" [3] as a response to serious infiltration of falsified medicinal products in the UK supply chain which were then reduced as a result of these implementation. As the UK pharmaceutical market is still attractive for counterfeiters, the second MHRA "*Anti-Counterfeiting Strategy 2012-2015*" [4] was launched in May 2012. On the MHRA`s website [5] all cases of counterfeit medicines that have been discovered so far in (table 1) or present a risk to (table 2) the licensed UK supply chain are published.

| Year | Product | Location of Discovery |
|---|---|---|
| **May 2009** | Seretide 250 Evohaler 8 ml pressurised inhalers | UK supply chain |
| **July 2007** | Sensodyne Original | UK supply chain |
| | Sensodyne Mint | UK supply chain |
| **June 2007** | Plavix | UK supply chain |
| | Casodex | UK supply chain |
| **May 2007** | Plavix (3x Batch) | UK supply chain |
| | Zyprexa (2x Batch) | UK supply chain |
| **August 2006** | Lipitor | UK supply chain |
| **July 2006** | Lipitor | UK supply chain |
| | Propecia | UK supply chain |
| **February 2006** | Viagra | Illicit supply chain |
| **July 2005** | Lipitor | UK supply chain |
| **September 2004** | Reductil | UK supply chain |
| **August 2004** | Cialis (2 Batch) | UK supply chain |

**Table 1:** Falsified medicinal products discovered in the licensed UK supply chain (*Source:* MHRA website [5]).

The table 1 shows that there was only one recall of a falsified medicinal product that has been discovered in the UK supply chain after the launch of the strategy till now, compared to other known falsified medicinal products as presented in table 2.

| Year | Product | Location of Discovery | Legitimate batch number |
|---|---|---|---|
| **May 2012** | Panadol Extra | Illicit supply chain | Yes, Middle East market |
| | Panadol Cold and Flu | Illicit supply chain | Yes, Middle East market |
| **February 2012** | Altuzan | US supply chain | Yes, Turkish market |
| **December 2011** | Viagra | Illicit supply chain | |
| | Viagra | | Yes, Turkish market |
| | Avastin Vial | UK supply chain, not beyond wholesale level | No |
| | Avastin Vial | | Yes, North Africa and Middle East |
| **November 2011** | Truvada | UK supply chain, not beyond wholesale level | Yes, Turkish market |
| | Truvada | UK supply chain, not beyond wholesale level | Yes, Turkish market |
| | Viread | UK supply chain, not beyond wholesale level | Yes, Turkish market |
| | Viread | UK supply chain, not beyond wholesale level | Yes, Turkish, Australia/New Zealand, and Belgium/Luxembourg markets |
| **September 2011** | Viagra | Illicit supply chain | Yes, Hong Kong market |
| **June 2011** | Viagra | Illicit supply chain | No |
| **May 2011** | Viagra | Illicit supply chain | No |
| | Viagra | Illicit supply chain | No |
| | Viagra | Illicit supply chain | Yes, Kazakhstan market |
| | Selsun 2.5% | Illicit supply chain | Yes, UK market |
| **April 2011** | Cialis | Illicit supply chain | Yes, Israeli market |
| **March 2011** | Viagra | Illicit supply chain | Yes |
| | Deca-Durabolin | Illicit supply chain | No |
| | Norditropin SimpleXx | Illicit supply chain | No |
| **February 2011** | Prograf (2 Batch) | Irish supply chain | No |
| | Prograf | Irish supply chain | Yes, Malaysian market |
| | Viagra | Illicit supply chain | No |
| | Plavix | Lebanese supply chain | Yes, Lebanese market |
| **March 2007** | Plavix (2 Batch) | UK supply chain, not beyond wholesale level | |
| **November 2006** | Plavix | Illicit supply chain | |
| | Co-Diovan 160 | Illicit supply chain | |
| | Hyzaar Forte | Illicit supply chain | |

| Year | Product | Location of Discovery | Legitimate batch number |
|---|---|---|---|
| **February 2006** | Viagra | Illicit supply chain | NO |

**Table 2:** Other falsified medicinal products that present a risk to the UK licensed supply chain (*Source:* MHRA website [5])

The following table 3 provides a classification of medicine counterfeiting practices which reportedly occurred in Europe [6], [7]:

| **MEDICINE COUNTERFEITING PRACTICES: Finished medicinal products** |
|---|
| ▪ ***Identical copy*** - identical formulation with packaging and labelling that is hard to differentiate from the original |
| ▪ ***Pure counterfeit*** - altered/replaced ingredients with similar packaging (but either no/different/wrong dose API or excipient) |
| ▪ ***Hybrid counterfeit*** - re-use of components/refilling (e.g. genuine containers [ampoules, bottles, vials, syringes] and packaging with substitute or no API) |
| ▪ ***Illegal relabelling/repackaging*** - genuine formulated product falsely repackaged/relabelled as being from the original manufacturer and intended for the same or diverted to a different market than originally intended by manufacturer (also includes use of fake pricing labels and products claiming wrongly to be an original product e.g. use of well-known name or trademark) |
| ▪ ***Diversion and illegal trade*** - of genuine medicinal products with genuine packaging and labelling (whether or not through the internet) |
| ▪ ***Unpackaged medicinal products*** - e.g. wholesale/retail of medicinal products without the primary authorised packaging |
| ▪ ***Placing a non-authorised medicinal product on the market*** - exploitation of regulatory weaknesses concerning regulation of personalised medicine trade within the EC borders |
| ▪ ***False documentation*** - e.g. granting a Certificate of Suitability (CoS or CEP)* by regulatory authorities without the given company being audited, false CEP, incorrect status on import documentation |
| ▪ ***False MAA*** - entire marketing applications is sold and used; their contents do not have any relationship with the actual operations involved in the manufacture of the API or dosage form |
| ▪ ***Waste/expired product re-entering the market*** - includes repackaging and relabelling of expired products |
| **MEDICINE COUNTERFEITING PRACTICES: Active pharmaceutical ingredients and excipients** |
| ▪ ***API procurement from uncontrolled/non-GMP origin*** - done by some authorised FP manufacturers because uncontrolled API source is cheaper |
| ▪ ***Illegal API relabelling/repackaging*** - unauthorised API material may also be shipped in containers labelled with the name of a different API |
| ▪ ***'Ghost API manufacturing plant'*** - API (possibly not produced via the registered manufacturing process) not manufactured by the 'registered producer' is sold to FP MAH (who may be unaware of this fact, as API label mentions only the authorised manufacturer; a broker/trader may play a crucial role in this practice) |
| ▪ ***'Ghost API supplier'*** - MAH purchases API willingly and knowingly from a different manufacturer than that specified in the MA (in this case the manufacturing process will normally differ from that described and authorised in the MA) |
| ▪ ***'Paper curtain'*** - API manufacture performed through different process than that specified in the MA (a double documentation system may be used at the manufacturing site: one hidden set containing the true data and another set containing faked data that comply with authority requirements and regulations; such documentation systems may even be in place at a site where the API is not manufactured at all) |

| |
|---|
| ▪ ***'Authorised facades'*** - manufacturer/trader with approved CEP and DMF supplies API material from a large number of unauthorised manufacturers (all labelling mentions only the authorised manufacturer. This set up is believed to be widespread regarding API material imported from China and possibly also India. In addition forged CoA and other forged documents will also be used in such situations) |
| ▪ ***Illicit intermediate production*** - unauthorised API materials from obscure sources are blended with the registered API material |

**Table 3:** Overview about medicine counterfeiting practices (Source: [6], [7]).

The EU Customs detained in 2011 [8] almost 115 million products (compared to 103 million in 2010 [9]) suspected of violating intellectual property rights (IPR). Medicines were on the top of the categories of articles stopped by the EU customs in 2011 with 24%. It is reported that the most popular counterfeited medicines are life-style drugs but also medicines such as pain killers, anti-anxieties, antidepressants or antibiotics were found. Overall in 2011, China was the main source from where medicinal products, suspected of infringing an IPR, entered the EU (68.20%) followed by India (28.22%) and Hong Kong (1.5%). The increase in the number of detained postal packages continued in 2011 (from 1035443 articles in 2010 consisting of nearly 69% of medicine) to 1911079 articles with 36.5% of the detected articles concerning medicines in 2011. Table 4 presents the number of detained cases/articles from the years 2010/2011, which belongs to the category “medicine”.

| Year | Total number of registered cases | Number of registered cases belonging to the category “medicine and other products (condome)” | % of total | Total number of detained articles | Number of detained articles belonging to the category “medicine and other products (condome)” | % of total |
|---|---|---|---|---|---|---|
| **2011** | 91254 | 2494 | **2,73%** | 114.772.812 | 27.460.538 | **23,93%** |
| **2010** | 79112 | 1812 | **2,29%** | 103.306.928 | 3.200.492 | **3,1%** |

**Table 4:** Overview about number of registered case, number of detained articles (*Source:* EU Customs report 2010 [9] and 2011 [8]).

According to the WHO [10] about 50% of medicine purchased over the internet from sites that conceal their physical address are counterfeit. In Germany, legitimate online pharmacies are permitted to operate after the implementation of the so-called “*Gesetz zur Modernisierung der gesetzlichen Krankenversicherung*” [11] in 2004. However, as consumers using the internet were not able to tell whether an online pharmacy has an official authorisation for mail order selling for Germany, the German

Institute of Medical Documentation and Information (DIMDI) [12] provides since 21st April 2009 the German Register of Mail Order Pharmacies on behalf of the Federal Ministry of Health (BMG). The register includes pharmacies with an official permission for mail order of medicine in Germany according to the German Drug Law. In addition it also contains mail order pharmacies from abroad if they have a mail order permission from Germany. According to the current country list of the BMG [13] it is permitted to ship medicine to Germany from Iceland, United Kingdom, Sweden (for prescription medicine only), the Czech Republic (for non-prescription medicine only) and the Netherlands (only if also an associated retail pharmacy exists). In addition a security logo can be found on all websites of those pharmacies who are included in this mail order register.

In November 2009 the research consultancy Nunwood [14] questioned for the pharmaceutical company Pfizer over 14,000 people online in 14 European countries including Germany. The "*Cracking Counterfeit Europe"* [15] research revealed a black market economy, in which every year estimated €10.5 billion will be generated by counterfeit medicines. Of those people surveyed one in five of these 14,000 people admitted to buy prescription-only medicines without a prescription from illicit sources, with Germany (38%) and Italy (37%) as the worst offenders.

Focussing on the Germany market, the European Alliance for Access to Safe Medicine (EAASM), a pan-European patient safety organisation, started in 2011 their campaign entitled "*Counterfeiting the Counterfeiter"* [16] to raise public awareness about online criminal activity and to protect and to inform patients. This was the second EAASM campaign after publishing the report "*The Counterfeiting Superhighway*" [17] in 2008. The new campaign demonstrated how easy a fake website can be set up and how many customers were attracted to such a website. The fake online pharmacy was promoted from 26th September to 27th November 2011 and offered a range of prescription medicine. At a point prior to the purchase a second screen appeared to deliver safety messages and consumers were redirected to a register of legitimate online or high street pharmacies via DIMDI in addition. The campaign's online pharmacy attracted over 180,000 unique visitors and if this website had operated over 12 months instead of the nine-week period, over one million visitors would have attracted with a revenues for the illegal traders of between

€12 and €35 million. Table 5 presents the statistics of the "*Counterfeiting the Counterfeiter*" campaign and highlights the importance of raising awareness of potential purchasers about the dangers of counterfeit medicine purchased on the internet.

| Number of unique visitors | Which website was visited | Importance to visitor |
|---|---|---|
| 182,602 | Landing pages | Size of the problem |
| 142,676. | Warning page | Delivery of key message |
| 16,378 | Extra warning information | Raising awareness |
| 12,227 | DIMDI website | Behaviour change where to buy safe medicine |

**Table 5:** Statistics of the EAASM campaign "*Counterfeiting the counterfeiter*" [16]**.**

In December 2011, the WHO performed a survey [18] in order to ascertain the regulations and current legal status of internet pharmacies in the Member States. The survey revealed that the majority of responding countries (66%) have no legislation in place to allow or prohibit internet pharmacy operations. In those countries having regulations in place, the internet pharmacy operations are more often forbidden than permitted (19% versus 7%) and in terms of prohibiting or permitting the online purchase of medicines from other countries, nearly 53% of countries within Europe have kind of policy in place.

The aim of this master thesis is to provide an overview about the measures required by the Falsified Medicine Directive 2011/62/EU with the main focus on the safety features for medicines at risk of counterfeiting including the presentation of the different verification systems that are currently in development by stakeholders in the EU.

## 3. Falsified Medicine Directive

As a measure for the increasing number of pharmaceutical crime incidents in the European Union every year, the Falsified Medicine Directive 2011/62/EU (hereinafter also called "the Directive") has been approved by the EU Council on 27 May 2011 and was published in the Official Journal of the European Union [19] on the 1 July 2011. The new Falsified Medicine Directive 2011/62/EU contain amendments to the *Directive 2001/83/EC* [20] and is divided into 6 Articles:

*Article 1*: describes the modification to Directive 2001/83/EC;

*Article 2:* defines the latest dates by which the modifications should be brought into force;

*Article 3:* deals with the report by the Commission to the European Parliament and to the Council on the effectiveness of these modifications;

*Article 4:* deals with the obligation of the Commission to study the technical options for the unique identifier of the safety features, modalities of verification of the authenticity and repositories systems;

*Article 5:* defines the date when the Directive shall enter into force;

*Article 6:* deals with to whom this Directive is addressed.

The EU Directive introduces safety and strengthened control measures across Europe to prevent the entry of falsified medicinal product into the legal supply chain and to reach patients. Such measurements include:

- *Obligatory safety features on the outer packaging of medicines to demonstrate that they are authentic (such as a serialization number);*
- *Obligatory logos, which must be placed on websites of legal online pharmacies with a link to official national registers;*
- *Obligations for manufacturing authorization holder to report any suspicion of falsified medicines;*
- *Strengthened requirements on the control and inspections procedures of active pharmaceutical ingredients (APIs);*
- *More stringent record-keeping requirements for wholesale distributors;*

The EU Directive will be implemented into national law by individual EU Member States by 2 January 2013 as transposition deadline. The global regulatory database *IDRAC*® from Thomson Reuters published in September 2012 a comparative table [21] providing information about the status of implementation of the EU Directive 2011/62/EU in each country of the European Economic Area (EEA). The following table 6 represent the current status in countries where some actions were already initiated:

| Country | Stage of Legislation | Comment | National Legislation available | Publication / Entry into force date |
|---|---|---|---|---|
| Belgium | Draft version | The publication date is planned by end of 2012. | ------- | ------- |
| Denmark | Final (partially) | By the Executive Order No. 828 only risk assessment from the Directive is implemented. | Executive Order No. 828 [22] | 2 Aug 2012 / 3 Aug 2013 |
| France | None | The implementation of the Directive is planned in the coming months according to "The Law 2011-2012: Strengthening of the Safety of | ------- | ------- |

| Country | Stage of Legislation | Comment | National Legislation available | Publication / Entry into force date |
|---|---|---|---|---|
| | | Medicinal Products and Health Products" [23]. | | |
| Germany | Draft | | Draft Law of 10 Feb 2012: Amending the Drug Law and other Provisions [24] | 15 Feb 2012 / NA |
| Italy | Draft | The draft law AS 3129 which delegates the implementation of Community Directives is currently under discussion at the Parliament. The decree of implementation of the Directive is not available yet. | ------- | ------- |
| Poland | Draft | | Draft Law Amending Pharmaceutical Law and Law on Narcotics [25] | 7 Aug 2012 / NA |
| Portugal | None | INFARMED has not published any guidance yet. The Circular Informative 263/CD [26] informing about the new rules for importation of active substances to the EU and information about the possibility of EC public consultation "Manufacturer of active substances" were published by Infarmed. | ------- | ------- |
| Spain | None | No final legislation available yet. Some information is available in AEMPS "Strategy Against Falsified Medicinal Products 2012-2015" [27]. | ------- | ------- |
| United Kingdom | None | Pre-consultation questionnaire [28]. | ------- | Jan 2012/NA |

**Table 6:** Overview about current status of implementation of EU Directive 2011/62/EU in EEA countries (*Source*: Thomson Reuters, single-source global regulatory database *IDRAC*® [21]).

However, there will be a longer transition period for certain processes. Article 2 of the Directive states that the date of application of provisions on the import of active substances from 3rd countries will be the 2nd of July 2013 whereas the obligatory logos for Internet pharmacies shall enter into force 12 months after the publication of the respective Implementation Act. For the introduction of the safety features there will be a 3-year transition period after publication of the Delegation Acts (6 years for those countries that already have product verification in place) once a final decision has been made on the technical options.

## 3.1 History and current status of the development of the Directive 2011/62/EU

**AUGUST 2012:**

Publication of the following documents:

- Concept paper "*Delegated act on the criteria to be considered and the verifications to be made when assessing the potential falsified character of medicinal products introduced in the union but not intended to be placed on the market*" for public consultation [29].
- The responses from the stakeholder on the concept paper concerning the "*Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use*" were published on the website from the EU Commission [30].

**JULY 2012:**

Publication of the following documents:

- "*Template for the written confirmation for active substances imported into the European Union for medicinal products for human use*" – final version [31].
- "*Importation of active substances for medicinal products for human use*" - question and answer document [32].
- "*New rules on importing active pharmaceutical ingredients into the EU*" - information leaflet [33].

**JUNE 2012:**

The responses from stakeholder on the concept paper on the detailed rules for a unique identifier for medicinal product for human use was launched on the website from the EU Commission [34].

**APRIL 2012:**

Publication of the "*Draft template for the written confirmation for active substances imported into the European Union for medicinal products for human use*" [35] for public consultation and an overview of a number of implementation measures [36] by the Commission.

**JANUARY 2012:**

The Commission released the concept paper "*Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use*" [37] for public consultation as the Directive 2011/62/EU places with Article 46b (1) an obligation on Member States to take measures "*to ensure that manufacturers of active substances on their territory comply with good manufacturing practice for active substances*".

**DECEMBER 2011:**

As the Directive 2011/62/EU is introducing EU wide rules for the importation of active substances, the Commission rolled out the concept paper "*Implementing act on the requirements for the assessment of the regulatory framework applicable to the manufacturing of active substances of medicinal products for human use*" [38] for public consultation.

**NOVEMBER 2011:**

The Concept paper "*Delegated act on the detailed rules for a unique identifier for medicinal products for human use, and its verification*" [39] was submitted for public consultation.

**JULY 2011:**

Publication of the new legislation on falsified medicine in the Official Journal of the European Union [19], which will be applicable on the 2nd of January 2013.

**FEBRUAY 2011:**

Adoption of the new legislation [40] for better protection of EU citizens from falsified medicine by the European Parliament.

**DECEMBER 2008:**

On 10th December, the "*Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source*" [41] and the final impact assessment report [42], presenting the results of a study to assess the economic, environmental and social impacts of the proposal were adapted by the Commission.

**NOVEMBER 2008:**

The report "*Policies to Combat Counterfeit Medicines – Contribution to Impact Assessment*" [43] was launched and included a contribution to an assessment of social, economic and environmental impacts on various policy options to address any possible shortcomings.

**JUNE 2008:**

The responses from stakeholder were made available for the public [44] and a summary of responses to the public consultation document on a legal proposal published [45].

**MARCH 2008:**

The Directorate-General for Enterprise and Industry (DG ENTR) launched a public consultation in preparation of a legal proposal to combat counterfeit medicines for human use [46].

## 3.2 Measures of the EU Commission

The EU Directive includes specific measures of the EU Commission in the form of Delegation Acts, Implementation Acts and guidelines. Table 7 is providing an overview of the specific implementation measures of the EU Commission [36].

| Type of Commission measure | Topic | Article in Directive 2001/83/EC | Target date for adoption/ publication |
|---|---|---|---|
| **Guidelines** | Principles of **good distribution practices for active substances** | 47 | 2013 |
| **Guideline** | Formalised risk assessment for verification of the appropriate **good manufacturing practice for excipients** | 47 | 2013 |
| **Guideline** | Specific provisions for **brokering** in the **guidelines** on good distribution practices | 85b | 2012 |
| **Guideline** | **Principles for inspections** | 111a | ----- |
| **Implementing act** | Design of the common logo for legally-operating online-websites, including the technical, electronic, cryptographic requirements | 85c (3*****) | 2013 |
| **Implementing act** | Implementing measure on the **requirements for the assessment of a third country in terms of API manufacturing** | 111b | 2013 |
| **Delegated act** | **Good manufacturing practice for active substances** | 47 | 2013 |
| **Delegated act** | **Criteria to be considered and verifications to be made** when assessing the potential falsified character of **medicinal products introduced into the EU** but not intended to be placed on the | 52b | 2013 |

| Type of Commission measure | Topic | Article in Directive 2001/83/EC | Target date for adoption/ publication |
|---|---|---|---|
| | market | | |
| **Delegated act** | The **characteristics and technical specifications** of the safety features | 54a (2a*) | 2014 |
| **Delegated act** | The **lists** of **prescription medicines that should not bear** the **safety features** and the list of **non-prescription medicines that should bear the safety feature**s | 54a (2b*) | 2014 |
| **Delegated act** | **Procedures for the notification** of medicinal products at risk of falsification and **a rapid system for evaluation** and decision on these notifications | 54a (2c*) | 2014 |
| **Delegated act** | The **modalities of verifications** of the safety features by the manufacturers, wholesalers, pharmacists | 54a (2d*) | 2014 |
| **Delegated act** | Provisions on the **establishment, management and accessibility of the repositories system** | 54a (2e*) | 2014 |
| **Decisions (´Autonomous Decisions`)** (at the request of a third country) | Inclusion of a **third country on a list** | 111b | ----- |
| **Information campaign** | The dangers of falsified medicinal products | 85c | Continuously ongoing |
| **Report** to the Council and the European Parliament | Overview of transposition measures on the rules on **penalties** applicable to infringements of the national provisions adopted pursuant to the Directive | 118a | By 2 January 2018 |
| **Report** to the Council and the European Parliament | Trends of falsifications | 3 of Directive 2011/62/EU | See Article 3 of Directive 2011/62/EU |
| **Report** | In respect of the delegated powers conferred to the Commission | 121a | By June 2015 |

**Table 7:** Implementation measures of the EU Commission (*Source*: "Specific implementation measures of the Commission in the context of Directive 2011/62/EC amending Directive 2001/83/EC on falsified medicine, April 2012 [36]; * = different specification as source).

The concept of delegation/implementation acts were introduced by the Treaty of the functioning of the EU (TFEU) [47]. Article 290 of the TFEU allows the EU legislation, the European Parliament and the Council of the European Union, to give the EU Commission the power "*to supplement or amend certain non-essential elements of the legislative act*". Introduced by Article 291 of the TFEU, the EU Commission has to exercise "executive" instead of "quasi-legislative" power. Normally it is the responsibility of the Member States to implement legally binding acts of the European

Union but if "*uniform conditions for implementing legal binding Union acts are needed*" the EU Commission must exercise executive power by introducing Implementation Acts.

A comparison between Delegation Acts and Implementation Acts is shown in the following table 8.

| **Delegation act (Article 290 TFEU)** | **Implementation act (Article 291 TFEU)** |
|---|---|
| Sensitive policy issues for the legislators European Parliament and EU Council. The legislators delegates power to the EU Commission to amend, supplement or delete non-essential elements of legislation acts. | Routine implementation of EU legislation by the EU Commission. |
| No binding framework – Common understanding on Delegated Acts [48]. | Binding framework (Implementing Acts Regulation 182/2011, in force since 1st March 2011 [49]). |
| Objectives, scope, duration and conditions can be different for every legislation act and will be decided on a case by case basis. | Implementation of clearly defined tasks. |
| Absence of comitology committees and requirement to get approval of the Member States representatives. | Comitology committees in place which are operating under two full procedures only: the advisory procedure and examination procedure. |
| Legislators (EP and Council) can object to an individual act on any grounds. | Referral to the Appeal Committee by the EU Commission in case that committee votes majority against the Implementation Act. |
| Legislators are granted with ultimate control mechanisms for Delegation Acts (right of objection and revocation the power of delegation to the EU Commission). | |

**Table 8:** Comparison between Delegation Acts and Implementation Acts.

## 3.3 New definitions in Directive 2001/83/EU

The EU Directive introduces 4 additional definitions into the Directive 2001/83/EC:

- Definition of "**active substance**" - Article 1 (3a):

"*Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.*"

- Definition of "**Excipient**" - Article 1 (3b):

"***Any constituent*** *of a medicinal product* ***other than the active substance*** *and the packaging material*".

- Definition of "**brokering of medicinal products**" - Article 1 (17a):

"*All activities in relation to the* ***sale or purchase of medicinal products, except for wholesale distribution,*** *that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person*".

- Definition of "**Falsified medicinal product**" - Article 1 (33):

The WHO definition [1] about "*counterfeit drug"* is controversial as it combines the concept of counterfeiting (with its specific meaning in relation to intellectual properties) with issues related to quality, safety and efficacy of medicine. Therefore the new Directive introduces a definition of **falsified medicine** as "*any medicinal product with a false representation of:*

*a) its identity, including its packaging, and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;*

This definition specifies among others that any medicinal products, which are e.g. intentionally under dosed should be classified as falsified medicinal products and not just as quality defective medicinal products.

*b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or*

With the second criterion b) it should be ensured that medicinal products, which are manufactured abroad (like India, China) for a marketing authorization holder (MAH) in the EU, have to be labeled as such and not solely with the name of the MAH. This criterion should also covers the situation where the medicinal product is labeled with the name and country of origin of an approved manufacturer but manufactured at a non-licensed site.

*c) its history, including the records and documents relating to the distribution channels used.*

The new definition in the EU Directive "*does not included unintentional quality defects*" and is "*without prejudice to infringements* of *intellectual property rights"* to focus on the public health impact of falsified medicinal products.

## 3.4. Obligation of Safety Features

The new Falsified Medicine Directive introduces requirements with the addition of Article 54 (o) as it is stated that *"for medicinal products other than radio-pharmaceuticals referred to in Article 54a (1),* ***safety features*** *enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:*

- *verify the authenticity of the medicinal product, and*
- *identify individual packs,*

*as well as a device allowing verification of whether the outer packaging has been tampered with".*

According to Article 54a (2) the new Directive places the EU Commission under the obligation to adapt Delegated acts setting out the details for the safety features like:

- "*the characteristics and technical specifications of the unique identifier of the safety features ……*" (Article 54a (2a)).
- "*the lists containing the medicinal products or product categories which, in the case of medicinal products subject to prescription shall not bear the safety features, and in the case of medicinal products not subject to prescription shall bear the safety features …….*" (Article 54a (2b)).
- "*the procedures for the notification to the Commission ……. and a rapid system for evaluating and deciding on such notification ……*" (Article 54a (2c)).
- "*the modalities for the verification of the safety features referred to in point (o) of Article 54 by the manufacturers, wholesalers, pharmacists and persons authorised or entitled to supply medicinal products to the public and by the competent authorities……*" (Article 54a (2d)).
- *"provisions on the establishement, management and accessibility of the repositories system in which information on the safety features, enabling the verification of the authenticity and identification of medicinal products, as provided for in point (o) of Article 54, shall be contained……..*" (Article 54a (2e)).

While drafting such Delegation Acts, the EU Commission needs to consult with expert groups and stakeholders. Later on, the draft Delegation Acts needs to present by the EU Commission directly to both legislators, the European Parliament and the EU Council, at the same time. Such a delegation act can only enter into force if no objectives have been expressed by the legislators within a period set by the legislation act. In order to adapt the delegation acts, Article 4 of the Directive 2011/62/EU requires the Commission to carry out an impact assessment with regard of the "*technical options of the unique identifier*", the "*options for the extent and the modalities of verification of the authenticity of the medical products bearing the safety*

*features*" and the "*technical options for establishing and managing the repositories system*". Each of these options should be assessed regarding costs, benefits and cost-effectiveness. However, this impact assessment "*will not be to assess the impact of introduction of the safety feature itself, as this is now a mandatory requirement in EU legislation*" [39]. Such a financial impact of the introduction of the safety features for all stakeholders were already assessed by the EU Commission in the Impact Assessment Report [42] in 2008 as partly presented in table 9.

| **One-off cost for Manufacturer for "tamper-proof" features** | | | | | |
|---|---|---|---|---|---|
| **All medicine (RX and OTC)** | | | **Only RX** | | |
| EU wide 15.000 packing lines (approx. 40% of all dispensed packs already containing tamper-proof feature) | € 150.000 for "tamper-proof" features | **€ 1.35 billion in total for one-off costs for tamper-proof feature** | EU wide 12.000 packing lines (approx..40% of all dispensed packs already containing tamper-proof feature) | € 150.000 for "tamper-proof" features | **€ 1.08 billion in total for one-off costs for tamper-proof feature** |
| **Annual costs for Manufacturer for "tamper-proof" features** | | | | | |
| EU-wide 29.7 billion packages dispensed per year (approx. 40% of all dispensed packs already containing tamper-proof feature) | Costs for "tamper-proof" feature € 0.06 per pack | **€ 1.07 billion annual costs in total regarding tamper-proof features** | EU-wide 14.8 billion packages dispensed per year (approx. 40% of all dispensed packs already containing tamper-proof feature) | Costs for "tamper-proof" feature € 0.06 per pack | **€ 533 million annual costs in total regarding tamper-proof features** |
| **One-off cost for Manufacturer for database set-up and adaptation of packaging lines** | | | | | |
| **All medicine (RX and OTC)** | | | **Only RX** | | |
| Approximately 2500 manufacturers with large portfolio | € 3 million for set-up of database | **€ 7.5 billion in total for set-up of databases** | Approximately 2000 manufacturers with large portfolio | € 3 million for set-up of database | **€ 6.0 billion in total for set-up of databases** |
| Approximately 1200 manufacturers with small portfolio | € 1.5 million for set-up of database | **€ 1.8 billion in total for set-up of databases** | Approximately 700 manufacturers with small portfolio | € 1.5 million for set-up of database | **€ 1.05 billion in total for set-up of databases** |
| EU wide 15.000 packing lines | € 150.000 for adapting packaging line | **€ 2.25 billion in total for adapting packaging lines** | EU wide 12.000 packing lines (about 3000 packaging lines will be used in the non-prescription sector) | € 150.000 for adapting packaging line | **€ 1.8 billion for adapting packaging lines** |
| **Annual costs for Manufacturer for database set-up and adaptation of packaging lines** | | | | | |
| EU-wide 29.7 billion packages dispensed per year | Costs € 0.02 (year 1-5)<br>Costs € 0.005 (year 6-10) | **€ 371 million** | EU-wide 14.8 billion packages dispensed per year;<br>(The prescription sector counts 50% of the dispensed packages per year). | Costs € 0.02 (year 1-5)<br>Costs € 0.005 (year 6-10) | **€ 185 million** |

**Table 9:** Financial impact of implementation of safety features to stakeholders (*Source*: Impact Assessment [42])

To get the public view of stakeholders for preparing both the delegation acts and the impact assessment, the European Commission released on the 18th of November 2011 the concept paper "*Delegated act on the detailed rules for a unique identifier for medicinal products for human use, and its verification*" [39] for public consultation.

The concept paper consists of the following 5 parts:

**Part A:** *"Characteristics and technical specifications of the unique identifier"* with consideration of the cost effectiveness;

**Part B:** *"Modalities for verifying the safety features"* by manufacturers, wholesalers, pharmacists and the authorities;

**Part C:** *"Provision on the establishment, management and accessibility of the repositories system";*

**Part D:** *"Lists containing the medicinal products or product categories which, in the case of prescription medicines shall not bear the safety features, and in the case of non-prescription medicines shall bear the safety features";*

**Part E:** *"other issues";*

The responses from stakeholders have been published on the website of EU commission [34] and revealed that there are still outstanding issues, which needs to be clarified. Most of the stakeholders welcome the measures to increase patient safety but some are skeptical about the project. The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) pointed out in its response that there is no incident of falsification from non-prescription (OTC) or generic medicine in the EU legal supply chain so far and "*financial resources of manufacturers of products which are not at risk of falsification / counterfeit could be far better used elsewhere either in developing new formulations or indications of existing products or for increasing the EU competitiveness*". The British Medical Association (BMA) expressed the concern about the "*workload implications in implementing*" and the expected initial cost for the necessary electronic equipment "*at a time of economic austerity*". The NHS European Office, which is representing the English National Health Service, believes that the "*proposed content of the Delegated Acts threatens to interfere and impede the way that medicines are dispensed in Member States, particularly with regards hospital pharmacies*".

The EU Commission is the opinion that the only way to uniquely identify a pack shall be by a randomized serialisation number, contained in a carrier ("*bar code or other*")

which must be affixed on the outer packaging. The serialisation number on the pack shall be checked against the number entered in a repositories system to verify authenticity. The composition of the serialisation number should contain at least a manufacturer product code and the pack number but could also contain additional product information such as the batch number, the expiry date as well as the national reimbursement number. The EU Commission differentiates between the features to enable the verification that the medicinal product is authentic and the identification of individual packs and the features to verify "*whether the outer packaging has been tampered with*". The EU Commission takes the view that the choice of the technical specification with regard to tamper-evidence shall lie with the manufacturer of the product [39] and it is unclear if the tamper verification features will be ever precised by regulations on national or European level. In the absence of existing regulations the DIN standardisation project "*Tamper verification features for medicinal product packaging*" [50] was initiated with the aim to specify the requirements and to provide guidance for the application of the tamper verification features like e.g. sealing labels, cellophane wrapping and special constructed folding cartons.

In respect to the "*characteristics and technical specification of the unique identifier*", the EU Commission has offered in the concept paper two policy options. Option no. 1 is a very flexible approach by leaving the decision of the technical realisation of the serialisation number and its carrier up to the individual manufacturers as the delegation act would only define a broad framework. The second policy option would be to achieve a harmonised system through legislation as details of the serialisation number as well as the carrier would be set out in the delegation act. Most of the stakeholders are in favour of the harmonisation through regulation to assure feasibility, cost-effectiveness, technical efficiency and interoperability as option no. 1 would be too complex and expensive as every manufacturer would perform his own technical solution and correspondingly interoperability could not be ensured, which might lead to fragmentation of the European Market.

Especially for pharmacies in those countries like the UK where different pharmacy computer systems are in place, option 1 could become to a serious problem as various different technical standards would create significant costs in terms of IT development whereas in option 2 pharmacists would only need to invest in a

standard reader. But there are also concerns as the response e.g. from the German Pharmaceutical Industry Association (BPI) shows that the harmonised approach could create a major problem due to the different national regulations in respect of the prescription status of medicinal products in Europe as this could lead to "*different requirements for the application of Unique Identifiers / Tamper-evidence-devices in different countries and would thus result in a different level of protection for European citizens living in different European countries"*.

Most stakeholders are in favour that the randomised serialisation number may include the batch number to improve inventory management and to facilitate product recalls while the expiry date would prevent pharmacists from dispensing expired medicinal products. The inclusion of the batch number would particularly support the wholesale distributors to comply with Article 80 (e) of the Falsified Medicines Directive as they have to keep records of the "*batch number of the medicinal products at least for products bearing the safety features referred to in point (o) of Article 54*". Some stakeholders like EUCOPE, which represent small pharmaceutical businesses in Europe or the BPI are the opinion that there should be no obligation and "*printing variable data on the outer packaging in a machine-readable way should only be carried out on a voluntary basis*" whereas stakeholders from the generic industry like the British Generic Manufacturers Association (BGMA) states that "*there are no provisions in amended Directive 2001/83/EC that give the Commission powers to require, in the delegated act, manufacturers to add either the batch number or the expiry date to the unique identifier. To do so would, therefore, be beyond the requirements of the legislation, and make the delegated act subject to legal challenge*".

The Directive states in Article 54a (5) that "*Member States may, for the purposes of reimbursement or pharmacovigilance, extend the scope of application of the unique identifier referred to in point (o) of Article 54 to any medicinal product subject to prescription or subject to reimbursement*". As some Member States have national product codes for reimbursement purposes in place (like the Pharmazentralnummer (PZN) in Germany) the EU Commission proposed that the national reimbursement numbers should be replaced by the randomized serialisation number (option 1) or the serialisation number should include the national reimbursement number (option 2).

The opinions of stakeholders with respect to this issue varies as some are in favour of the proposed options, some are in favour of an optional usage of the national reimbursement number while other stakeholders (like the BPI, ABDA, securPharm, EUCOPE, EAEPC-EFPIA-GIRP-PGEU or PHAGRO) recommend a third option consisting of a globally unique product code which includes the national product and reimbursement numbers, an unique identification number with the pack (serial number) and expiry date and batch number on a voluntary basis.

Regarding the "*technical characteristics of the carrier*", the EU commission requested input of the stakeholders on the alternatives of linear barcode, 2D-barcodes and radio-frequency identification (RFID) tags, including an assessment of cost benefits. *Linear barcodes* are currently used in Belgium, Greece and Italy as carrier of the serialisation number of medicinal products. However they are limited in respect of carrying information in this code without requiring a lot a space. In respect of costs linear barcodes would only cause minimal additional costs and pharmacies do have already 1D-reader in place.

The *2D-Barcode* as carrier allows the inclusion of a large amount of data (more than 3000 characters) but maintaining a print size small enough. The shape of the Data Matrix can be either square or rectangular and the size depends on the number of rows and columns. Such barcodes are still readable even if 25% of the code is damaged due to the storage of information multiple times. 2D-Barcodes are being used increasingly for industrial and consumer goods, they are already required for medicinal products like in France, South Korea, Turkey and could additionally become convenient for patients as Smartphones are already able to read such codes. The European Federation of Pharmaceutical Industries and Association (EFPIA) has included in its response an estimation of costs for the implementation of unit serialization, covering the Data Matrix printing, equipment and IT system, with €125 million annual costs for the industry (EU-27), € 8 million annual costs for large manufacturer (defined as having €7B sales and 500M units per year in Europe) and approximately 1.6 cent per pack. According to the joint response of EAEPC-EFPIA-GIRP-PGEU the costs for 2D scanner in Pharmacies and for scanners in a wholesale environment are estimated with €250-300 respectively €1,200 per device.

The Radio-frequency identification as carrier uses radio waves to exchange data between a reader and an electronic tag attached to the medicinal product. It could save any space problem as most RFID tags could likely be placed under the product label but are relatively expensive compared to other carrier. The European Directorate for the Quality of Medicines and Healthcare (EDQM) has pointed out in its response that RFID tags would add additional cost on top of the serialization cost with €0.10 to €0.15 per tag and costs of RFID tag readers up to €3000. Whereas packs with linear barcodes and 2D barcodes can only be handled individually, the RFID represent a technique for reading multiple packs at once. The use of the RFID technique has been successfully demonstrated by the BRIDGE project [51] with one of the objectives to implement a "*fully operational drug product tracking system*" using a 2D Data Matrix "*on all levels of product packaging – item, bundle, case, pallet and vehicle*" and RFID tags for cases and pallets. Stakeholders have expressed their concerns about e.g. possible interactions of RFID tags with biological products, the interference with metallic packaging materials and glass, that there are no available long term studies available to present results about the effect of radio waves on the efficacy of medicinal products and the problem in respect of recycling of packaging.

The most stakeholders are in favour of the 2D-matrix as data carrier as the technology has technical and economic advantages in comparison to the other concepts. Some like the Asociación Española de Medicamentos Genéricos (AESEG) and the European Generic Medicines Association (EGA) would prefer to have a linear barcode to be "*in line with the scope of the Directive*", containing the product code and serialization number. However, both, the EGA and AESEG concede that in case that additional information should be printed, "*the 2D-matrix barcoding will be required*".

In part B of the concept paper the EU Commission asks for comments on the "*modalities for verification the safety features*". They pointing out that the concept of a unique identifier only works if there is a reliable repositories system in place which allows that serialisation numbers are checked into the repositories system and checked out. The costs for repositories systems "*shall be borne by the manufacturing authorisation holders of medicinal products bearing the safety features*" as stated in Article 54a (2e). It is the EU Commission`s opinion that "*the check-out of the safety*

*feature is a key element in the process of ensuring the detection of falsified medicine*". In this regard the wording "*verification of the serialisation number*" shall mean the check of the *"number against the entry in the repositories system*" whereas the "*check out of the serialisation number*" shall mean that "*the number is verified and checked out of the repositories system*". In the context of the modalities of the verification of safety features, the EU Commission has submitted three policy options: the first option refers to a systematic check out of the serialisation number at the end of the supply chain by pharmacies, hospital pharmacies or retailers whereas the wholesale distributors are not required to perform the check out or to verify the serialisation number. However the EU Commission states in the concept paper that a disadvantage of this policy option would be that the verification is made at the end of the supply chain and that "*packs with falsified medicines may circulate for months in the European Union before they are detected*". The second and third proposal of the EU Commission are based on the first proposal but the second option includes "*additional random verification at the level of the wholesale distributors*" whereas option 3 requires "*additional systematic verification by the wholesale distributors*" but for both options with no obligation to check out serialisation numbers from the repositories system to avoid confusion in respect of the systematic check out at the point of dispensation. The advantage of policy option 3 would be the traceability of each individual pack however this option is associated with major additional operational costs especially for wholesalers.

Especially the UK regulator MHRA has a different point of view on this topic as it questions the basic assumption in the concept paper "*that medicines subject to the safety feature provision and therefore included in the repository system must, at some point, be checked out*". The MHRA is the opinion that there is no requirement under the EU Falsified Medicine Directive that this would be the only possible option as Article 54a (2d) emphasises that "*When establishing those modalities, the particular characteristics of the supply chains in Member States, and the need to ensure that the impact of verification measures on particular actors in the supply chains is proportionate, shall be taken into account*". The UK regulator states in its response that they "*do not believe that the Commission has the right under the Directive provisions to propose a scheme that mandates checking out at point of dispensing*" as Article 54 (o) of the Directive requires that safety features should

enable the verification of authenticity of medicinal product and the identification of individual packs but no mandatory verification at the point of dispensing. They pointed out that introducing mandatory scanning at the point of dispensing would "*require a huge financial outlay to provide the necessary scanners and high speed, high capacity, resilient connectivity to the repositories at all healthcare outlets. The additional ongoing costs of the technology and time taken to comply with the requirements throughout the healthcare system and beyond will be reflected in increased prices and increased professional fees*". This matter has also been taken up by the BGMA as they state in its response that "*there is nothing in the Directive that specifically requires a check out process as opposed to verification. The Commission may lack powers to enforce a check out procedure*": Most stakeholders are in favour of additional random verifications at the level of wholesale distributors whereas the systematic verification by the wholesale distributors is considered as option only by a few stakeholders (like State Institute Control Czech, Farmindustrie) due to additional costs and the impact of workload which might lead to reduced frequencies of deliveries to pharmacies.

As the delegation act shall contain provision on the establishment, management and accessibility of the repositories system, this will be discussed in the concept paper in part C "*Provisions on the Establishment, Management and Accessibility of the Repositories system*" Three policy options for governance of the system are provided by the EU Commission for consideration and commenting: stakeholder governance, EU governance and the national governance. In the *stakeholder governance* the development of the appropriate infrastructure for the repositories system would be in the hand of the stakeholders whereas the delegation act would set out the legal framework, the objectives to be achieved and the obligations on the relevant actors like manufacturers, wholesale distributors, pharmacists/retailer. The EU Commission is the opinion that the stakeholder governance might be the most cost-efficient option but they also pointed out that it might be difficult for Member States "*for the purposes of reimbursement, pharmacovigilance or pharmacoepidemiology, use the information contained in the repositories system……."* as stated in Article 54a (5). *EU governance* would mean to have a pan-European repositories system governed by an EU-body like the EU Commission or the European Medicines Agency (EMA), providing a single point for checking the serialisation numbers in and out. However

the EU Commission pointed out in the concept paper that the complexity of a system with a central repositories system, the simultaneous connections of all actors and the immediate authentication of individual packs would need to be considered. The last policy option covers the *national governance* by establishing a system of national repositories in all Member States. All of these systems would have to be connected to each other in order to allow intra-Union trade as well as to all actors (in the Member State and for supplying medicine in the territory of the Member States). This policy option would reduce the complexity as only limited number of actors would be linked to the national repositories system and it would allow adaption of the characteristics of the national repositories system in respect of the national characteristics of the distribution chain.

The opinion of the stakeholders differs regarding the question who should run the system. Some stakeholders like the EFPIA, EAEPC, GIRP and PGEU are in favour of the stakeholder governance and have jointly developed their own verification model called “European Stakeholder Model ESM” (*see section 4.2*) whereas other stakeholder would prefer a non-stakeholder model. The European Department for the Quality of Medicine and Healthcare developed with eTACT (*see section 4.1*) another verification system which is publicly governed and stated in its response that “*national environments and constraints make it necessary to provide for a realistic scenario in which centralised public governance (option 2) is mixed with decentralised interfacing of national systems (option 3), at least for the existing national systems of mass serialisation*”. The AESEG and the EGA responded that they do not have a “*preference for a specific model for running repository systems*”. Whatever system is chosen, “*the division of costs should be proportionate and relative according to the price of the products. Lower priced products should contribute in a relative way compared to high priced products*”. Some other stakeholders like Aefi, Agenzia Italiana del farmaco, European Industrial Pharmacists Groups (EIPG) and Farmindustria would like to see the national governance.

In the concept paper further questions were asked about issues which have to be considered in the delegation act like the information of commercially sensitive nature such as information about the number of packs, point of dispensation as well as point of re-packing, the protection of personal data and the re-packaging of medicinal

products. The Directive requires the EU Commission in Article 54a (3) to "*take due account of least the following when adopting measures under the following:*

*a) The protection of personal data as provided for in Union law*

*b) the legitimate interests to protect information of a commercially confidential nature;*

*c) the ownership and confidentiality of the data generated by the use of the safety……"*

Most stakeholders are the opinion that every stakeholder should remain the owner of his own data and no personal data should be carried in the repository system.

Part D of the concept paper covers the topic of *"Lists containing the medicinal products or product categories which, in the case of prescription medicines shall not bear the safety features, and in the case of non-prescription medicines shall bear the safety features".* The Directive 2011/62/EU states in Article 54a (1) that *"medicinal products subject to prescription shall bear the safety features*" and "*medicinal products not subject to prescription shall not bear the safety features*" unless they have been listed by the EU Commission in a Delegated Act as stated in Article 54a 2(b) where it is mentioned that "*those lists shall be established considering the risk of and the risk arising from falsification related to medicinal products or categories of medicinal products*". According to the concept paper the so-called "*white list*" shall include all those prescription medicinal products which are exempted from the obligation whereas the "*black list***"** shall include non-prescription medicinal products which need safety features after performance of a risk assessment for falsification. According to the EU Commission the following criteria shall be considered for the risk assessment:

- *The price of the medicinal product:* the EU Commission assumes that very low price medicinal products are less at risk of being falsified. According to the proposal all of such medicinal products under € 2 should be considered as "very low price" whereas products with a manufacturer`s gross price of more than € 2 should be considered a "high price" products.
- *The sale volume of the medicinal product:* regarding this point the EU Commission assumes that medicinal products which are on the market in very low volumes are less at risk of being falsified. The sales volume should be

established against the typical annual sales figures of medicinal products in the EU.

- *The number and frequency of previous incidents of falsified medicinal products being reported in the EU and third countries:* according to the EU Commission opinion such numbers of incidents may be a risk indicator for falsification.
- *The specific product characteristics:* concerning this matter the EU Commission assumes that specific characteristics for products make the risk of falsification unlikely like e.g. products which will be directly delivered from the manufacturer to hospital pharmacies.
- *The seriousness of the conditions intended to be treated:* which means that depending on the indications the use of falsified medicinal products may have very serious consequences for patients (like cancer).
- *Other potential risk to public health;*

The EU commission propose in its concept paper a points-based system for risk assessment and hence drawing up the black and white lists. The factors which should be taken into account are a) the price: high price (*5 points*) – low price (*1 point*)), b) the sales volumes: high volume (*5 points*) – low volume (*1 point*)), c) the number of incidents in EU or third country: severe incidents of falsification (*5 points*) – no incident (*1 point*), d) the specific characteristics of the product: risk of falsification (*5 points*) – no risk of falsification (*1 point*), e) the seriousness of the condition intended to be treated: severe conditions (*5 points*) – non-severe (*1 point*)) and f) other potential public health risks with maximum 5 points.

On the basis of this scheme a prescription drug with six points or less should be placed on the "*white list*" whereas a non-prescription drug with more than 10 points should be on the "*black list*". In practice this would mean that only low price prescription products with a very low sales volumes, no previous incidents of being falsified in the EU or third country, with no risk of falsification, no other public health risks and for mild disease would be on this white list.

Between some stakeholders, especially from originator and generic companies, a battle is already ongoing in respect to the question which product should have to bear the safety features. For the EFPIA all prescription medicine, including generics, should be required to have the safety feature, whereas the EGA has an opposite

view by proposing that generics as low-risk products should be generally be exempt. The EGA stated in its response that "*if safety features applied to all prescription medicines in the EU, the Commission would fail to apply the principles of proportionality and cost-effectiveness".* On the 10 July 2012, the EGA complained in a letter to the EU Commission of misinformation by the EFPIA on counterfeiting in the generics sectors. Starting point for this dispute was a press release on the EFPIA´s webpage [52] in which it was stated that "*Counterfeit medicines have been documented in every therapeutic category, in both* ***generic*** *and branded medicines, and in every region of the world. Recent cases of counterfeit oncology treatments as well as of counterfeit generics underline the urgent need for action and stringent measures – such as the ESM - to protect patients worldwide".* This comment refers to a counterfeit version of Adderall® detected in the United States. The Food and Drug Administration (FDA) issued a warning on the 29th of May 2012 on its website [53] after receiving complaints from the manufacturer Teva. Adderall®, approved in the United States only for the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy is currently on the FDA's drug shortage list [54] due to active pharmaceutical ingredient supply issues and this nationwide shortage in pharmacies may have led to purchase of the medication in the Internet. The EGA argues that the statement of the EFPIA is misleading, firstly as Adderall® was sold via illegal websites in the United States and not within the European legal supply chain and secondly because Teva`s Adderall is a branded product and not a generic. However, the EFPIA believes that the legislation is to prevent counterfeit drugs entering the legal supply chain and although there is a higher risk of more expensive medicine to be falsified, there is currently no system in place to detect counterfeit drugs in the supply chain to be able to make a statement about number of falsified generics or brands.

As prices for medicinal products vary from country to country due to national price regulations and currency fluctuations, parallel trading is a very profitable business and entirely legal between EU member states due to the EC treaty [47]. Such parallel import occurs when a medicinal product will be manufactured for and placed into circulation in one market and then imported into another market without the authorization of the owner of the intellectual property right. Through the purchase of pharmaceutical medicine from wholesalers in low-price countries (like Greece or

Spain) and the import of these products for sale in high-price countries (e.g. Germany or Holland), high profit margin can be achieved. Any repackaging of medicinal products by parallel traders will be still permitted but with the inclusion of the new Article 47a (1), the following requirements have to be met in case of removal or coverage (partial or full):

- The authenticity of the medicinal product has to be verified by the manufacturing authorisation holder prior to removal or coverage of the safety features;
- He has to comply with the requirements by replacing "*those safety features with safety features which are equivalent as regards the possibility to verify the authenticity, identification and to provide evidence of tampering of the medicinal product*".
- The replacement must be conducted in accordance with GMP for medicinal products [56] and be "*subject to supervision by the competent authority*".

The safety features shall be considered as equivalent if they "*comply with the requirements set out in the delegated acts adopted … to Article 54a (2)*" and "*are equally effective in enabling the verification of authenticity and identification of medicinal products ……*"

With the new Article 47a (2) manufacturing authorisation holders "*including those performing the activities*" are classified as producers and "*held liable for damages in the cases and under the conditions set forth in Directive 85/374/EEC"* [55].

New with the insert of a subparagraph in Article 51 (1) is now the additional task of the Qualified Person (QP) of the finished product manufacturer to "*ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging***"**.

## 3.5 Other measures required by the Directive 2011/62/EU

In addition to the introduction of the safety features, the new Directive 2011/62/EU provides further measures to protect consumers from falsified medicinal products.

### 3.5.1 Internet sales

The reasons why people might buy medicine online vary in different ways. Some of the buyers might be too embarrassed to talk with healthcare professionals about their

problems, others might have fears that the doctor could be reluctant to prescribe a particular medicine, are attracted by the lower costs of the medicine in the internet compared to high street pharmacies or by the fast delivery service for medicine and healthcare products, which is especially convenient for people who are elderly, disabled or lives in remote areas. For legal internet pharmacies all buyers needs to provide the prescription before any prescription-only medicines can be dispatched. However the internet has created a huge opportunity for counterfeiter in which often prescription only medicine (especially medicines for sexual dysfunction, weight loss or hair loss) will be sell without a valid prescription or consultation with a healthcare professional.

A completely new title VIIA "*Sale at a distance to the public*" is inserted into the Directive setting out the provisions covering internet sales. The requirements for persons offering medicinal products for "*sale at distance*" are specified in Article 85c (1) as those persons must to authorized or entitled to supply medicinal products "*also at a distance*" in accordance with the national legislation of the Member States and are committed to notify the Member States about name/permanent address of the place of activity, the starting date of activity, the website address and the "*classification in accordance with Title VI of the medicinal products*".

In the future there will be assistance available for the public to be able to recognize all those websites which are legally offering medicinal products by implementation of an EU "*common logo*" which should be in place 1 year after the publication of the relevant implementation act at the latest. All these websites should contain at least the contact details of the competent authority, a hyperlink to the websites of the competent authorities concerned and the common logo on every webpage in agreement with Article 85c (1d).

According to Article 85c (4) each Member State is required to set up a website providing information about a) the national legislation for the sale of medicinal products on the internet, b) the purpose of the common logo, c) the list of persons who offers medicinal products for sale at the distance, d) background information on the risk of illegally supplied medicinal products and e) with a hyperlink to the EMA website. The requirement b) and d) are also applicable for the EMA (Article 85c (5))

and on its website the relevant EU legislation and hyperlinks to the websites of the Member States must be published.

However for those member states who contend that the supply of medicinal products via the internet is a risk of health there is an opt-out clause as according to Article 85c (2) "*Member States may impose conditions, justified on grounds of public health protection, for the retail supply on their territory of medicinal products for sale at a distance ……..*".

To warn the public for the risks of purchasing falsified medicinal products via the internet, there should be awareness campaigns run by the EU Commission in cooperation with the EMA and Member States (Article 85d). The Member States should also organise meetings with patient and consumer organisations "*to communicate public information about the actions undertaken in the area of prevention and enforcement to combat the falsification of medicinal product*" (Article 118b) and urgent public announcement should be issued when defective or falsified medicinal products being deemed to have reached patients (Article 117a (3)).

The Member States are instructed in Article 85c (6) to take action by using "*effective, proportionate and dissuasive penalties*" against non-authorised websites supplying medicinal products for "*sale at a distance to the public*" on their territory.

### 3.5.2 Measures with respect to active pharmaceutical ingredients (APIs)

The rules for the control of manufacturers and distributors of pharmaceutical starting materials have been significantly tightened. The Directive includes a new requirement which was added to the existing Article 8 (3) saying that for granting a marketing authorisation *"a written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46"* should be provided. The written confirmation shall be accompanied by *"a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice".* The new Article 46 (f), replaced in the

Directive, calls the duties of the holder of the manufacturing authorization in respect of pharmaceutical active ingredients and excipients to:

- "*to comply with the principles and guidelines of good manufacturing practice* [56] *for medical products*";
- "*to use only active substances, which have been manufactured in according with good manufacturing practice for active substances*" [57] and
- "*dstributed in accordance with good distribution practices* [58] *for active substances*".

It is now the legal obligation of the holder of manufacturing authorization to judge compliance "*by the manufacturers and distributors of active substance with good manufacturing practice and good distribution practices by conducting audits at the manufacturer and distribution sites of the manufacturer and distributor of active substances*". The Directive however allows flexibility regarding the question who should conduct the audit, which means that such audit could be conducted by himself or "*through an entity acting on his behalf under a contract*".

The replacement of Article 46 (f) in the Directive includes further obligations to the holder of a manufacturing authorization to:

- verify of suitability of excipients for use of medicinal products (*Article 46 (f)*);
- inform the competent authority and the marketing authorisation holder in case of information that medical products are or are suspected of being falsified (*Article 46 (g)*);
- verify that manufacturer, importers or distributors of APs are registered with the competent authority (*Article 46 (h)*);
- verify of the authenticity and quality of the active substances and excipients (*Article 46 (i)*);

Of particular concern is the manufacture of active substances in third countries. Article 46b states that *"Member States shall take appropriate measures to ensure that the manufacture, import and distribution on their territory of active substances, including active substances that are intended for export, comply with good manufacturing practice and good distribution practices for active substances".*

Article 46b (2) of Directive 2001/83/EC as amended requires a "*written confirmation*" for the import of active substances from third countries into the EU. These "*written confirmation*" from the competent authority of the exporting country should meet the following requirements:

- The GMP regulations of the exporting country are at "*least equivalent*" to those of the EU.
- All manufacturing plants should be regularly and strictly monitored including "*repeated and unannounced inspections*". Measures in case of GMP violations will be taken.
- The EU (i.e. the authorities of the Member States) will be informed without any delay in case of any GMP violations.

In practice this would mean that for any inspection of a site resulting in the determination of non-compliance with GMP, the competent authorities should be informed and prohibit the import of active substance from this particular site.

For such a "*written confirmation*" the standards like the Good Manufacturing Practice for active substances of the World Health Organisation [59] or ICH Q7 [60] are regarded as equivalent to those required according to the EU legislation [32].

As a "*written confirmation*" is only required for active substances, the UK agency MHRA expressed in its response [61] to the EU commission`s concept paper "*Implementing Act on the requirements for the assessment of the regulatory framework applicable to the manufacturing of active substances of medicinal products for human use*" [38] concern that this might lead to a shift of manufacturing activities from the EU to third countries as "*the manufacturer of the finished dosage form in the third country would not be burdened with obtaining a written confirmation before (importing and) using the active substance*". As the obligation to verify compliance will be placed on the "*manufacturer of the medicinal product importing the product into the Community*", this "*perverse incentive created by Directive 2011/62/EU*" could "*seriously harm the European pharmaceutical industry and further reduce finished dosage form manufacture in Member States*".

According to Article 46b (3) such "*written confirmation*" can be waived if an exporting country is included in a list, where all of those countries are listed, which were

evaluated as “equivalent countries” regarding the level of their GMP rules by the EU Commission. At the request of the third country there is the requirement that the EU Commission performs an assessment of the third country`s regulatory system and if necessary, inspections of manufacturing sites to become member of those list according to Article 111b (1). However so far only Switzerland, Israel, Australia, Brazil and Singapore has requested to be listed [62] and will be included in the listing of the EU commission as soon as the equivalence-assessment will be finalised.

Another exemption of the “*written confirmation*” is in case of exceptional circumstances to ensure availability of certain medicinal products as stated in Article 46b (4). In case that a third country is not named on the EU Commission`s list and also not willing to provide such “*written confirmation*”, it falls to the Member States to conduct inspections in that third country to prevent potential stock shortage. In this case the exception will be granted for the period of the valid GMP certificate and the European Commission needs to be informed. The MHRA [61] is concerned that the additional burden to conduct such inspection “*will have a significant impact on Competent Authority inspection resources, and may have a knock-on effect for the resourcing of other GMP inspection programmes*”.

Especially concerned is the MHRA about India as over 1/3 of all UK authorised medicines use active substance manufacturers in India “*where the regulatory framework is fragmented and contacts with the regulatory authorities are limited*” [63]. As there is no requirement for third countries to indicate whether they are willing to issue such “*written confirmations*” before July 2013, the MHRA worries that the EU member states will not be able to know about the availability of written statements before this particular implementation date. In its response [63] on the EU Commission`s draft template for the written confirmation they said that from recent discussion with third country regulators “*is has become evident to the UK that these regulators either have little or no knowledge of these new requirements or have indicated that they have no plan to comply*” and therefore they are warning that the serious consequences of these “*EU equivalence*” would not only be the loss of manufacturing in the EU but also the serious shortage of medicine.

In India, members/council were invited in August 2011 by the Pharmaceutical Export Promotion Council of India (Pharmexcil) [64] to provide comments on the EU Falsified

Medicinal Directive 2011/62/EC. Recently, on the 13th of September 2012, the Pharmexcil had an interactive session with the EU Commission regarding the new importing regulations for APIs into the EU [65]. According to an article in "*The Hindu Business Line*" as an outcome of this session it is planned that the Indian Government will appoint a competent authority in two weeks to ensure compliance of API exporters with the EU import regulations [66]. However Pharmexcil clarified recently in a statement [67] that "*it may not be appropriate to indicate that the Government has taken a decision to notify the competent authority in 2 weeks time*" and that they have taken up the requirement of a "*written confirmation*" for export APIs to Europa "*with the Department of Commerce, Government of India and all aspects of the matter are under active consideration of the related Government agencies*".

### 3.5.3 New requirements for wholesalers and brokers

The new Directive provides increasing obligations for wholesale distributors as specified in the table 10 and specific provisions for brokers as summarized in table 11.

| Obligation | Task | Reference in Directive 2011/62/EU |
|---|---|---|
| **Any distributors** | To notify intention to import medicinal product from another member state to marketing authorisation holder and competent authority to which the medicinal product will be imported. | Article 76 (3) |
| **Wholesalers** | To check the safety features of the medicinal products they have been received. | Article 80 (ca) |
| **Wholesalers** | To record the batch numbers of those medicinal products bearing safety features. | Article 80 (e) |
| **Wholesalers** | To maintain a quality system (setting out responsibilities, processes and risk management measures). | Article 80 (h) |
| **Wholesalers** | To inform competent authority and marketing authorisation holder in case of receiving or being offered (suspected) falsified medicinal products. | Article 80 (i) |
| **Wholesalers** | To verify that supplying wholesale distributors holds wholesale distribution authorisation and complies with GDP. | Article 80 |
| **Wholesalers** | To verify that manufacturers or importers who supplying products holds a manufacturing authorisation. | Article 80 |
| **Wholesalers** | To verify that brokers fulfil the requirements | Article 80 |

| Obligation | Task | Reference in Directive 2011/62/EU |
|---|---|---|
| | set out in the Directive when obtaining products through brokering. | |

**Table 10:** Additional obligations for wholesale distributors as specified in the Directive.

The concept of "*Brokering of medicinal products*" was newly introduced into the Directive by Article 1 (17a). Thereafter a broker can be a firm or individual that brings parties together to negotiate but brokers do not buy, receive or store medicinal products themselves.

| Obligation | Task | Reference in Directive 2011/62/EU |
|---|---|---|
| **Brokers** | To ensure that medicinal products traded are having a marketing authorisation. | Article 85b (1) |
| **Brokers** | To have permanent address and contact details within the EU. | Article 85b (1) |
| **Brokers** | To fulfil the requirements of Article 80 (d – i):<br>- To have an emergency plan for recalls;<br>- To keep records for any transactions;<br>- To make records available for inspections;<br>- To comply with GDP;<br>- To maintain a quality system;<br>- To inform competent authority and marketing authorisation holder in case of (suspected) falsified medicinal products. | Article 85b (1) |
| **Brokers** | To register their activity with the competent authority of the Member State of the permanent address | Article 85b (2) |
| **Brokers** | To notify competent authorities of any changes without delay, | Article 85b (2) |

**Table 11:** Specific provisions for brokers.

Under the Directive brokers will be subject for inspections (Article 111 (1d)) and removed from the national registry in case that they does not comply with the requirements of the Directive (Article 85b (4)).

### 3.5.4 Further obligations for Member States and European Medicine Agency (EMA)

In addition to the aforementioned obligations in the relevant chapters there are further obligations for Member States and the EMA resulting from the new Directive as summarized in table 12:

| Obligation | Task | Reference in Directive 2011/62/EU |
|---|---|---|
| **Member States** | To enter information related to manufacturing authorisation in the Union database. | Article 40 (4) |
| **Member States** | To register Importers, manufacturer and distributors of APs by entering in the Union database. | Article 52a (7) |
| **Member States** | To take measures to prevent medicinal products imported for re-export (new term "**introduced**") from entering into circulation if suspected as falsified. | Article 52b |
| **Member States** | To enter information about the wholesale distributor authorisation in the Union database. | Article 77 (4) |
| **Member States** | To establish a registry for brokers that shall be publicly available. | Article 85b (2) |
| **Member States** | To establish form and content of the authorisations, inspection reports, GMP/GDP certificates in cooperation with the EMA. | Article 111a |
| **Member States** | To establish a system with the aims to prevent (suspected) dangerous medical products reaching patients (covering receipt/handling of notification of suspected falsified medicinal products, recalls/with-drawals of medicinal products and provide rapid alert notification in case of serious risk to public health). | Article 117a |
| **EMA** | To cooperate with member states in the coordination of inspection in third countries. | Article 111 (1) |
| **EMA** | To develop and manage the Union Database. | Article 111 (6) |

**Table 12:** Further obligations for Member States and the EMA.

Since 2007 the EMA has already the "*EudraGMP*" database [68] (in the Directive called "*Union database*") in place which includes details of manufacturing and importation authorisations, GMP certificates from EEA countries, non-compliance statements (with the second database release in 2009) and information on manufacturing inspections performed by regulatory authorities from all EEA countries (with the new database release in 2011). Some of the information are publicly available as part of EMA`s transparency initiative with the exception of any information of commercially and/or personally confidential nature. In the future further modules will cover information about planned inspections countries outside the EU, wholesale distribution authorisation, GDP certificates and EU active substance manufacturer, importer, distributor registrations.

### 3.5.5 Control measurements and penalties

With the new Directive, the duties of competent authorities have been extended with respect to the supervision of activities. As control measures for the implementation of the obligations, all actors within the supply chain must be aware of inspections. Article 111 (1a) states that manufacturers (located in the EU or in third countries) and wholesale distributors of medicinal products "*shall be subject to repeated inspections*". Article 111 (1b) specify that competent authorities of the Member States shall implement a system of API supervision including risk based inspections. Furthermore paragraph 1b specifies that inspections may be carried out at sites of manufacturers or importers of excipients and sites of manufacturers or distributors of active substances located in third countries when there is any suspicion of non-compliance with GMP/GDP. Further inspections may be conducted in the EU or third countries on the request of a Member State, the EU Commission or the EMA as stated in article 111 (1c) and at marketing authorisation holders and brokers of medicinal products (Article 111 (1d)). .

As a consequence there is a higher risk of criminal liability for all actors. Article 118a states that "*the member states shall lay down the rules on penalties*" and lists that these penalties:

- "*must be effective, proportionate and dissuasive*";
- "*shall not be inferior to those applicable to infringements of national law of similar nature and importance*";
- "*shall take into account the risk to public health presented by the falsification of medicinal products*";

The penalties shall address:

- "*the manufacturing, distribution, brokering, import and export of falsified medicinal products, as well as the sale of falsified medicinal products at a distance to the public*";
- "*non-compliance with the provisions ……. on manufacturing, distribution, import and export of active substances*";
- "*non-compliance with the provisions ……on the use of excipients*".

The new inserted article 47a (2) states that "*Manufacturing authorisation holders……., shall be regarded as producers and therefore held liable for damages in the cases and under the conditions set forth in Directive 85/374/EEC*". The Directive 85/374/EEC [55] establishes the principle of liability for defective products

which "*does not provide the safety which a person is entitled to expect*". The injured person has the burden to prove the actual damage; the defect in the product and the causal relationship between damage and defect but does not have to prove any negligence or fault on the part of the producer or importer. In the future it is to be expected that courts will consider the safety features required by the new Directive as minimal safety standard.

# 4. Update of the development progress of verification systems within the European Union

The new Falsified Medicine Directive requires the implementation of a tracking and verification system. As the concrete implementation of the requirement has not been detailed yet, different systems are currently being developed. All of these projects are carrying a risk of uncertainty as these developments takes place before the EU Commission has adopted the respective delegated act. While this means to gain time it also means to invest money into projects with uncertain future. The progress of the different verification systems will be described in the following sections.

## 4.1 eTACT

One attempt has been made by the European Directorate for the Quality of Medicines and Healthcare with the eTACT drug traceability project [69] which relies on the Track & Trace approach. The system monitors the movement of pharmaceutical products through the European supply chain and enables a control of the medicinal product at any time of the delivery stage. In this project 2D Datamatrix barcodes will be used containing Unique Medicine Identifiers (UMIs) which consists of a combination of the product number, a serial number, the batch number and the expiry data. Such UMIs will be generated at the manufacturer`s level, uploaded to the eTACT system and systematic verifications performed by all stakeholders upon dispensing.

The eTACT project will be under public governance by the EDQM in co-ordination with regulatory authorites to ensure the protection of sensitive data. One advantage of the eTACT traceability project is the possibility for patients to check the authenticity of medicinal products via internet (by entering of the Unique Medicine Identifier using

web service) and mobile phone (by barcode scan on the pack and verification using smartphone application).


**Figure 1:** eTACT system (*Source*: EDQM eTACT website [69]).

The live demonstration of the IT eTACT system was presented in an EDQM workshop on the 26/27th of January 2012 to the key stakeholders (regulatory authorities, business stakeholders (as EFPIA, EGA, PGEU and EAHP) and patient organisations. More eTACT workshops are planned for further discussion with stakeholders and based on the comments the EDQM will receive, a real-scale system will be developed from 2013 on.

At the current stage there is no cost calculation for the eTACT system possible but the EDQM refers to Turkey`s fully operating track-and trace system "ITS" [70] with operational costs less than €0.01 per box and is therefore confident that the costs of eTACT might be lower as the current projected cost per box of the European Stakeholder Model (ESM) [71].

## 4.2 European Stakeholder Model (ESM)

The European Stakeholder Model (ESM) [72] or more recently called European Medicines Verification System (EMVS) is an industry proposed solution developed by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in cooperation with the EAEPC (European Licensed Parallel Distribution Industry), the PGEU (Pharmaceutical Group of the European Union) and the GIRP (European Association of Pharmaceutical Full-line Wholesalers). The ESM is an end-to end

system and does not require the capturing of all movements and changes of ownership in the supply chain. It is focused on three key points: the upload of codes by the manufacturers, the code checks by pharmacists and the secure replacement of codes during repackaging steps. For this purpose a machine-readable unique code will be printed to each individual pack and the content of such codes will be sent to a database before the product release. By scanning of the code at the point of dispensing at the pharmacy, the information will be compared with that held in the database. If the information does not match, this means that the verification failed.

According to the Joint Position Paper on EDQM`s "eTACT" project [73] the stakeholders are the opinion that the "*timely, secure and cost-effective implementation of a product verification system is best assured with a system that is designed and run by those who will use it day-today, such as pharmaceutical manufacturers, pharmacists, wholesalers as well as parallel distributors*". In March 2011, the EFPIA published together with the stakeholders the Joint Position Paper "*Ten Core Principles to protect patients from falsified medicines"* [74] with*:*

1. *"Combining tamper-evident packaging with a unique serial number.*
2. *Guaranteeing continuity of protection throughout the entire supply chain.*
3. *Ensuring a single coding and identification system on each pack across the EU.*
4. *Ensuring product verification database systems can work together across the EU.*
5. *Verifying every serialized pack at pharmacy level.*
6. *Maximising all the potential benefits of mass serialisation.*
7. *Focusing on securing patient safety and protection patient privacy.*
8. *Using safety features that are simple, robust and cost-effective.*
9. *Working together in the Interest of Patient Safety.*
10. *Involving other stakeholders".*

The ESM consists of a series of national data repositories in the EU Member States, which are linked via a European Hub. Altogether they are forming the European Medicines Verification System (EMVS) which serves as verification platforms to check authenticity by pharmacies and other registered parties. The European Hub, that links the national data repositories, will be run by a stakeholder organization

called the European Medicines Verification Organisation (EMVO). Whereas all serial numbers and product status details will be held at the national level, the European Hub will serve as:

- "*A centralised location for the storage of product master data e.g. product description and other static details about the product;*
- *A single entity from which national systems can receive new/revised product serialisation data;*
- *A means by which multi-country packs can be systematically marked as 'unavailable' in all relevant markets once a pack has been dispensed in one market;*
- *A mechanism by which parallel distributed products can be reconciled at a dose level over the lifetime of a batch as they undergo any repackaging process;*
- *A central point from which product recall actions can be initiated (without prejudice to the ability of the responsible manufacturing entity to initiate a recall in accordance with established recall procedures at national level);*
- *A central point from which those alerts that cannot be handled solely at the national level can be managed (e.g. an EU-wide recall). The system design will generate alerts in case the automatic checking procedures detect an exceptional event*" [75];

The European Stakeholder Model will be under stakeholder governance with national systems established by stakeholders. In addition, a ready-made system will be available for implementation at national level, the national Blueprint template, which is likely to be more cost-effective and simpler than establishing national systems from the very beginning.

The ESM model has already been tested with a great success at national level in a pilot study in Sweden between 2009 and 2010. Overall 25 pharmacies in the greater Stockholm area participated in these pilot study with a total of 25 different products provided by fourteen leading pharmaceutical companies. The used Data Matrix code contained of four elements of information, the Global Trade Item Number (GTIN), batch number, expiry date and unique randomised serial number. In April 2010 the EFPIA [76] has published the results of this pilot project and it has been shown that the model was a practicable approach for the effective identification of counterfeit medicine as well as for recalled or expired products.

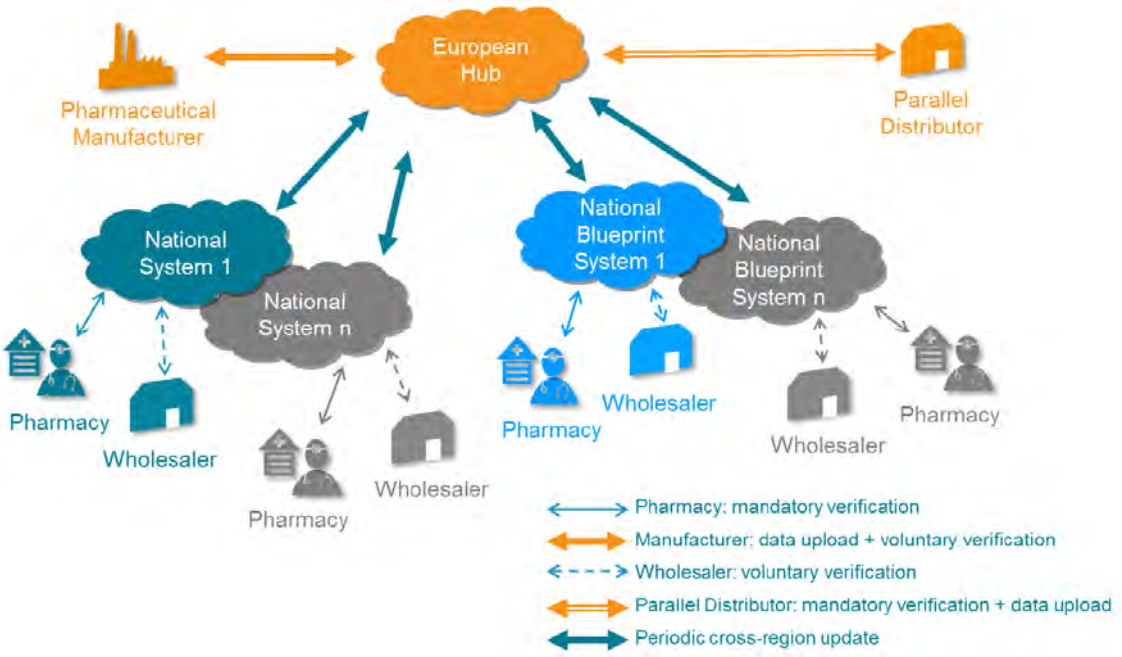


**Figure 2:** EMVS System Architecture (*Source*: EFPIA "Call for Tender – European Medicines Verification System (EMVS)" [77].

In April 2012, the EFPIA began the tendering process for the key components of the EMVS [77]. The EDQM was invited to be one potential service provider to act on behalf of EU member states to oversee standards in healthcare but has rejected the EFPIA invitation "*as an inter-government organization with no commercial interests, the EDQM is therefore neither in a position nor is willing to enter into a tender process launched by strictly private organisations. However, the EDQM will follow the progress of this initiative and continue to liaise with the various stakeholders as they will be part of any system eventually put in place in Europe*" [78].

## 4.3 securPharm

The German medicine traceability pilot "securPharm" is a common initiative [79] of the associations of drug manufacturers (BAH, BPI, Vfa), wholesalers (PHAGRO), pharmacists (ABDA) and the marketing company (WuV). SecurPharm will also use the stakeholder model for the repository system and will be rolled out in 2013 with certain prescription medicine selected by the participating pharmaceutical companies. It is intended that in the first step a national solution will be developed and that the national solutions will be linked to a European network in the 2nd step. For all those medicines which requires verification, a 2D-Datamatrix Code as a machine readable identifier will be printed on all packages consisting of the data elements "***P**harmacy **P**roduct **N**umber* (*PPN)*", "*randomized serial number*", "*batch*

*number*" and "*expiry date*" at the point of manufacture in order to allow them to be scanned and authenticated by pharmacists at the point of dispensing in an 'end-to-end' system, which only involve manufacturers and pharmacies actively. As first pharmaceutical company, participating in the securPharm project, Sanofi-Aventis has already printed a medicinal product batch with this 2D-Datamatrix code [80].

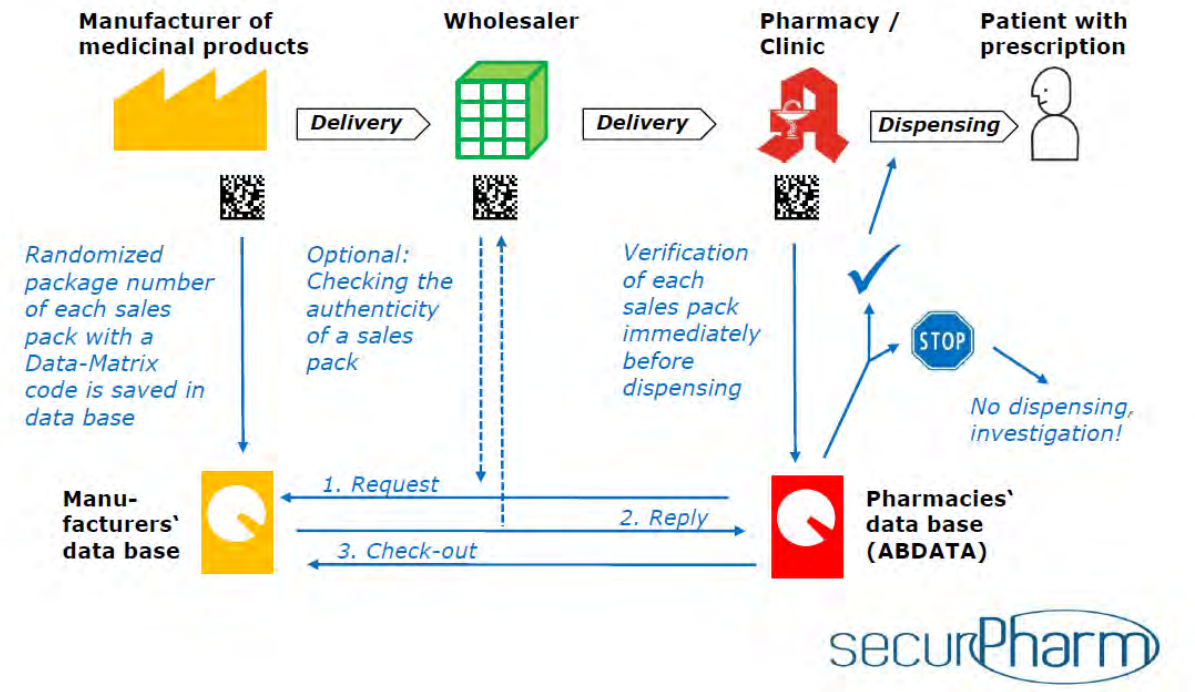


**Figure 3:** securPharm`s end-to-end verification system (*Source*: securPharm [79])

The "Informationsstelle für Arzneispezialitäten GmbH" (IFA) has been commissioned by the "securPharm" stakeholders to launch the conditions necessary for the verification on the basis of ISO standards.

In Germany the "Pharmazentralnumber (PZN)" is a requirement for the identification of medicinal products as defined in §131 Paragraph 5 SGB V [81] and many processes like the reimbursement and medical product identification are dependent on this PZN product number. As there is the need of a European-wide, unique product number for the verification in terms of the EU Directive, the Pharmacy Product Number (PPN) was created. The PPN consists of 3 parts, the two-digit "Product Registration Agency code (PRA-Code)", the 8 digit "Pharmazentralnumber (PZN)" and the check digits PPN. In case of a 7 digit PZN (PZN7) it needs to be converted to a PZN8 by prefixing a 0 (zero) before the PZN7. For the converting of the PZN into the PPN, the PRA Code "11" (for Germany) is added to the beginning of

the PZN as a prefix. This Code is assigned to the IFA and only in use for the registered Pharmacy Product Number in Germany. The following table 13 shows reserved and registered PRA-Codes [82].

| PRA Code | Assigned to | Used for |
|---|---|---|
| 00-10 | Reserved | |
| 11 | IFA | PZN – registered Pharmacy Product Number Germany |
| 12 | EUROCODE IBLS | Registered Blood Product Number |
| 13-99 | Reserved | |
| AA-ZZ | Reserved | |

**Table 13:** Assigned PRA Codes [82].

The check digits will be calculated over the complete PPN data element via a specified algorithm [83] as shown in an example in the Annex. Figure 4 shows an example of a) the Pharmacy Product Number (PPN) and b) the PPN including the Data Identifier "9N". Specific information can be found in the document "*IFA-Coding-System – PPN Code Specification*" [84] and on the securPharm website [79].

**a)** **b)**

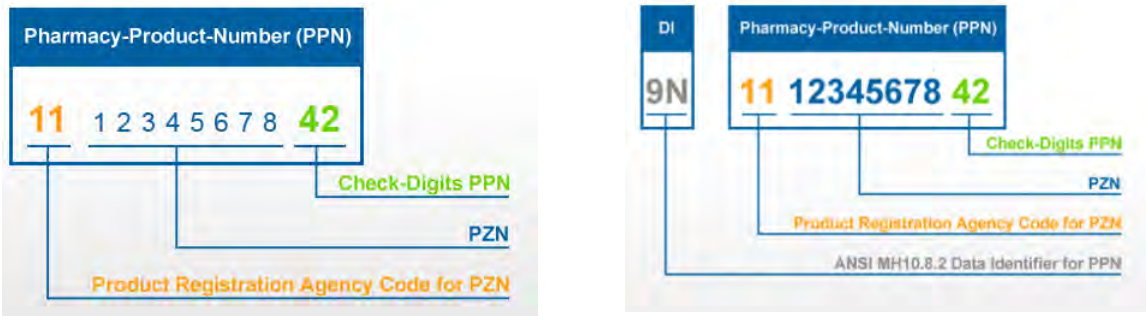


**Figure 4:** a) example of a Pharmacy Product Number (PPN) and b) the PPN including the Data Identifier "9N"

In March 2012, the securPharm steering committee endorsed to use alternatively a GS1 compatible 2 D-Datamatrix code to the proposed PPN code from the IFA during the pilot phase. As one of the several alternatives it has been decided to use a "National Trade Item Number (NTIN)" by embedding the PZN number into an international identification number using a GS1 Germany prefix [85].

| **N**ational **T**rade **I**dentification **N**umber (NTIN) | | |
|---|---|---|
| GS1 Germany Country prefix | PZN with 8 digits | Check digit (1 digit) |
| **4150** | 12345678 | 2 |

**Figure 5:** Structure of the NTIN in Germany (Source: GS1 NTIN Guideline [85]).

The following table 14 provides an overview about the current development of verification systems in Europe.

| eTACT project | European Stakeholder Model (ESM) | securPharm |
|---|---|---|
| EU level project | EU level project | National project (Germany) |
| Public governance by EDQM to ensure the prevention of misuse of information. | Stakeholder governance called European Medicines Verification Organisation (EMVO). | Stakeholder governance |
| Track & trace verification | End-to-end verification | End-to-end verification |
| 2D Data matrix barcode | 2D Data matrix barcode | 2D Data matrix barcode |
| Live demo available; not been piloted in real life setting | Pilot-Project in Sweden (2009-2010) | Pilot-Project in Germany will be start in 2013. |
| System offers possibility for patients to check the genuine of medicinal products via internet/mobile phone | Check for patients not applicable | Check for patients not applicable |
| Check of secondary packaging level possible. | Check of individual medicinal products. | Check of individual medicinal products. |

**Table 14:** Overview about the verification systems currently being in development.

## 4.4 Traceability regulations in France & Turkey

As the first two countries, France and Turkey adapted the 2D-Datamatrix system in their regulations. In February 2007 the French Agency of Sanitary Safety and Health Products (AFSSAPS) published a "*Notice to human-use medicinal product marketing authorization holders and head pharmacists of the pharmaceutical establishments***"** [86] to request that a specified 2D datamatrix barcode shall be printed on the outer packaging of medicinal products as of 1st January 2008. Effective on 31st of December 2010, all marketed medicinal products for human use in France, irrespectively of their prescription status, are required to have the 2D-Datamatrix barcode containing the CIP-13 standardized GS1 code, the batch number and the expiry date on the outer-packaging. The aim of this new regulation is apart from others to combat counterfeiting and reimbursement fraud, to increase the transparency of the distribution chain and to improve the efficiency of batch recalls as from 31 December 2010 on, manufacturers, distributors, pharmacies and hospitals are required to be able to trace products by an Electronic Receipt Notice (EDI).

Turkey is the sixth-largest pharmaceutical market in Europa, the 14th worldwide [87] and according to the "*Pharma 2020*" Report [88], it is expected that "*Turkey and India might well be in the top 10*" pharmaceutical markets by 2020. As a transit country

between Asia and Europe, Turkey belongs to one of the largest global provider of counterfeit drugs. Due to a weak medical insurance system numerous cases of prescription reimbursement scams occurred which "*may cost the Turkish Social Security Institution (SGK) at least $150 million per year*" [89].

In order to prevent the spread of counterfeit medicine originated in Turkey, but also to prevent fraud against the medical insurance system, the Ministry of Health of the Republic of Turkey implemented a "Pharmaceutical Track and Trace System" known as "İTS" [70]. This Track and Trace System was rolled out in two phases. In Phase 1 only the manufacturers were "*obliged to make production notifications and pharmacies were obliged to make consumption notifications*" but with the start of phase 2 on the 1st of January 2012 "*the production, importation, dispatch, consumption, dispatch return, deactivation, purchase approval, exportation and dispatch cancellation notifications*" are obligatory for all stakeholders like Manufacturers, Importers, Exporters, Drug Warehouses, Pharmacies, Drug consuming centers (Hospitals, Family Physicians etc.) and Reimbursement companies.

The Track and Trace system "ITS" is designed to track the location of every drug unit by recording of transactions by the system through notifications in all phases from production to consumption. After the transactions, all respective stakeholders must transfer the final status and the information about the ownership of the drug units to İTS. The traceability is ensured by a unique registration number consisting of the combination of both, the Global Trade Item Number (GTIN) and the serial number, and additional information regarding batch number and expiry date.

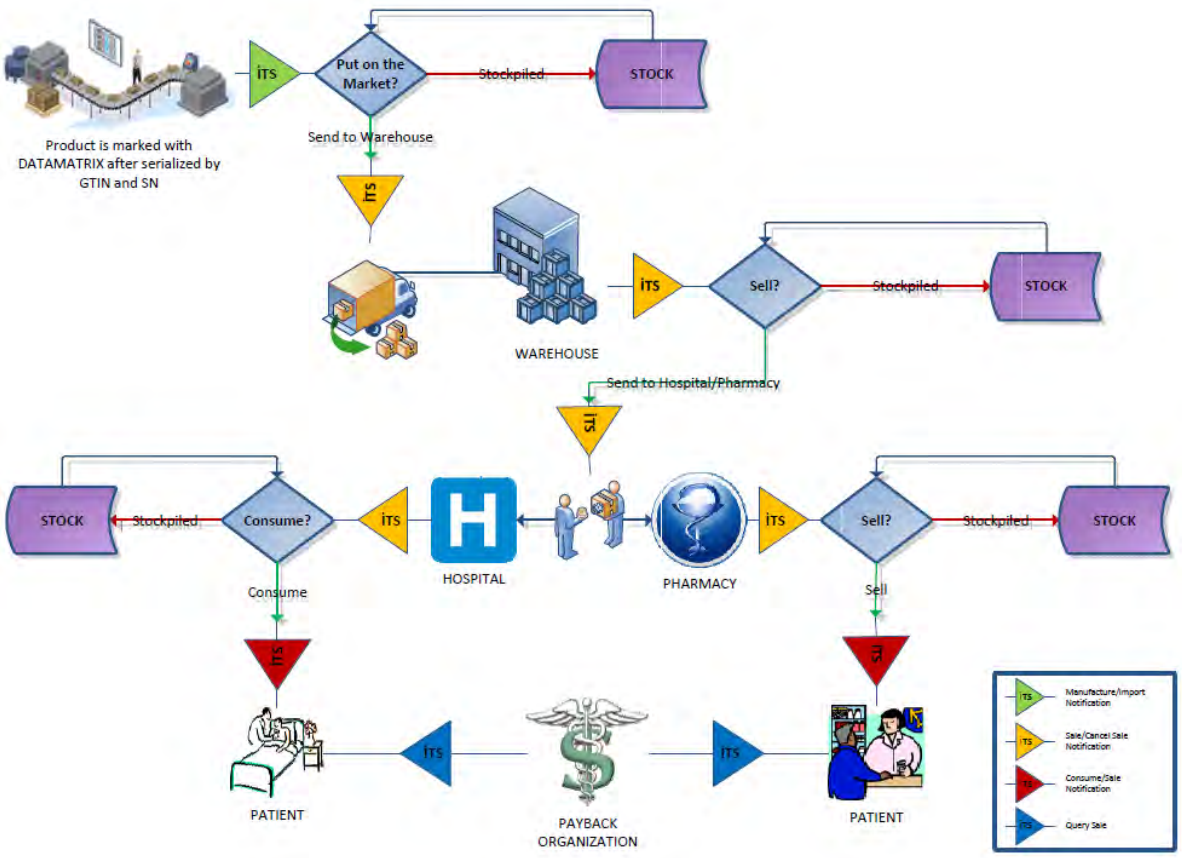


**Figure 6:** Workflow Diagram of the Drug Tracking System (ITS), *Source*: Overview of Drug Tracking System (ITS) in the Pharmacies of Ankara - Preliminary Research [90].

## 5. Conclusions and outlook

Although there is a low prevalence of falsified medicinal products in the legal supply chain within Europe, the impact of such rare occurrences has been massive as recently seen in the case of heparin [91] or clopidogrel [92]. Was the problem previously mostly limited to “life-style medicine”, it has continued to spread and includes now all sort of medicine. To be able to provide a better protection for patient and consumer and to strengthen the confidence of the public in the legal supply chain, the Directive 2001/83/EC was amended in a number of places by the Falsified Medicine Directive 2011/62/EU, published in the Official Journal of the European Union on the 1st of July 2011.

The new Directive will affect all stakeholders like manufacturers, importers, re-packers, wholesale distributors, EU active substance manufacturers, internet pharmacies, competent authorities, the EMA and the EU Commission with obligations to be implemented. Although the new legislation is generally welcomed by

the stakeholders, there are several aspects which needs to be defined in more details. As the Directive 2011/62/EU requires the EU Commission to take measures in form of guidelines, Implementation Acts and Delegation Acts, the Commission has already released several concept papers for public consultation with concrete questions to get the view of the stakeholders on specific topics.

Each of the measures required by the Directive will have a specific impact on costs for the entire pharmaceutical supply chain. There is already a battle ongoing between the originator and generic pharmaceutical industry about the question which medicinal products should bear the safety features. The generic industry would like an exemption for generic products as they are of low costs and therefore of low risk whereas the R&D industry is the opinion that all prescription drugs have to carry the safety features.

Another discussion is related to the verification system which will be implemented in the future. Currently different systems will be developed by stakeholders, which raise the question if these systems will co-exist in the future or if one will prevails other the other.

For distributors it will show up in the future how e.g. the new obligation to notify the marketing authorisation holder and competent authority in the Member State of importation from the intention to import medicinal product, even within one EU Member State to another, will affect the trading as this might become to a substantial intervention into the principle of “free movement of goods” [47].

The requirement that wholesale distributors “*must verify that the medicinal products received are not falsified by checking the safety features on the outer packaging*” raised lot of concern from stakeholders as the obligation to scan individual packs would have negative implementations on the daily business of distribution chain operations.

The new Directive still allows the repackaging of medicinal products but only if the safety features will be replaced by “*equivalent safety features*”: As such a replacement of these safety features may be the weakest link in the effectiveness of the measures to protect the public from falsified medicinal product, it is therefore

important to define the term "*equivalent*" in more detail to enable a shared understanding between the original packers and the re-packers of medicinal products.

There is currently no estimation about the direct or indirect cost caused by the new provisions in Article 46b (2) in respect of the manufacturing of active substances in third countries. As starting materials for medicinal products are mostly coming from third countries like China and India, there is great concern of the EU manufacturer for medicinal products about the consequences if these countries will not comply with the EU import regulations for active substances. In the worst case scenario this would mean that the EU manufacturer would be forced to purchase the active pharmaceutical ingredients elsewhere which would have huge financial impacts. The UK regulatory agency MHRA has already warned that among others the "*EU equivalence*" could cause shortages of medicinal products.

A completely new chapter "*Sale at a Distance to the Public*" was inserted in the Directive 2011/62/EU to protect the public as most of the falsified medicinal products within the EU are purchased through illegal internet websites. However, all measures can be effective only if the public take these warnings seriously.

As the detailed procedures on how specific requirements of the Directive should be fulfilled will only be covered in Delegation and Implementation Acts, the EU Commission will be very busy to review all comments from stakeholders with partially divergent views to prepare the legislations. The future will show how effective all of these measures are to protect the public from the dangers of falsified medicinal products and how they impact on the costs for medicinal products.

## 6. Summary

The Falsified Medicine Directive 2011/62/EU was published on the 1st of July 2011 in the Official Journal of the European Union, amending the Directive 2001/83/EC in a number of places to provide measures for the protection of patients and consumer of the ever increasing risk of falsified medicinal products while tightening the penalties for those behind the illegal activities. In the future there will be the obligation that medicinal products at risk of counterfeiting have to bear safety features to ensure authenticity and traceability. Furthermore there will be a strengthening of supervision

for all actors in the distribution chain and additional measurements with respect to active pharmaceutical ingredients. A completely new chapter was inserted in the Directive to take actions regarding the increasing problem of illegal medicines purchased over the internet as according to the WHO approximately 50% of the medicinal products available via internet sales are falsified.

The Directive requires the EU Commission to provide specific measure in form of guideline, Implementation Acts and Delegation Acts. The process for Delegated Acts is a new regulatory procedure for amending or supplementing non-essential parts of a legislative act. The first transition of the measures into national law will be in force from the 2nd of January 2013 on but there is a longer transition period foreseen for several requirements like the safety features, which needs to be defined by Delegation Acts.

The aim of this master thesis is to provide an overview about the measures required by the Falsified Medicine Directive with the main focus on the safety features for medicines at risk of counterfeiting including the presentation of different verification systems that are currently in development by stakeholders in the EU.

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## ANNEX

The PPN check digits will be calculated over the complete PPN data element via a specified algorithm [83]. The ASCII value of the alphanumeric character will be used for the calculation. Each character will be converted into the corresponding ASCII value and multiplied with an increasing weight factor. The weight factor starts with “2” on the left and is incremented by “1” for each of the following characters. From all multiplication a total sum will be calculated and divided by 97. The remainder is the check digit and provides the last digits of the PPN. An example of the calculation of the PPN Check digits is shown in table 15.

| | **PRA Code** | | **PRN** | | | | | | | | **PPN check digit** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PPN** | **1** | **1** | **0** | **3** | **7** | **5** | **2** | **8** | **6** | **4** | **1** | **4** |
| ASCII value | 49 | 49 | 48 | 51 | 55 | 53 | 50 | 56 | 54 | 52 | | |
| Weight factor | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | | |
| Product of ASCII value and weighting | 98 | 147 | 192 | 255 | 330 | 371 | 400 | 504 | 540 | 572 | | |
| **SUM** | 98 | 245 | 437 | 692 | 1022 | 1393 | 1793 | 2387 | 2927 | 3499 | **3409/97** = 35 Rest 14. | |

**Table 15:** Calculation of the PPN Check digits [83].

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

Schriesheim, den 14 Oktober 2012 _____

(Sonja Seeberger)