

ADVISORY

Advice on the implementation of EU-Directive 2011/62/EU

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1. Introduction

According to the European Commission (hereinafter 'EC') of the European Union (hereinafter 'EU'), the threat to public health and safety from falsified medicinal products is on the rise:

'Falsified medicines [...] are a major threat to public health and safety. As falsifications become more sophisticated, the risk of falsified medicines reaching patients in the EU increases every year. Falsified medicines represent a serious threat to global health and call for a comprehensive strategy both at European and international level.'¹ In order to control and combat the threat mentioned, the EC has introduced new legislation to put in place preventive measures to improve the protection of the public. The basis for this new legislation was defined in the Directive 2011/62/EU² (hereinafter: 'Directive'), amending Directive 2001/83/EC³ (hereinafter: 'the original Directive').

Following adoption by the EC and the European Parliament, the new legislation on falsified medicinal products was published on 1 July 2011 in the Official Journal of the EU. This new legislation came into force on 2 January 2013 and introduces new harmonised EU-wide measures to ensure that medicinal products are safe and that the trade in medicines is rigorously controlled.

In order to expand on this basis, the EU has launched a concept paper and set out public consultations⁴ on a number of different topics with the EU member states. The responses from these public consultations will be used as discussion points when the EC prepares the delegated acts, which serve as a minimum requirement for adoption of the Directive into the national laws and regulations of the EU member states.

The remainder of this chapter will set out the objective of this report and the approach taken in developing this report.

1.1 Objective

The European Generic Medicine Association (hereinafter: 'EGA') has asked KPMG to conduct an independent study and advise on the implementation of the Directive.

1.2 Approach

In order to conduct an independent study and provide advice, we have combined our experience within the fields of anti-counterfeiting and the pharmaceutical industry, along with the collection of information from the following sources of data:

- We have conducted interviews with representatives from selected stakeholders from the following sectors: several innovative and generic pharmaceutical producers and various pharmaceutical associations.

¹ http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm#geninf.

² http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf.

³ http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83/2001_83_ec_en.pdf.

⁴ http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm.



- We performed a review of the responses to the public consultations set out by the EC to gain an understanding and additional insight into the various perspectives of the stakeholders involved;
- We performed research on other sources of publicly-available information.

Based on this, we have been able to provide insight into the following topics:

- The motivation for the amendment to the original Directive;
- The 'risk assessment' as defined in the Directive, which is used to determine which medicinal products should bear the safety features;
- The most important considerations and challenges that should be addressed in the delegated acts to increase the possibility of the Directive being successfully implemented.

1.3 Scope of this report

The Directive covers a wide range of topics aiming to improve the protection of the public. While conducting our independent study, we have specifically focussed on the following topics:

- Unique identifiers (Article 54.o of the Directive);
- Repository and verification system (Article 54.a.2.e of the Directive);
- Risk assessment (Article 54.a.2.b of the Directive);
- Tamper-evident packaging (Article 54.o of the Directive).

Chapter 3.1 provides additional explanation of these topics.

1.4 Outline

The remainder of this report is organised as follows. Chapter 3 provides relevant background information and the definitions required for the discussions and conclusions in the succeeding chapters. The motivation behind the Directive is discussed in Chapter 4. Next, the criteria for the risk assessment are described and discussed in Chapter 5. In Chapter 6 we provided a number of considerations that should be addressed when implementing the Directive. Finally, Chapter 7 provides a number of conclusions based on the study we performed.

1.5 Limitations

KPMG does not accept or assume any liability or responsibility to any party other than EGA as the addressee of the report. KPMG cannot be held responsible or liable for any claim in respect of, or arising from, or in connection with, the issuance of the Report to or use in some other way by third parties.

The advice included in this Report was developed in response to the Amendment by the Directive 2011/62/EU dated 8/6/2011 of the original Directive 2001/83/EC, and it may be possible that this legislation will undergo changes at a later date. Later amendments to the Directive are not included in the scope of this report.

2. Executive Summary

According to the European Commission (EC), the threat from falsified medicinal products to public health and safety is on the rise and therefore the EC has introduced new legislation, amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, aimed at improving the protection of public health through the prevention of the entry of falsified medicinal products into the legal supply chain in the European Union (EU). By means of researching publicly-available information, conducting interviews and using our broad experience in the field of anti-counterfeiting, we have provided insight into the following topics:

- The background for this Directive;
- The use of the 'Risk Assessment' in the Directive;
- The most important considerations and challenges that should be addressed to ensure the successful implementation of the new legislation.

Currently, the problem of the falsification of medicinal products in the EU is relatively small compared to the rest of the world. Additionally, the majority of the known cases of falsified medicinal products have occurred outside of the legal supply chain, to which the Directive does not apply. However, because of the potentially devastating effects of falsified medicinal products on patients, it is acknowledged that this health problem merits attention and is to be taken seriously. Therefore, the EC is being proactive and wants to create a robust preventive system before the problem increases. If the issue is not addressed and the EC acts only after the fact, the EC may not have sufficient time to contain the problem before it escalates. A recent incident⁵ underlines the need for above mentioned measures.

The Risk Assessment is proposed in the Directive as a tool to determine which products are in or out of scope for bearing the safety features. The most important criterion for this Risk Assessment is the combination of price and volume as it is an indicator for the potential profit for the counterfeiter. The criteria mentioned in the Directive that refer to the number and frequency of previous cases of falsified medicinal products and the severity of the conditions intended to be treated appear to be good indicators at first sight, but are difficult criteria to apply. As an initial assessment we suggest to focus on products that score high on the 'price-volume' scale, and additionally, we suggest identifying a limited number of medicinal products that are specifically designed to treat very severe conditions. Once an initial system is up and running, a central register of falsified medicinal products can be set up which can be used in the long run as an additional criterion within the Risk Assessment.

The Directive contains many uncertainties regarding the implementation, which could lead to budget overruns and time constraints if they are not properly addressed. Implementing the safety features initially on a smaller-scale would mean that the majority of these uncertainties could be dealt with; and the additional expenditure and reputational damage possibly arising from unexpected drawbacks will remain limited. Therefore, we advise carrying out a carefully-phased implementation. The EC should be starting on a smaller scale in the initial phase and further expand over time. In this way, many expected and unexpected problems could be resolved during the initial phases leading to a more robust and cost-effective implementation in the later phases.

This phased implementation can be executed in several ways. One could start for example with a limited number of EU member states in the initial phase. However, in that case one should address the possible

⁵ <http://apotheke-adhoc.de/nachrichten/markt/nachricht-detail-markt/omeprazol-faelschungen-durchsuchungen-bei-gehe/>
Note: this incident is currently under investigation.



risk of 'code harvesting', as medicinal products with unique codes could be distributed to countries that are not included in the initial phase. Alternatively, the initial phase could include all member states but focus only on a limited number of products (e.g. the ones most threatened by counterfeiting), with a combination of both options being preferable. Additionally, we advise the EC to at least postpone setting out tamper evident packaging, as implementing effective tamper-evident packaging is a difficult and costly task, which may lead to the risk of creating a false sense of security. Also, tampering with the packaging of medicinal products is currently not known as a large threat.

An important topic around the implementation is how its costs will be allocated to the different stakeholders, considering the significant start-up costs. As the participation of manufacturing authorisation holders that are required to add safety features to their products could change over time, a model is required that provides a good balance between the costs and benefits for a stakeholder. Moreover, as the repository and verification system has potential for other commercial uses (e.g. direct ordering, automatic reimbursement, etc.) there could be additional beneficiaries in the future that could bear part of the costs.

3. Background on the Directive

In this chapter we will cover the background on the Directive including an explanation of certain terminology that will be helpful to understand the succeeding chapters in this report.

3.1 The approach of the Directive

As mentioned in Chapter 1.3 this report focuses on the following topics: ‘unique identifier’, ‘repository and verification system’, ‘risk assessment’ and ‘tamper-evident packaging’. We will cover these topics in the following paragraphs.

3.1.1 Unique identifier

The purpose of the unique identifier is to allow the verification of the authenticity of each pack of the medicinal product supplied and to identify individual packs, regardless of how they are supplied including through distance selling.

3.1.2 Repository and verification system

The EC requires the setting up a repository and verification system in order to flag possibly falsified medicinal products within the legal supply chain⁶ of the EU. Using this system, unique identifiers are registered when entering the legal supply chain and may be verified at the points of dispense (and possibly at other distribution points in the legal supply chain).

3.1.3 Risk assessment

The goal of Article 54.a.2 of the Directive is to determine which medicinal products shall or shall not bear the safety features, taking into consideration the cost-effectiveness. In determining this, the following two aspects are taken into account:

- The relative risk of the medicine in question being falsified;
- The risk arising from falsified medicines (i.e. the potential hazard).

In order to do so, Recital 11 of the Directive proposes the use of the ‘risk assessment’, which consists of a minimum of six criteria, to determine which products are in and out of scope. This will result in establishing lists of exceptions, referred to as the ‘white list’ and the ‘black list’ – the white list contains medicinal products subject to prescription that shall not bear the safety features, whereas the black list consists of medicinal products not subject to prescription that shall bear the safety features.

⁶ The ‘legal supply chain’ concerns the network consisting of the different parties that are involved via legal means in producing, handling or distributing a specific medicinal product. Note that, for example, medicine sales over the internet notoriously use illicit supply channels – this is further discussed in chapters 4 and 5.



Article 54.a.2.b of the Directive provides a non-comprehensive enumeration of the criteria required in a risk assessment:

- The price and sales volumes of the medicinal product;
- The number and frequency of previous cases of falsified medicinal products being reported within the Union and in third countries and the evolution of the number and frequency of such cases to date;
- The specific characteristics of the medicinal products concerned;
- The severity of the conditions intended to be treated;
- Other potential risks to public health.

These criteria will be further explained and discussed in Chapter 5 of this report.

3.1.4 Tamper evident packaging

Article 54.o of the Directive states that techniques should be in place allowing verification of whether the outer packaging of a medicinal product has been opened or tampered with.

3.2 Falsified medicinal products

The focus of the Directive is to prevent the entry of falsified medicinal products into the legal supply chain of the EU.

The term 'falsified medicinal products' refers to any medicinal product with a false representation of its identity, source or history. It is defined in the Directive, and widely accepted by other major international organisations⁷, as any medicinal product with a false representation of:

- 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;
- Its source, including its manufacturer, its country of manufacture, its country of origin or its marketing authorisation holder;
- Its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

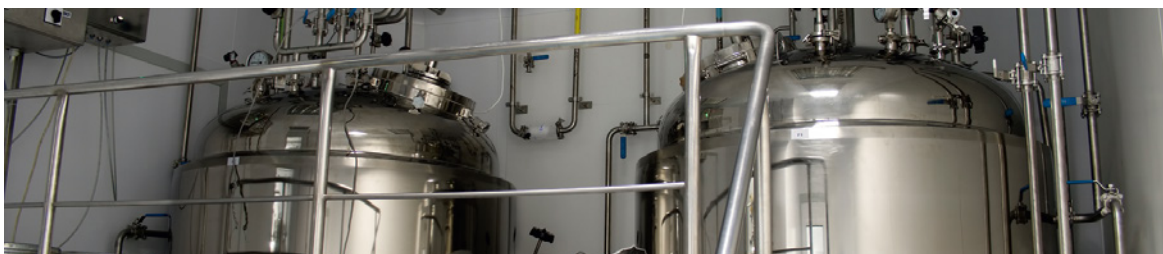
In some situations, the counterfeit is so similar to the genuine product that it deceives health professionals as well as patients and can only be detected using chemical analysis⁸. Even pharmaceutical producers sometimes cannot distinguish their own product from the falsified product.

⁷ <http://www.mhra.gov.uk/home/groups/ei/documents/websiteresources/con149816.pdf> and <http://www.imb.ie/images/uploaded/documents/3.1%20Falsified%20Medicines%20v.2.pdf>.

⁸ E Deconinck; P Y Sacré; D Coomans; J De Beer, 'Classification trees based on infrared spectroscopic data to discriminate between genuine and falsified medicines'.

4. Motivation for the Directive

The Directive was created in response to the growing concern about falsified medicinal products in the EU, as discussed in the previous chapters. In this chapter, the motivation for the Directive will be explored. We will discuss the current and expected state of falsified medicines in the EU.



4.1 Historical trend of falsified medicinal products

In this section the historical trends in falsified medicinal products will be discussed. The challenges associated with identifying the extent of the problem will be examined first, as this places the number of historical incidents in its proper context.

4.1.1 Challenges in quantifying incidents of falsified medicinal products

Because precise and detailed data is difficult to obtain, it is a challenge to determine the magnitude of the problem of falsified medicinal products in the EU.

Information on the number of incidents tends to be incomplete, because there is currently no obligation to report incidents. Information on falsified medicines has been gathered voluntarily by various organisations and detailed reports are available to the public only in situations where there was an impact on patient safety.

Furthermore, because there is no public, centralised system for registering incidents, cases are difficult to compare; there is no standardised definition for what is meant by an incident and how to quantify its impact. A clear definition of what constitutes an incident is required before the number of incidents can be correctly calculated, so that for example 'one reported case' consisting of a shipping container filled with falsified medicines should not be considered the same as 'one reported case' of a postal package containing a blister pack with fake pills.

4.1.2 Incidents of falsified medicinal products in the past five years

We have gathered information from various sources to provide an overview of incidents in the past five years. The sources of information that are available include reports from various organisations, marketing authorisation holders (hereinafter: MAHs), and drug regulatory and enforcement authorities.

Regulatory authorities such as the FDA, Interpol, EU and PSI have published figures on a semi-regular basis relating to known cases of falsified medicinal products. As seen in the table below, the figures available do not always differentiate between products meant for the legal or illegal supply chains and in many cases the (final) destination of these products is unknown. Nevertheless, the information available still provides a rough overview of incidents.

Body	EU ⁹	Interpol ¹⁰	FDA ¹¹	PSI ¹²	MHR ^{A13}	MHRA
Region	EU	World	USA	World	UK	UK
Supply chain (legal/illicit) ¹⁴	Both	illicit	Both	Both	Legal	Both
# of	articles ¹⁵	pills ¹⁶	incidents ¹⁷	incidents ¹⁸	selected incidents ¹⁹	incidents ²⁰
Year						
2007	4,081,056	-	31	1,759	4	4
2008	8,891,056	-	56	1,834	0	0
2009	11,462,533	167,000	65	2,003	1	1
2010	3,200,492	>2,000,000	72	2,054	0	0
2011	27,460,538	2,400,000	59	1,986	2	8
2012 ²¹	-	3,750,000	-	-	0	2

These sources all emphasise the complexity of estimating the actual number of incidents. Despite this they conclude that counterfeiting is a problem, the rate of growth is uncertain and there is no indication that the issue will become less serious in the near future if no countermeasures are taken.

⁹ http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/2012_ipr_statistics_en.pdf and similar reports.

¹⁰ These figures relate to operation Pangea, which focuses on combating the sale of illegal medicines online. Other operations relating to falsified medicinal products are operation Mamba, Storm and Cobra. Source: <http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations>.

¹¹ http://www.healthcaredistribution.org/meetings/seminars/2011tnt/FDA_Presentation.pdf.

¹² <http://www.ifpma.org/global-health/counterfeits.html>.

¹³ <http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Adviceandinformationforconsumers/counterfeitmedicinesanddevices/FalsifiedMedicineRecallsandpreviouslyseencounterfeits/index.htm>.

¹⁴ The legal and illicit supply chains are described in more detail in section 4.2.2.

¹⁵ The number of articles is counted as numbers of individual pieces and also includes counterfeit medical devices.

¹⁶ Other statistics are also available such as number of arrests, sites closed etc.

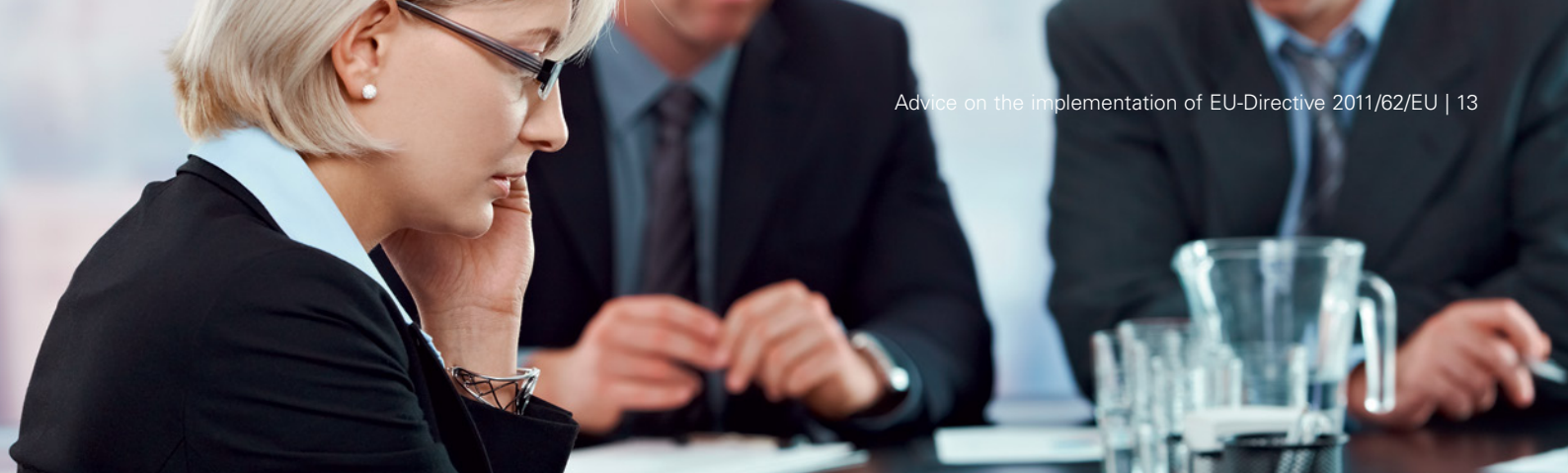
¹⁷ This is the number of counterfeit drug cases opened by the FDA that year.

¹⁸ These incidents also include pharmaceutical theft.

¹⁹ These are (selected) incidents that have entered the UK legal supply chain or are only discovered at wholesale level.

²⁰ Both products that have been discovered in the licensed UK supply chain; and products that present a risk to the UK licensed supply chain.

²¹ At the time of writing the 2012 annual report numbers have not been released by PSI, EU, and FDA.



4.2 Contributory factors

When looking at the cases of falsified medicinal products, we see two key interrelated contributory factors that influence the likelihood of counterfeiting occurring:

- Regulatory system: Weak regulatory systems with little or no disciplinary action;
- Supply chain: The illegal supply chain provides easy access for consumers and counterfeits.

4.2.1 Influence of regulatory systems on the number of incidents

According to the latest estimates²² from IMPACT²³, a distinction can be made based on geographical regions. As expected, certain less-regulated countries in Africa, Asia and parts of Latin America have areas where more than 30% of medicines sold can be counterfeit. In a large part of the former Soviet states, more than 20% of the market value is thought to be counterfeit. These countries are less developed in terms of laws and regulations, and thus their pharmaceutical supply chains are more vulnerable to breaches and other incidents. Insufficient penal sanctions make counterfeiting attractive for criminals,²⁴ whereas most industrialised countries with effective regulatory systems and market control have a smaller proportion of falsified medicinal products in the legal supply chain (i.e. much lower than 1%)²⁵.

4.2.2 Incidents outside of the legal supply chain

Reported cases concerning falsified medicinal products within the EU occur mainly outside of the legal supply chain²⁶. The internet²⁷ allows individuals to remain relatively anonymous when buying popular lifestyle drugs (e.g., weight loss medicines) or so-called 'shame drugs' (e.g., erectile dysfunction medicines²⁸). Additionally, medicinal products that are in high demand or even forbidden by law are traded more easily²⁹ over the internet.



²² <http://www.who.int/impact/FinalBrochureWHA2008a.pdf>.

²³ International Medical Products Anti-Counterfeiting Taskforce of the World Health Organisation

²⁴ <http://www.fip.org/files/fip/CounterfeitMedicinesTonX.pdf>.

²⁵ http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/counterfeit-ia_en.pdf, Annex 6.

²⁶ <http://www.fasken.com/files/Publication/b9956381-caf9-4017-8b3a-2600b2210725/Presentation/PublicationAttachment/f54feded-9733-4a0d-9198-eae1af468c23/The%20Falsified%20Medicines%20Directive%20Bulletin.pdf>.

²⁷ When we mention internet sales, we mean the illicit supply chain and not sites that are connected to a licensed pharmacy.

²⁸ <http://www.mhra.gov.uk/PrintPreview/DefaultSP/CON108892>.

²⁹ <http://www.independent.ie/lifestyle/health/women-warned-of-dangers-from-illegal-abortion-pills-sold-online-26896287.html>.



4.3 Conclusion

The EU indicates that there is an alarming increase in falsified medicines being discovered. We found that this statement is difficult to substantiate, due to inconsistent and incomplete registration of falsified medicinal products. The figures that are available indicate that falsification of medicinal products exists, but the rate of growth is uncertain. Additionally, we found that the falsification of medicinal products is mainly concentrated outside of the EU or outside of the EU legal supply chain.

We do agree with the EC's initiative for the Directive, for the following reasons:

- There may not be a major problem with the falsification of medicinal products within the legal supply chain of the EU at the moment, but this could change in the future. Due to the potentially devastating effects of falsified medicinal products on consumers, this topic merits attention and is to be taken seriously;
- Adding safety features to medicinal products within the legal supply chain could increase consumers' trust in the legal supply chain, since products outside the legal supply chain do not carry such features. This may convince consumers who buy their medication outside the legal supply chain to switch back;
- Based on interviews with stakeholders we found that in some cases medicinal products are traded from outside into the legal supply chain. Therefore, we recognise the possibility and risk that the problem of falsified medicinal products outside the legal supply chain could affect the situation within the legal supply chain in the future.

5. Risk Assessment

As explained in Chapter 3.1.3, the goal of Article 54.a.2 of the Directive is to determine which medicinal products shall or shall not be obliged to bear the safety features, taking into consideration the cost-effectiveness in the form of a risk assessment.

The Directive states that medicinal products not subject to prescription ('over the counter', hereinafter: 'OTC') shall in principle not bear the safety features (Article 54.a.1). This is remarkable, as several of these OTC products contain the same active ingredients as some medicinal products subject to prescription. Additionally, the OTC supply chain is much less regulated. For these reasons, OTC products are just as threatened by counterfeiting as prescribed medicinal products and therefore we suggest including these in the assessments for the safety feature requirements.

In this chapter we will discuss each criterion listed in Chapter 3.2 and provide input and insight into the possible weight and application of each criterion.

5.1 The price and volume of the medicinal product

The first criteria of the risk assessment mentioned in the Directive are the price and volume of the medicinal product.

5.1.1 Price versus profit margin

Generally counterfeiters are interested in maximising their profits, which is determined by the profit-volume ratio.

The profit margin can be defined as the difference between the price for which the falsified product can be sold and the cost of goods sold, which includes production costs. However, the production costs for the counterfeiter are lower than for the manufacturer, as the counterfeiter often skips or skimps on the active ingredient and does not have to comply with regulations on production, e.g. counterfeiters have been found³⁰ to use chalk or glucose as the primary ingredient for falsified medicinal products.

When the costs for the active ingredient of the medicinal product are taken out of the equation, only certain minimum production costs (e.g. for imitating packaging, leaflets and pills) remain. These minimum production costs are fairly independent of the type of medicinal product, therefore, the price of the medicinal product is a good indicator for the profit margin the counterfeiter can expect when selling the falsified medicinal product in the legal supply chain.

³⁰ <http://edition.cnn.com/2012/07/17/health/living-well/falsified-medicine-bate>.



5.1.2 Point of entry into the legal supply chain

The volume and the sales price for a counterfeiter are closely linked to the point of entry of the medicinal product into the legal supply chain. The selling price at the beginning of the distribution process (e.g. between manufacturer and wholesaler) is relatively low in comparison to the selling price at the end of the distribution process (e.g. at the retail pharmacy). Also, at an early stage in the supply chain it is easier for the counterfeiter to introduce relatively large volumes of the medicinal product. For instance, due to their function in the supply chain, a wholesaler's primary business is to buy and sell in larger volumes of dispensing units. A pharmacy deals with smaller volumes of dispensing units, as it buys and maintains inventory based on its patients' needs and is unlikely to maintain inventory levels anywhere close to that of a wholesaler.

The counterfeiter will try to maximise its profits by one of the following:

- Selling to the wholesaler where high volumes can be sold at a lower price;
- Selling to the retailer where lower volumes can be sold but at a higher price;
- Selling to the patient where the lowest volume can be sold at the highest price.

Therefore, while using the criteria of price and volume in the risk assessment, we advise also taking the point of entry into the supply chain into consideration when determining a minimum price and volume for the white list.

5.1.3 Larger volumes, more risk

From the perspective of a counterfeiter there are, however, certain difficulties around pushing large volumes of falsified medicinal products in the legal supply chain. As mentioned above, relatively large volumes are usually traded in the early stages of the supply chain involving a limited number of related parties. Trading very large amounts of falsified medicinal products creates a risk for the counterfeiter as it attracts more attention. Moreover, due to the limited number of related parties, it is easier to trace the medicinal products back to their origin if and when they are discovered.

Based on our experience in the field of anti-counterfeiting, sophisticated counterfeiters tend to mitigate this risk by introducing smaller volumes over time through different parties.

5.1.4 Specialty products

A specific category of medicinal products, referred to as 'specialty products' exists for which the price is extremely high and volumes are very low (e.g. orphan drugs³¹). These specialty products are often packed at the manufacturer specifically for a single person when ordered by the dispensing pharmacy. The name of this person is often even stated on the label of the package. Due to their traceability, these products are generally not interesting for a counterfeiter and could be added to the white list by default. Figure 1 summarises considerations for applying the price and volume criteria in the risk assessment.

³¹ An orphan drug is a type medicine that has been developed specifically to treat a rare medical condition.

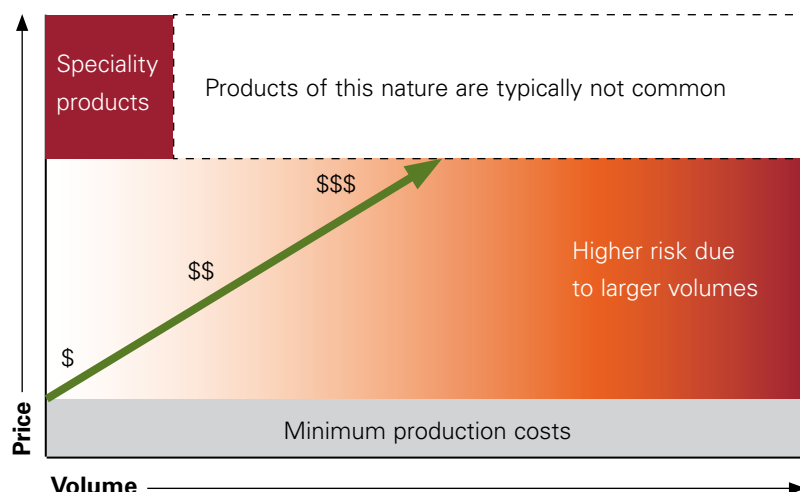


Figure 1: Illustration of how the criteria 'price' and 'volume' influence the incentive to counterfeit

5.2 The number and frequency of previous cases of falsified medicinal products concerned

The second criterion of the risk assessment mentioned in the Directive reads: *"The number and frequency of previous cases of falsified medicinal products being reported within the Union and in third countries and the evolution of the number and frequency of such cases to date."*

By including this criterion in the risk assessment, it is implied that the number of falsifications in the past is an indicator for the chance of falsification in the future. Where there was more falsification in the past, the risk of falsification is higher, more controls are therefore required, and the product should not be placed on the white list. It also implies that the product continues to present a risk to public safety.

Although historical information is valuable when trying to quantify the risk of falsification, the exact interpretation of this information should be considered carefully (as discussed in Chapter 4):

- To be able to use historical data with regards to 'numbers' and 'frequencies' of incidents, it needs to be clear what is meant by an incident and how to quantify its impact;
- The words 'being reported' indicate that some form of registration of detected cases should be or is in place. To our knowledge there is currently no centralised system in existence for registering incidents of falsified medicine within the EU or globally, nor are we aware of any protocol for sharing information on incidents of falsified medicinal products. In the absence of a controlled centralised registration system or protocol for sharing this information one would have great difficulties comparing, let alone quantifying, the various incidents;



- The part ‘in third countries’ suggests that registration³² in the rest of the world is in place. Besides the obvious issues concerning the completeness and reliability of worldwide registrations, the relevance of this criterion can be questioned because of the incomparability between the regulations in the EU and third countries – counterfeit incentives in Africa are probably very different to those in the EU³³ and the reliability of these numbers is therefore not self evident;
- ‘The evolution of the number and frequency of such cases to date’ suggests that changes in volumes registered over time should affect the risk assessment as well. It is evident that a significant increase or decrease in the volume of registrations provides an indication of the degree to which medicinal products are being counterfeited. It should be considered that since no structured registration is currently in place, every change in the registration method will lead to a change in results. Careful consideration should be given to applying this criterion in the risk assessment to avoid the situation where changes in the registration method lead to incorrect results.

5.3 The specific characteristics of the medicinal products concerned

The third criterion of the risk assessment mentioned in the Directive is ‘the specific characteristics of the medicinal products concerned’.

This criterion should be interpreted as the various features of medicinal products that influence their attractiveness for falsification. We distinguish the following categories of features:

- Medication that, by its nature, has the tendency to be bought outside of the legal supply chain (shame, secretive usage, etc.);
- Medication that, because of its effect, cannot be easily obtained through the legal supply chain (steroids, doping, etc.);
- Medication that, for legal reasons, cannot be obtained through the legal supply chain (permission not yet granted);
- Medication that, because of reimbursement rules or insurance policies can be difficult to obtain through the legal supply chain.



³² With ‘registration’ the registration of cases of falsified medicinal products is meant.

³³ To illustrate this point we note that there are indeed serious problems with substandard falsified medicine in third countries, but effective controls on the distribution of pharmaceutical products have sharply limited the distribution of counterfeit products in the EU (OECD: the economic impact of counterfeiting and piracy). This is also reflected in the WHO estimates (2009) which indicate that most developed countries with effective regulatory systems and market control currently have a very low proportion of falsified medicinal products (less than 1% of market value), while many developing countries have areas where more than 30% of the medicine sale can be counterfeit. (WHO: <http://www.who.int/medicines/services/counterfeit/impact/TheNewEstimatesCounterfeit.pdf>).

As the part of the Directive that we studied applies only to the legal supply chain in the EU (see Chapter 3), the safety features proposed by the Directive will not protect consumers who buy the above-mentioned categories outside of the legal supply chain. However, some medicinal products in the above-mentioned categories can be obtained through the legal supply chain. Based on our experience, we have found that because these products are available in large quantities outside the legal supply chain, stakeholders buy them outside the legal supply chain and bring them into the legal supply chain. Therefore, medicinal products that are available in large quantities outside the legal supply chain should be considered for the requirement of bearing the safety features (based on the other criteria).

5.4 The severity of the conditions intended to be treated

The fourth criterion of the risk assessment mentioned in the Directive is the severity of the conditions intended to be treated.

It is highly debatable whether this criterion is important when taking into account the perspective of a counterfeiter. Multiple examples exist³⁴ which show that the behaviour of counterfeiters is rarely influenced by the consequences of selling inferior-quality falsified products. However, when a person's life depends on the application of a medicinal product, one may want to consider adding safety features to the product, even if the chance of it being counterfeited is very low.

It must also be considered that by defining this criterion in the Directive, one would have to assume that the conditions to be treated and their severity are always clear. This could be the case for certain medicinal products that are designed to treat specific health issues, however, there are also medicinal products that can be used to treat different kinds of conditions or conditions of varying severity. Additionally, the consequences of applying a falsified medicinal product can be highly dependent on the physical state of the person in question (e.g. an elderly person can be more dependent on their daily medication than a teenager). For these reasons, applying this criterion in the risk assessment can be extremely complex.

5.5 Other potential risks to public health

Based on our experience and the research we have carried out, we have not been able to identify other possible criteria for the Risk Assessment.

³⁴ This shows up for example in a survey conducted by the World Health Organisation in 2007, which estimated that 20,000 people lose their lives every year globally due to consumption of fake medicines, especially malaria pills. (East African Business Week by Emma Onyango, 15 April 2012). Another example is that several dozen babies died of malnutrition in rural central China after being fed fake baby milk powder which contained little nutritional value. The babies' heads grew abnormally large while their torsos, arms and legs were just skin and bones. (http://en.wikipedia.org/wiki/2008_Chinese_milk_scandal) In relation to airplane parts, a 14-month investigation by the powerful US Senate Armed Services Committee concluded in 2012 that counterfeit parts in the Hercules transports and other American-made military equipment are prone to failure with potentially 'catastrophic consequences.' (Greg Weston, CBC News, Posted: 9 January 2013).



5.6 Conclusion

In this chapter we have discussed each of the criteria for the Risk Assessment, as proposed by the Directive. Based on this discussion, we can conclude that the most important criterion is the combination of price and volume: the higher the outcome of the 'price times volume' calculation for a medicinal product, the higher the potential profit for the counterfeiter and therefore it is more attractive to falsify and more important to attach safety features.

The criterion of 'number and frequency of previous cases of falsified medicinal products' could be a good way of identifying medicinal products that should bear safety features. However, at the moment, there is not a global centralised system that registers incidents of falsified medicine in a consistent matter. Therefore, the development of such a system would be required ahead of applying this criterion. The criterion of 'specific characteristics of the medicinal products concerned' is only relevant for medicinal products that (because of their characteristics) are mainly sold outside of the legal supply chain and are brought in by stakeholders as they are easily available.

Finally, we propose that the EU should be cautious about applying the criterion of 'severity of the conditions intended to be treated' in the Risk Assessment, as this is a very complex criterion to apply. Perhaps it is possible to define a limited number of medical products that, because of the severity of the conditions they are intended to treat, should never be placed on a white list.

6. Considerations for implementation

One of the measures of the EU directive is to add safety features to allow verification of the authenticity of medicinal products subject to prescription and identify individual packs. More specifically, in accordance with Article 54.a.2 of the Directive, the delegated acts shall set out the modalities for the verification of the safety features by the manufacturers, wholesalers, pharmacists and persons authorised.

Although the Directive does not mention any details on how the EC plans to execute these projects, the Directive suggests that this project will be implemented simultaneously for all medicinal products that are in scope based on the results of the risk assessment (see Chapter 5). Once fully operational, such an EU-wide system will need to involve all 27 member states³⁵ in 23 official languages³⁶, an unknown number of dispensing doctors, hospitals, and other health professionals and approximately 17 billion medicines subject to prescription³⁷ annually.

In this chapter, we address a number of challenges and considerations that the EC will face when implementing a system on that scale. By doing so, we provide input that can help mitigate the possible risk of failure and the exceeding of budgeted time or costs. The challenges are divided in the following categories: 'concept', 'organisation', 'technical details and infrastructure' and 'financial'. Chapters 6.1 to 6.4 will each cover one of these categories and we will end this chapter with a conclusion of our considerations.

6.1 The concept

We agree with the Directive that a mass serialisation concept could be a suitable solution to prevent falsified medicinal products from entering into the EU legal supply chain. When developing such a large scale serialisation project, a number of concerns come to mind.

6.1.1 Differences in classification per country

At the moment, there are still differences in the classification of medicine between the member states of the EU. For instance, medicinal products can be considered prescribed in one member state while they are considered OTC in another. As the Directive applies to prescribed medicinal products only, safety features will have to be applied by manufacturers and repackagers depending on the country to which the products are to be shipped.

³⁵ As of April 2013: http://europa.eu/about-eu/countries/index_en.htm.

³⁶ http://ec.europa.eu/education/languages/pdf/doc3275_en.pdf.

³⁷ This number was estimated, as different sources give different numbers, depending on definitions of prescribed medicines, the area (EU or Europe) and the period. A paper by the EC (http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/counterfeit-ia_en.pdf) states 15 billion medicines during 2008, while the public consultation states 18 billion annually.



6.1.2 Flexibility for growth and other potential use(s)

In addition to preventing falsified medicinal products from entering the supply chain in the EU, such an advanced data repository and verification system provides the opportunity for other uses, such as direct ordering, dialogue between pharmacists and patients, facilitation of reimbursement, and connection to patient information systems for pharmacists. In order to take advantage of these potential benefits, the systems require flexibility to expand into other domains in the future. Therefore it is highly recommended to design the system(s) in such a way that adding on new features is possible without having to rebuild systems or part thereof. It would be sensible for manufacturing authorisation holders to consider participating in serialisation concepts voluntarily because of the additional advantages they can offer patients and pharmacists.

6.1.3 Code harvesting

In concept, the data repository and verification system will hold a unique identification code for each medicinal product that enters that legal supply chain and will register once the product is dispensed to the consumer, i.e. by scanning the identification code. This way, each unique identification number can only be dispensed once.

There are conceivable situations in which an authentic medicinal product is dispensed to the consumer and the identification number is not registered as 'dispensed' in the system. This could for instance be the case when certain groups of dispensing stakeholders are not (yet) using the system. This creates the opportunity for counterfeiters to collect ('harvest') these un-dispensed codes and use them on their falsified medicinal products.

Based on interviews with various stakeholders, we found that there is limited understanding of the risk of code harvesting and no clear strategy is in place to mitigate against this risk. Therefore, more thought and dialogue is required on this subject and we suggest that the delegated acts should incorporate a strategy against the risk of code harvesting.

6.1.4 Tamper-evident packaging

Article 54.o of the Directive states that techniques should be in place allowing verification of whether the outer packaging of a medicinal product has been opened or tampered with.

Based on our research, tampering with the packaging of products currently occurs on a very small scale, by stealing or replacing the contents of the product for personal use and re-sealing the packaging to avoid discovery³⁸. This small-scale occurrence is not surprising, as performing such actions on a large scale would still require the counterfeiting of packaging in order to sell the product on to a stakeholder in the legal supply chain and in that way gain a financial benefit. Therefore tampering with packaging cannot be seen as a large problem within the legal supply chain of medicinal products.

Additionally, the European Committee for Standardisation³⁹ is currently developing a CEN standard for the official definition of tamper-evident packaging. Once this CEN standard is published, the requirements for the packaging of medicinal products will become clear.

However, the tamper-evident packaging techniques that are being required by the Directive do not provide security, as they are easy to imitate. One option currently being considered is shrink-wrapping. Shrink-wrap can be easily obtained and is cheap to imitate (a second-hand shrink-wrapping machine can be acquired for as little as €1,500 on eBay⁴⁰). Implementing tamper-evident packaging using techniques that are not proven to be effective creates the risk of giving a false sense of security to the consumers.

In order to overcome the issue of imitation mentioned above, one could add genuine marks to the tamper-evident packaging to recognise their authenticity. However, this leads to a number of costly activities that would need to be executed:

- Strong genuine marks need to be developed for the different types of tamper-evident packaging;
- Manufacturers and repackagers need to be supplied with the technology and materials to apply these genuine marks;
- The dispensing stakeholders (and possibly also others) need to be trained and supplied with the right equipment to check whether the correct genuine marks are in place.

The arguments mentioned above show that implementing effective tamper-evident packaging is a difficult and costly task.

Considering the arguments mentioned in this section, we advise the EC to take the necessary steps to be able to at least postpone setting out requirements for tamper-evident packaging in the delegated act until a later point in time. This will give the EC some time to re-assess whether tamper-evident packaging is necessary once the unique identifier verification system is in place.

³⁸ For example: <http://listverse.com/2010/12/27/10-notorious-cases-of-product-tampering/>. Only two cases within this list relate to medicinal products and date back from the 1982 and 1998.

³⁹ Based on a working draft WI00261406, by technical committee CEN/TC-261 'Packaging'.

⁴⁰ http://www.ebay.com/itm/Smipack-S870-L-Sealer-Shrink-Wrap-Machine-Largest-Model-/271171059165?pt=UK_Packaging_Materials&hash=item3f230dfddd.

6.2 Organisation

Setting up a successful repository and verification system requires a major organisational component to be in place in order for it to work effectively on a day-to-day basis. This section will point out a number of challenging organisational components.

6.2.1 Procedures

To ensure that the repository and verification system is consistently used throughout the EU, clear and effective procedures need to be formalised for the activities that take place, such as:

- In time, one can expect that new medicinal products will enter the market and attributes (such as price, name, volume etc.) of existing products constantly change. These changes may cause the EU to re-assess the presence of products on the white/black lists. Therefore, it is essential that there are procedures for maintaining the white/black lists, implementing changes in the repository system and notifying them to the relevant stakeholders (e.g. suppliers of the specific medicinal product) in a timely manner. Furthermore, the EC should take into account the challenges around adding and removing products from the white/black lists (e.g. code harvesting, timeframes for complying). Based on interviews, we found that it can take several months for smaller suppliers to adjust their production process for adding a unique identifier to the packaging of medicinal products;
- It remains to be seen whether the Directive provides enough incentive for every dispensing stakeholder to actually follow through with the verification of each individual dispensed unit. For instance, some pharmacies may find that the system is difficult to work with or costs them too much time to operate. Forcing these pharmacies by law to comply may not be sufficient;
- Medicinal products are produced for distribution to multiple countries and the ultimate dispensing country is unclear (commonly referred to as 'multi-country packs'). Manufacturers may choose this practice to help cut costs in their supply chain. With respect to the directive, this would create a problem as the manufacturer does not know the country of dispense at the time when the unique identifier is typically added to the package. The EU should address this issue in the delegated acts;
- In order to comply with local language and regulations, imported medicinal products are often repackaged when distributed across borders within the EU (commonly referred to as 'parallel trade'). It is important that procedures are in place to instruct repackagers when and by whom unique identifiers should be replaced. Based on an interview, we found that currently these procedures need to be developed. The current procedure is that within a batch all old identification codes (generated by the manufacturer) will be linked to a batch of new codes (generated by the repackager) in the system on an aggregated level. Therefore, tracking and tracing of a single medicinal product can become complicated;



- The delegated acts should take into account other points of dispense other than typical retail pharmacies and wholesalers. The point of dispense of a medicinal product can be a prison, ship, healthcare professional, hospital, etc. Based on the responses to the public consultation, we found that in Austria dispensing doctors are common practice and make up 41% of the total of points of dispense in the country. For such points of dispense, the unit of dispense can differ from the unit of packaging e.g. almost all hospitals dispense from bulk packages (e.g. containers with 500 pills). The unique identifier and tamper-evident packaging can still not guarantee patient safety in such situations, as they cannot be verified at the moment the product is dispensed to the consumer.

6.2.2 Support

Before the repository and verification system can be fully operational, the users of the systems (e.g. employees of the pharmacies and wholesalers/repackagers) require training in the use of the system. Once the system is up and running, the users need to be able to receive ad hoc support when they run into difficulties (e.g. damaged packages, unreadable unique identifiers). For this reason, helpdesks will need to be set up and properly staffed for immediate responses to questions. Bear in mind that such helpdesks would need to provide 24-hour coverage to approximately 4,600 manufacturers within the pharmaceutical industry⁴¹ and 177,000 points of dispense⁴².

6.2.3 Handling of exceptions

In verifying the authenticity of a medicinal product, an 'exception' can occur in the event of an invalid unique identification code or if the code has already been registered as 'dispensed', indicating a possibly falsified medicinal product. In case of such an exception the medicinal product cannot be dispensed and a case management process will have to be started. During this case management process, different parties will spend time identifying the cause of the exception and take steps required for remediation (e.g. send the product back to the supplier where it will be investigated in detail). In addition to suspected falsified medicinal products, this case management process would also handle issues of damaged labels and poorly printed or duplicate printed codes at the supplier (false positives). Based on an estimated 17 billion medicinal packs dispensed annually in the EU, mentioned in the beginning of this chapter, and assuming that 0.01% (1 in every 10,000) of these products will cause an exception, the verification system will generate 7,000 exceptions every day⁴³. This can cost a significant amount of time for all the parties involved (e.g. manufacturer, wholesaler and pharmacist).

6.2.4 Governing body

Once the system is operational, a central governing body is required to make decisions affecting national repository systems. This will become necessary during emergency situations, when recalls of invalid unique identification codes or drug recalls need to be executed.

⁴¹ http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Manufacture_of_pharmaceuticals_statistics_-_NACE_Rev._2.

⁴² Estimate based on approximately 154,000 community pharmacies (http://ec.europa.eu/health/files/falsified_medicines/2012-06_safety-features/pgeu_2_en.pdf), approximately 3,000 dispensing doctors (answer PGEU from public consultation) and 20,000 hospitals (4 per 100,000 inhabitants EU) (http://www.euro.who.int/__data/assets/pdf_file/0004/98401/E74486.pdf).

⁴³ Based on 220 working days per year and assuming around 90% of medicines will have to bear the safety features.



6.2.5 Operational risk

There are numerous operational risks once the repository and verification system is in place, such as:

- Failure of essential components of the system (e.g. disruption of repository servers);
- Breach of the system's digital or physical security. It will not only be counterfeiters who are interested in the information within the repository system, but also hackers with other kinds of motivations (e.g. to sell data for marketing purposes or simply for fun);
- Theft or loss of data (violating data privacy laws). The data that the repository systems will hold will be valuable, especially if there is a link to personal information (e.g. if the system is also used for reimbursement purposes).

Due to the importance of the system, the occurrence of the incidents mentioned above can be very costly and unexpected. In addition to this, the possible consequences of these incidents should be investigated. For instance, failure of essential components or security breaches could lead to falsified medicines reaching patients undetected and cause health problems. Publicity about these cases could harm the credibility of the system as a whole and the trust of the consumers in the legal supply chain.

Therefore, it is essential that the delegated acts state requirements for how these risks should be managed in the event they occur and to put in place preventive, detection and response measures.

6.3 Technical issues and infrastructure

A large component of a successful repository and verification system is relying on the well-executed technical aspects. It is likely that the system will consist of multiple interlinking systems and devices which can be located throughout the different countries of the EU. In this section we will highlight a number of important considerations when implementing such a large-scale system.

6.3.1 Scale

As mentioned at the beginning of this chapter, approximately 17 billion medicinal products enter the legal supply chain of the EU annually. As the white/black lists serve as exceptions, we anticipate that a majority of the 17 billion medicinal products will require the safety features proposed in the Directive. Setting up a system that is capable of storing and communicating this amount of data throughout the EU is very challenging. Any minor hiccups on that scale could result in high remediation costs that could be avoided or minimised if they were discovered and resolved during a pilot project. Therefore, we suggest the EC considers a phased approach in which the system can be piloted on a smaller scale and then be rolled out in phases, ensuring that each phase is well-established before moving on to the next one. This will provide valuable insights and the ability to build a more robust and sustainable system, to which large volumes of data are added each year.

6.3.2 Harmonisation across national systems

The Directive states a number of requirements for the implementation of the data repository and verification system and the safety features, but leaves space for further interpretation in the delegated acts. In this way a vacuum was created and at this moment, stakeholders are trying to fill up this vacuum.

For instance, stakeholder groups are proposing different data repository and verification systems. During our interviews we learned that EFPIA⁴⁴ has already completed the supplier selection phase for their system called 'ESM' and are planning to have a prototype ready before the end of 2013⁴⁵. Another stakeholder, the EDQM⁴⁶, has created a blueprint for their system called eTact⁴⁷, which is based on their own interpretation of the Directive. At the same time, other stakeholders might also be planning to design a system. Finally, there are a few countries that already have a repository or verification system in places for other purposes such as reimbursement control (e.g. Turkey and Belgium).

Based on the current situation described above, a situation may evolve in which every country chooses to use a different system and possibly even a situation in which multiple systems are being used within a single country. Independent of how the EC chooses to set up the overall infrastructure, this will require the complex task of interlinking the systems (e.g. centralised EU hub) and making sure that duplicated information is synchronised across systems. Additionally, every system has its own definitions and methods of storing information, which could lead to false interpretation of information when combining the information across systems. Especially when we combine this challenge with the scale described in the previous section, relatively small interpretation or synchronisation issues could lead to very problematic situations diminishing the credibility of the system as a whole.

⁴⁴ EFPIA: European Federation of Pharmaceutical Industries and Associations.

⁴⁵ <http://www.efpia.eu/esm>.

⁴⁶ EDQM: European Directorate for the Quality of Medicines & HealthCare.

⁴⁷ <http://www.edqm.eu/en/eTACT-1466.html>.

6.3.3 High-speed data connection

Another challenge with respect to the verification at the point of dispense, is the use and availability of high-speed data connections. According to a study conducted by the EU in 2011, broadband coverage is below 80% in Lithuania, Poland, Romania and Slovenia. Also, we have to keep in mind that at some points of dispense in Europe that are not heavily populated, no internet connection is available at all (e.g. Highlands in Scotland or a doctor dispensing medicine from his car in Romania). Untimely verification or failure to scan could potentially lead to a code-harvesting problem (see Chapter 6.2). The challenge described above could be overcome if the delegated act did not require the verification to always take place at the 'moment of dispense' (i.e. at the moment the product is handed over to the consumer). In that case, for regions where high-speed data connections are rare, the verification could be performed at a central location ahead of distributing the medicinal products to the actual points of dispense. Although this would solve the issue, it does create the risk that falsified medicines could be brought into this final distribution channel without being detected.

6.3.4 Consumer access

The EC could consider providing consumers with a way of accessing the repository and verification system. For instance, an application for mobile devices could enable the consumer of a dispensed product to scan the unique identifier on the product, serving the following purposes:

- The application could supply additional information to the consumer, for example about the medicinal condition the product is intended to treat and instructions on how the medicine should be used;
- The scan by the consumer indicates that the medicinal product has been dispensed. This information can be uploaded to the repository system and the system can check whether all preceding steps in the verification process have been executed and registered correctly (e.g. has the unique identifier been scanned at the point of dispense). In this way, points of dispense that cause problems can be identified better and suitable actions can be initiated.





6.4 Financial

It is inevitable that putting in place a system such as that described in the Directive will require substantial investments by stakeholders. This raises questions about how large this investment will be and how this investment will be allocated across the stakeholders. In this section, these questions will be considered.

6.4.1 Uncertainties

Based on the Directive, there are key questions around organisation, governance and infrastructure that remain open and would greatly influence the total costs of implementation. Based on responses to the Public Consultation, we found that different stakeholders have very diverse expectations on how these key questions will be answered in the delegated act. An example refers to the 'harmonised union system', as mentioned in Recital 32 of the Directive. Some stakeholders see this as a single system in which every MAH, wholesaler and dispenser has to participate, while others see it as a standardised way of operating that can be achieved using different IT systems from various suppliers. The decisions must be carefully spelled out as the cost implications could be significant (e.g. multiple scanners, software systems).

6.4.2 Burden of costs

Based on interviews and the responses to the public consultation, we found that a key topic is how the costs required for the implementation and maintenance of the safety features will be allocated. The Directive states (Article 54.a.2.e) that the costs of the repository system shall be borne by manufacturing authorisation holders. Based on this, a number of important considerations come to mind:

- Depending on the exact approach of the risk assessment, some medicinal products will be in scope and others will be out of scope for the safety feature requirement. The question that arises is whether it is reasonable that only the manufacturing authorisation holders producing in-scope products will share the costs of the safety features or whether they should be allocated over the whole industry;
- For the moment, consider the situation where only the manufacturing authorisation holders producing in-scope products will share the costs. The group of in-scope products may change over time as the risk assessment is being re-evaluated and characteristics (such as price and volume) of medicinal products evolve. In this way, new parties may be added to the group of manufacturing authorisation holders sharing the costs. This poses a dilemma, since a large part of the initial implementation costs have already been paid for. As these new manufacturing authorisation holders benefit from the initial implementation, it is fair to say that they should also bear part of the costs, but how much? A similar dilemma exists for manufacturing authorisation holders that no longer hold medicinal products that require safety features. These manufacturing authorisation holders have paid for the initial implementation of the safety features, but no longer benefit from it. Will these manufacturing authorisation holders be reimbursed for part of their investment?
- As mentioned in Chapter 6.1, the repository and verification system could have a number of additional benefits (e.g. automated reimbursement, supply chain optimisation). These additional benefits may save operational costs for all stakeholders as well as for external organisations (e.g. governments, insurance companies). Therefore, in order to compensate for these benefits, other stakeholders (other than the manufacturing authorisation holders) and these external organisations could bear part of the investment in the system as well in the long run;



- Since at least some manufacturing authorisation holders will have to bear the costs of the safety features, it is important to realise that these costs may be added to the sales price of the medicinal products therefore consumers may end up having to pay for the safety features;
- The costs for the modification of existing IT systems and packaging lines can be considerable and contain a large fixed component. In relation to the number of medicinal products produced, these costs are much higher for smaller manufacturing authorisation holders than they are for the larger ones. This may result in smaller manufacturing authorisation holders withdrawing certain products from the EU market or a considerable rise in prices for products they produce. The EC could consider reimbursing part of these costs or minimising participation costs for smaller manufacturing authorisation holders to avoid or minimise these risks.

6.4.3 Cost-effectiveness

Article 54.a.2.a of the directive states the following:

'When establishing the safety features, due consideration shall be given to their cost-effectiveness.' In general, taking the cost-effectiveness into consideration when setting up a project that introduces new measures is important, as the investment should lead to notable benefits. However, in case of the Directive, the definition of cost-effectiveness requires clarification, as it can be interpreted in different ways:

- First of all, one could look at cost-effectiveness when choosing the measures and the scale on which they should be implemented. In case of the Directive, this could be the case when determining which medicinal products should bear the safety features.
- However, this leads to a moral dilemma, as the benefit of adding safety features could prevent health issues or even save lives. This is similar to the situation of considering cost-effectiveness when improving the safety on the roads: at what number of annual fatal car accidents have we been effective enough? There is no right answer to such questions.
- Additionally, it is very difficult to measure the cost-effectiveness of adding safety features to medicinal products. In response to adding these safety features, counterfeiters may decide to discontinue their actions due to the risk of getting caught, so one can never measure how much falsification was prevented because of the safety features;
- Another way of looking at cost-effectiveness is when considering the different ways safety features can be implemented. For instance, it is undesirable to implement the repository and verification system in such a way that it requires a lot of time for the manufacturers and pharmacies to operate. However, such requirements should be set out explicitly instead of referring to the general aspect of cost-effectiveness.

6.4.4 Scenarios

Based on the above considerations, a number of approaches can be taken towards implementing the Directive. In this section we will describe three likely scenarios⁴⁸. The cost estimates are based on assumptions and information gathered from answers to the public consultations, interviews we conducted, the ESM model presentation and our additional research. The calculations, with all their uncertainties and assumptions, are meant to provide insight for high-level consideration. Due to the fact that accurate information on projected costs is not available at the time of this report, the amounts mentioned in this chapter should only be considered as rough estimates.

The following scenarios are in line with the objective of the Directive:

- **Scenario 1** – In this scenario, 90% of all prescribed medicinal products in the legal supply chain in the EU member states will bear the safety features and will have tamper-evident packaging;
- **Scenario 2** – In this scenario, 90% of all prescribed medicinal products in the legal supply chain in the EU member states will bear the safety features and will not have tamper-evident packaging;
- **Scenario 3** – In this scenario, 40% of all prescribed medicinal products in the legal supply chain in the EU member states will bear the safety features and will not have tamper-evident packaging.

The table below shows the main findings of our study on the three scenarios with regards to patient safety, cost-effectiveness and chance for successful implementation.

	Scenario 1 90% of prescribed incl. tamper-evident packaging	Scenario 2 90% of prescribed excl. tamper-evident packaging	Scenario 3 40% of prescribed excl. tamper-evident packaging
Patient safety	Medium	Medium	Medium
Cost-effectiveness	Low	Medium	High
Potential for successful implementation	Very low	Low	Medium

⁴⁸ Note that it would be interesting to add a fourth scenario in which both OTC medicinal products and prescribed medicinal products will bear the safety features, however as this is not in line with the Directive we have not included such a scenario.



Explanation on patient safety

- **Scenario 1** – In this scenario most prescribed medicinal products are well protected. Due to the exclusion of OTC products, patient safety remains at a medium level;
- **Scenario 2** – The level of patient safety is similar to that in Scenario 1. The slightly positive effect of tamper-evident packaging will be negated by the additional time and costs needed for implementation (moment the safety level is reached), the risks of mistakes in repackaging and dispensing and the false sense of security it can possibly provide (see Chapter 6.1.4);
- **Scenario 3** – The level of patient safety is similar to that in Scenarios 1 and 2. The effect of the lower amount of products bearing safety features is limited, as these products are less threatened or not at all. At the same time, the smaller number of in-scope products will lead to a significantly shorter implementation schedule and increased credibility in the system due to infrequent disturbances and better case-management of issues.

Explanation of cost-effectiveness

- **Scenario 1** – Compared to Scenario 2, the extra costs for this scenario relate to the implementation of tamper-evident packaging within packaging lines. We estimate the costs for minimally-effective tamper-evident packaging to be approximately €500 million per year⁴⁹. As indicated above, the implementation of tamper-evident packaging barely increases the patient safety and therefore the cost-effectiveness of this scenario is relatively *low*;
- **Scenario 2** – Compared to Scenario 3, the extra costs for this scenario consist of adding safety features to a substantial additional number of products. We estimate these extra costs to be approximately €180 million per year⁵⁰. As mentioned above, these additional products are not actually threatened by falsification. However, in this scenario we do not have costs for tamper-evident packaging and therefore the cost-effectiveness of this scenario is medium;
- **Scenario 3** – The cost-effectiveness of this scenario is considered high, as the costs allow for safety features only on those medicinal products that are threatened by falsification and no costs are included for tamper-evident packaging.

⁴⁹ We estimated the costs of tamper-evident packaging based on 15 billion units of dispense per year (90% of the 17 billion mentioned in the beginning of Chapter 6), 12,000 packaging lines (http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/counterfeit-ia_en.pdf page 74) and investment costs of €150,000 per packaging line over 5 years and €0.024 per unit of dispense per year.

⁵⁰ Total costs for scenario 2 are estimated to be €730 million per year and total costs for scenario 3 are estimated to be €550 million per year.

Explanation of potential for successful implementation

- **Scenario 1** – The potential for successful implementation in this scenario is considered very low because of the considerations mentioned in Chapters 6.1 through 6.4. Implementing safety features for 90% of the products as well as tamper-evident packaging leads to a lot of complexity that can be avoided;
- **Scenario 2** – Compared to Scenario 1, the additional complexity of tamper-evident packaging (see section 6.1.4.) is avoided which raises the potential for a successful implementation from very low to low. However, this scenario still requires implementing the safety features for 15 billion (90% of 17 billion) units of dispense per year;
- **Scenario 3** – The potential for successful implementation in this scenario is considered medium as the implementation is limited to 7 billion (40% of 17 billion) units of dispense per year. For example, the handling and correction of unexpected disturbances is considerably easier on this smaller scale.





6.5 Conclusion

In this chapter we have covered a number of important points on a variety of topics. When moving from the Directive to the delegated acts and consequently towards the implementation of the safety features, these various aspects should be taken into consideration. In this way, the possible risks of failure and of exceeding the budgeted time or costs can be prevented. Dealing with most of the considerations mentioned in this chapter can be very challenging when implementing the safety features for all in-scope medicinal products at once. Implementing the safety features on a smaller scale first would make this task more manageable.

For this reason, we suggest that the implementation should follow a phased approach:

- Initially, build up the system on a smaller scale, by starting with a limited number of EU member states, and only the most threatened products (to be classified using the Risk Assessment tool) and without the tamper-evident packaging. The consequences of all expected and unexpected disturbances will be limited to these countries/products, which will be more cost-effective and minimise the risk of losing public credibility during the implementation. At the same time, an initial draft of procedures and guidelines could be prepared, for instance with respect to repackaging, multi-country packs and exceptional points of dispense (e.g. hospitals, dispensing doctors, prisons). Note that when doing such a phased implementation, one should address the risk of 'code harvesting' as not all products with unique identifiers may be dispensed at a point which is subject to the implementation requirements;
- Once the system is operational on the initial scale, other countries or medicinal products (based on the Risk Assessment) can subsequently be added. During this periodic expansion of scale, the effects on the infrastructure and organisation can be measured and additional capacity can be added along the way as needed. Then procedures and guidelines can be expanded further as new exceptions will arise. During this period, the EC can also research whether tamper-evident packaging is necessary, based on the developments within the supply chain;
- After a number of rounds of scale expansion, participation in the safety feature requirement can be extended to include all countries and relevant products.

From a financial point of view, there are many uncertainties around organisation, governance and infrastructure that can greatly influence the total costs of implementation of the safety features. These uncertainties should be worked out in detail in order to provide a good estimate of the total cost of the implementation. In order to allocate these costs, the EC may want to consider an approach in which every stakeholder bears a part of the total costs in proportion with the benefits derived.

净重 (Net Weight): Kg
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