



Council of the
European Union

Brussels, 7 October 2015
(OR. en)

11804/15
ADD 3

PHARM 32
SAN 269
MI 549
DELECT 120
ECO 106
ENT 186
COMPET 445

COVER NOTE

From:	Secretary-General of the European Commission, signed by Mr Jordi AYET PUIGARNAU, Director
date of receipt:	2 October 2015
To:	Mr Jeppe TRANHOLM-MIKKELSEN, Secretary-General of the Council of the European Union

No. Cion doc.:	SWD(2015) 189 final
Subject:	COMMISSION STAFF WORKING DOCUMENT IMPACT ASSESSMENT Accompanying the document COMMISSION DELEGATED REGULATION (EU) No .../... supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use

Delegations will find attached document SWD(2015) 189 final.

Encl.: SWD(2015) 189 final



Brussels, 2.10.2015
SWD(2015) 189 final

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT

Accompanying the document

COMMISSION DELEGATED REGULATION (EU) No .../...

**supplementing Directive 2001/83/EC of the European Parliament and of the Council by
laying down detailed rules for the safety features appearing on the packaging of
medicinal products for human use**

{C(2015) 6601 final}
{SWD(2015) 188 final}

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A. Need for action

Why? What is the problem being addressed?

The lack of obligatory technology solutions protecting medicinal products against falsification led to an increased presence of falsified medicines in the EU. To fight this problem, Directive 2011/62/EC introduces two obligatory safety features: (i) a unique identifier (a number or sequence, unique to an individual medicine pack, contained in a carrier/barcode), and (ii) an anti-tampering device. The Directive puts the Commission under the obligation to set out (i) the technical details of the unique identifier; (ii) which actor in the supply chain will verify the safety features; and (iii) who will establish and manage the repositories system storing the unique identifiers.

What is this initiative expected to achieve?

The general objective of this initiative is to step up the fight against falsified medicines by setting out the detailed rules for the safety features. The initiative should improve the protection of public health while fostering the internal market and the competitiveness of EU pharmaceutical companies.

What is the value added of action at the EU level?

Article 54a(2) of Directive 2001/62/EU obliges the Commission to adopt a delegated act setting out the characteristics and technical specifications of the unique identifier, the modalities for the verification of the safety features and the provisions on the establishment and management of the repository system containing the unique identifiers. The delegated Commission Regulation will ensure harmonised rules across the EU and equal protection to all European patients against falsified medicines. This can only be achieved at EU level.

B. Solutions

What legislative and non-legislative policy options have been considered? Is there a preferred choice or not? Why?

Only legislative options were taken into consideration, as requested by Directive 2011/62/EU. Considered options are:

1.Characteristic and technical specifications of the unique identifier

Option 1/1: Full harmonisation of both identifier composition and carrier to protect patients against falsified, recalled and expired medicines – preferred option as, in addition to protecting patients from fake medicines, it facilitates the handling of recalled and returned products and harmonises the existing national product coding systems.

Option 1/2: Partial harmonisation of the composition of the identifier: The manufacturer may choose the carrier/barcode and part of the information it contains.

2.Verification of the unique identifier

Option 2/1: Systematic verification of the unique identifier at the dispensing point (e.g. pharmacies).

Option 2/2: Systematic verification at the dispensing point plus risk-based checks by wholesale distributors - preferred option as it increases the ability of detecting fake medicines while still being cost-effective.

3. Establishment, management and access of the repository

Option 3/1: by the stakeholders, under Member States' supervision - preferred option as it allows stakeholders to set up the system better suited to their needs, while still guaranteeing supervision by national authorities.

Option 3/2: by public authorities at EU level.

Option 3/3: by public authorities at national level.

Who supports which option?

Most manufacturers, wholesale distributors, pharmacies and national competent authorities support (i) fully harmonising the technical specifications of the unique identifier (option 1/1) across the EU; (ii) a systematic check of the unique identifier at the dispensing point complemented by a risk-based check by the wholesale distributors; (iii) a repository system set up and managed by the stakeholders.

On the other hand, a limited number of generic companies favour partial harmonisation to continue using pre-printed cartons. This option will however create further costs for wholesale distributors and pharmacies. Two national medicines agencies favour either a EU or a national governance of the repository system. One agency called for national governance only.

C. Impacts of the preferred option

What are the benefits of the preferred option (if any, otherwise main ones)?

The preferred options have a positive social impact as they protect patients from falsified, recalled and expired medicines. All options have an economic impact on manufacturers due to the need to upgrade the packaging lines to apply the unique identifier, to set up and access the database. However, the preferred options mitigate costs by (i) eliminating the divergent national packaging requirements, and (ii) ensuring that wholesale distributors and pharmacies will only require one piece of software and one type of reader. The presence of risk-based checks by wholesalers allows detecting falsification earlier in the supply chain and tracing falsified medicines back to their point of entry.

What are the costs of the preferred option (if any, otherwise main ones)?

Irrespective of the options chosen, it is estimated that the costs to upgrade the packaging line for applying the unique identifier can reach €0,033 per pack of medicines. Total annual costs for originators (manufacturers of branded products) range from € 20 million to € 110 million. Total costs for generics companies range from € 30 million to € 210 million. However, these costs will be partly offset by savings stemming from the harmonisation of national coding systems and the reduced costs of handling recalls and returns.

As regards the verification of the unique identifier, the total costs of risk-based verification by wholesale distributors would be about € 33 million per year for the sector. A pharmacy/retailer or general practitioner will incur annualised costs of € 530, and a hospital pharmacy up to € 750, to modify software, buy scanners and verify authenticity.

Concerning the database costs, the experience of the current pilot stakeholder's models suggest costs can reach € 205 million/year for the manufacturers, corresponding to € 0,022 per pack of medicine.

How will businesses, SMEs and micro-enterprises be affected?

SMEs could potentially be more affected by the costs of introducing the safety features than large pharmaceutical companies, which would benefit from economy of scale. However, Directive 2011/62/EU does not provide for exemption from bearing the unique identifier based on the size of the company, as this could compromise the protection of patients.

Will there be significant impacts on national budgets and administrations?

The preferred options do not create significant direct costs for national budgets and administrations.

Will there be other significant impacts?

The consultant ECORYS assessed the impact of the implementation of the unique identifier on the competitiveness of the pharmaceutical sector, in particular on manufacturers, wholesale distributors, parallel importers and pharmacies. Taking into account the production value (ex-factory) of the sector, the cost addition appears modest at less than 1%.

D. Follow up

When will the policy be reviewed?

Directive 2011/62/EC requires the Commission to monitor the measures it takes. The Commission must submit a report to the European Parliament and to the Council to assess the rules related to the safety features at the latest five years after the date of application of the delegated acts.

PROCEDURAL ISSUES AND CONSULTATION OF INTERESTED PARTIES

1.1. Introduction

On 8 June 2011, the European Parliament and the Council adopted Directive 2011/62/EU¹², which puts in place obligatory technology solutions, including a unique identifier and an anti-tampering device, to prevent falsified medicine from entering the legal supply chain.

Falsified medicines are medicines with false identity (e.g. name, composition), history (e.g. batch number) or source which are passed off as genuine, authorised products. They are not the same as counterfeit medicines – although overlaps between the counterfeit and falsified medicines exist.³ Falsified medicines may contain ingredients, including active ingredients, which are of low quality or in the wrong dosage – either too high or too low. Since they have not gone through the necessary evaluation of quality, safety and efficacy as required by the EU legislation, they can be a major health threat. Directive 2011/62/EU strengthens public health protection by providing measures to fight the falsification of medicines even when there is no infringement of intellectual property rights.

Although incidents implicating falsified medicines have only been systematically recorded after the entry into force of the Directive in January 2013, some incidents of falsification were detected before 2013 either due to their severe public health consequence or because they also involved counterfeiting (see Annex 4). Among the more severe incidents in the last few years, contaminated heparin – a blood thinner – has been connected to dozens of deaths worldwide in 2008, including in the US and in the EU. Although the “cases” of falsified medicines reported to date are not sufficient to provide reliable statistics, they can still provide insight on the type of medicines affected and their point of entry. For example, even though most incidents implicate prescription-only brand medicines, falsifications of generic⁴ and over-the-counter⁵ medicines have also been reported. Recently, a patient in Germany noticed spelling mistakes on the label of a medicine, leading to the discovery of a considerable amount of falsified generic medicines. Falsified medicines have been detected both in the legal (e.g. authorised pharmacies, wholesalers and parallel traders) and illegal (e.g. supplies from/to unauthorised internet sites) supply chain. Falsified medicines in the legal supply chain are less prevalent in the EU, but this trend seems to be on the rise (2 cases reported in 2012 vs 12 in 2013 and 15 in 2014). Products against sexual dysfunction,

¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:174:0074:0087:EN:PDF>

² The proposal for Directive 2011/62/EU had been supported by an impact assessment report of the Commission services published in 2008 (the “2008 impact assessment”). Where appropriate, the results and findings of the 2008 impact assessment are referred to in this report.

³ The term “counterfeit medicines” is only used when there is an infringement of intellectual property rights (IPR). Although it is possible to have falsified medicines that are also counterfeit, not all falsified medicines are necessarily counterfeit, since falsification does not always imply infringement of IPR. For example, a medicine that is marketed by the legitimate market authorisation holder but does not contain one or more of the active ingredients that claims to contain, is falsified but not counterfeit (see as example Annex 4, Table of “Incidents of falsification of medicines for human use notified through the rapid alert notification system”, entry 32).

It is also possible to have counterfeit medicines that are not falsified (for example medicines that are authorised as generics in their country of manufacture but infringe IPR if imported into the EU). In practical terms, though, most counterfeit medicines intercepted to date fulfil the definition of falsified medicines.

⁴ See Annex 4, Tables of “Incidents of falsification”, entries 9, 17, 27

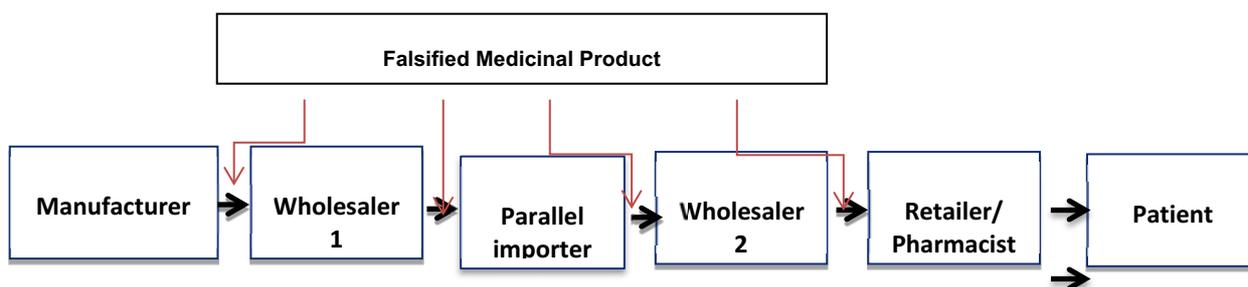
⁵ See Annex 4, Tables of “Incidents of falsification”, entries 9, 27, 32

heartburn, eating disorders, anxiety and cancer are among the medicines most targeted by traffickers in the EU.

Counterfeit medicines can be used as reliable indicators of the increasing trend in medicine falsification over the past years since, in practical terms, the large majority of counterfeit medicines also fulfils the definition of falsified medicines. Counterfeit medicines seized at the EU's outer border tripled between 2006 and 2009, reaching approximately 7.5 million items. Over 30 million counterfeit medicines have been seized by customs at EU borders over the last five years. Today, approximately 1.5m packs of counterfeit medicinal products enter the legal supply chain per year in the EU representing approx. 0.005% of all medicinal products made available. In other words, 1 pack out of 20 000 packs would be a counterfeit⁶.

Falsified medicinal products can enter the legal production and supply chain at various stages:

Potential sources of falsified medicinal products in the legal distribution chain



This scheme however does not provide a realistic view of the complexity of the medicine distribution chain. Many operators, such as manufacturers, parallel importers⁷, several wholesale distributors and retailers/pharmacies may handle a medicine between its manufacturing and its dispensing to the patient. Despite the existing regulatory framework and its controls⁸, the complexity of the medicine distribution chain provides several opportunities to traffickers that try to penetrate the legal supply chain to offer fake medicines to legal operators. Most commonly, fake medicines permeate the supply chain through wholesalers, but permeation through other operators cannot be excluded. For example, in 2012, fake Avastin containing a variety of toxic chemicals (including benzoic acid, acetone,

⁶ 2008 Impact Assessment - Accompanying document to 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. SEC(2008) 2674.

⁷ Parallel importers buy products marketed by the original manufacturer at a lower price in one country and sell them at a higher price in another country. Before selling the product in the country of destination, they may need to remove the outer packaging and ensure a repackaging.

⁸ In the European Union, the manufacture and distribution of medicinal products in the internal market has an important cross-border dimension. Since 1965, the EU has introduced a harmonised regulatory framework for medicinal products to protect public health and to ensure the free movement of medicines in the internal market. A cornerstone of this regulatory framework is the pre-marketing authorisation of medicines, i.e. only medicinal products that are authorised by the Member States or the European Commission after an in-depth assessment of their quality, safety and efficacy can be placed on the EU market. Moreover, all actors in the medicines distribution system – from manufacturing to distribution through the supply chain till the dispensing point – have to be authorised. Their activities are also subject to regular inspections by competent authorities.

propandiol) but no active substance reached the EU after being manufactured in Turkey, sold by a Syrian trader to an (unauthorised) Egypt distributor, then sold to a Swiss distributor, from there to a Danish distributor and eventually to a British distributor. In 2014, several medicines (Herceptin, Remicade, Alimta, Avastin and Mabthera, among others) stolen from Italian hospitals were offered for sale under false credentials (hence becoming falsified medicines because of fake origin) and reintroduced in the legal supply chain after being bought by authorised Italian wholesalers and parallel importers in Germany, Finland and the UK.

So far, fake medicines, when discovered, have been detected through controls at customs or by wholesale distributors, parallel importers or pharmacies noticing the irregular packaging/labelling of the medicine. Systematic measures, possibly by electronic means, are needed to reinforce controls at the potential points of entry.

In addition to the health consequences of fake medicines for patients, this threat also has a negative impact on public trust in the regulatory system. Both the public health risk and the loss of trust have major adverse economic impacts for industry and social security systems.

1.2. Organisation and timing

A Commission Delegated Regulation supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the outer packaging of medicinal products for human use is included in the Commission's 'agenda planning' under reference number 2015/SANTE/396.

An Inter-Service Steering Group was set up and met on 10 October 2011, 4 March 2013 and 10 June 2013. The meetings were attended by representatives from Directorates-General Budget, Secretariat General, Enterprise and industry, Taxation and customs union and Internal market. The Legal Service and Directorate-General Communication networks were also consulted. To gain additional expertise, there were close contacts with the European Medicines Agency on this file.

1.3. Consultation and expertise

1.3.1. Consultation of Member States

The Commission has consulted experts from the national competent authorities of the Member States: An expert group on the delegated act on safety features for medicinal products for human use was set up and met nine times between December 2011 and March 2015. Member States largely agreed to harmonise the technical specifications and to coordinate the verification mechanism for the implementation of the safety features. Most Member States asked that the unique identifier should contain as much information as possible in particular batch number, expiry date and reimbursement number and should be readable by electronic means. Member States also stressed the need for a system that can be reliably operated across the EU, taking into account the specificities of the supply chain of individual Member States. Member States finally asked the Commission to take into appropriate consideration the fact that, in the EU, there are other parties that can supply medicines to patients besides pharmacies.

1.3.2. Stakeholder consultations

In June 2011, the Commission held a meeting with key European associations representing manufacturers, wholesale distributors and pharmacies to discuss the delegated act on the safety features. The aim of the meeting was to collect their first views on possible options for the characteristics and technical specifications of the unique identifier.

On the basis of this preliminary discussion, the Commission submitted for public consultation a concept paper on the delegated act on the detailed rules for a unique identifier for medicinal products for human use, and its verification. The consultation took place from 18 November 2011 to 27 April 2012. All the ‘General principles and minimum standards for consultation of interested parties by the Commission’ were met. The concept paper put forward various ideas and options for implementing the unique identifier. This public consultation was also used as a means of gathering further quantified information on the costs and effectiveness of the various policy options. In total, 90 replies were received (mainly from industry, wholesale distributors and pharmacy, but also from the Member States). The responses have been published by the Commission on the Europa website⁹. A summary of the responses is presented in Annex 2.

In a nutshell, all respondents expressed their full support for the Commission’s initiative, on the grounds that the unique identifier would create better protection for European patients against falsified medicines. Most respondents except the European Generic Association supported harmonising the technical specifications of the unique identifier across the Union to ensure interoperability among different manufacturers and different EU Member States. Most stakeholders also supported the checking of the unique identifier at the end of the supply chain, namely at the pharmacy's level. Most industry supported a repository system set up and managed by the stakeholders. On the contrary, two national medicines Agencies out of seven who replied favoured the EU or national governance of the repository system while one authority called for national governance only. Their views were also expressed during the meetings of the expert group. The European Consumer Organisation stressed the importance to protect personal data in the repository system.

In December 2012, the Commission presented the outcome of the public consultation to the Member States and key European associations.

The Commission further consulted with key European stakeholders in December 2013 and April 2014.

1.3.3. External expertise

In November 2012, with the help of an external contractor, ECORYS, the Commission conducted an ex-ante evaluation of competitiveness proofing of the unique identifier for medicinal products for human use and its verification. The contractor investigated the consequences of the different policy options on the competitiveness of the pharmaceutical industry and identified corrective or mitigating measures. The relevant dimensions of competitiveness analysed in the study were: cost competitiveness, capacity to innovate and international competitiveness. The link to the report is in Annex 3.

⁹ http://ec.europa.eu/health/human-use/falsified_medicines/developments/2012-06_pc_safety-features.htm

1.4. Scrutiny by the Commission Impact Assessment Board

The impact assessment was submitted to the impact assessment board (“IAB”) for scrutiny. In its opinion, the IAB stressed the need to:

- Clarify the requirements stemming from the Directive 2011/62/EC and the scope for excluding or including specific medicines or categories of medicines;
- Better demonstrate the need to prevent circulation of falsified medicines at the wholesale level. The options addressing recalls and returns should be discussed separately;
- Better describe the impact on the various actors and patients and present underlying calculations;
- Provide more detailed feedback on the views of stakeholders.

The impact assessment report has been amended in line with the IAB suggestions.

2. PROBLEM DEFINITION

2.1. What is the problem?

The problem is that there are no obligatory technology solutions in place that effectively prevent falsified medicine from entering the legal supply chain.

To tackle this problem, Directive 2011/62/EU amends Directive 2001/83/EC establishing the Community Code for medicinal products for human use and introduces obligatory ‘safety features’ as part of the outer packaging of prescription medicinal products.

The term “safety features” encompasses two distinct elements:

- ‘a unique identifier’, to identify individual packs of a medicinal product and to verify the authenticity of the medicinal product;
- ‘an anti-tampering device’, to verify whether the outer packaging has been tampered with.

The ‘unique identifier’ is an identification number that is unique to a single pack of medicine. A carrier (bar code) placed on the outer packaging ‘holds’ the unique identifier. The authenticity of each pack is verified by (i) entering its identifier number into a repository system at the time of manufacture, and (ii) checking the unique identifier against its entry in the repository system at one or more points in the supply chain.

Directive 2011/62/EU places the Commission¹⁰ under the obligation to adopt delegated acts setting out, *inter alia*:

- (a) the characteristics and technical specifications of the unique identifier; the modalities for the verification of the safety features; the establishment and management of the repository system containing the unique identifiers.

¹⁰ Art. 54a(2) of Directive 2001/83/EC

- (b) the lists of medicinal products subject to prescription that shall not bear the safety features, and of medicinal products not subject to prescription that shall bear the safety features), in accordance with the strict criteria defined in Directive 2011/62/EU.

Before adopting these delegated acts, Article 4 of Directive 2011/62/EC requires the Commission to perform a study assessing benefits, costs and cost-effectiveness of:

- (c) the technical options for the unique identifier (i.e.: what will be the composition of the unique identifier or the format of the barcode holding it?);
- (d) the options for the extent of verification of the authenticity of the medicinal product bearing the safety features and the practical arrangements for such verification (i.e.: who will check the barcode? Wholesale distributors, pharmacies?);
- (e) the technical options for establishing and managing the repository system (i.e.: who will establish and manage the database?)

This study was conducted in the form of an impact assessment, with a view to adopting the respective delegated acts in 2015. The results of the impact assessment process are summarised in this report.

As provided for by the Directive, the scope of this impact assessment is limited to the benefits, costs and cost-effectiveness of the unique identifier. This study does not discuss options for the anti-tampering device, as the technical characteristics of the anti-tampering device are not in the scope of the delegated acts (the Commission will leave the choice of the most appropriate device to the manufacturer).

In addition, Directive 2011/62/EU does not require this study to discuss the criteria for establishing the lists of exceptions from bearing/not bearing the safety features, since these criteria are already set out by the Directive itself. The scope of the safety features, as well as potential exceptions from the scope, was extensively discussed during the co-decision procedure back in 2011. The Council and the European Parliament agreed on introducing the safety features for prescription medicines only. Consequently, Directive 2011/62/EU excludes medicinal products not subject to prescription from bearing the safety features. No other category of medicines is explicitly excluded, although the Directive provides for the possibility of excluding some prescription medicines from bearing the safety features or allowing some non-prescription medicines to bear the safety features, by way of exception and following an assessment of the risks of and arising from falsification. As set in Directive 2011/62/EU, the risk assessment has to consider the following criteria:

- (a) *the price and sales volume* of the medicinal product;
- (b) *the number and frequency of previous cases of falsification* reported within the Union and in third countries and the evolution of the number and frequency of such cases to date;
- (c) *the specific characteristics* of the medicinal products concerned;
- (d) the severity of the conditions intended to be treated;
- (e) other potential risks to public health.

The Commission will establish the lists of exceptions taking into account the above criteria as well as the lists of medicines provided by the Member States in accordance with Article 1(12)(4) of Directive 2011/62/EU. A Member State expert group with the appropriate scientific and technical expertise will also be consulted on the lists (and their future amendments, if any). The Commission held nine meetings with the expert group between 2012 and 2015.

The Commission has limited flexibility with regard the application of the above criteria. Being a prescription medicine without past incidents of falsification, for example, is not sufficient to be included in the list of prescription medicines not having to bear the safety features. Rather, prescription medicines need to have a full set of specificities in line with criteria (a) to (e) that identifies them as being at negligible risk of falsification and not posing significant risks if falsified. For example, a medicine with low price and low volume of sales, no past incidents of falsification, which does not belong to categories of medicines at high risk of falsification (such as medicines that facilitate weight-loss or treat erectile dysfunction, for example), does not treat a severe disease (such as cancer, for example) and does not pose a serious threat to public health if falsified, could be a candidate for exemption from bearing the safety features. Discussions with the Member States expert group identified only an extremely limited number of medicines that would fulfil the criteria above. The number of prescription medicines exempted from bearing the safety features will therefore be negligible in relation to the hundreds of thousands of prescription medicines authorised in the Union.

Concerning the list of non-prescription medicines having to bear the safety features, the key factor determining whether a medicine should be placed on the list will be the presence of proven incidents of falsification. To date, only three incidents of falsifications involving two non-prescription medicines have been reported in the legal supply chain in the EU. The delegated act will therefore require only an extremely low number of non-prescription medicines to bear the safety features.

In view of the above, the contribution of the lists of exceptions from bearing/not bearing the safety features to the overall costs of implementing the safety features can be considered negligible.

2.2. What are the underlying drivers of the problem?

The causes of the problem are various and can be summarised as follows:

2.2.1. Ineffective rules for protecting EU citizens from falsified medicines and other inappropriate medicines

The EU legislation allows Member States to introduce specific national labelling requirements to be used to ascertain the price of the medicine, its reimbursement conditions, authenticity and identity. The introduction of such provisions is, however, voluntary.

Only a few Member States currently have provisions in place to ascertain the authenticity and identity of medicines. Those provisions are not harmonised across the Union and are too few to adequately prevent the entry of fake medicines into the EU legal supply chain. The limited, non-systematic use of (1) electronic means to identify medicines and acquire batch and expiry date information, and (2) electronic record keeping across the EU also creates inefficiencies in traceability of medicines and of falsified medicines in particular. In fact, the use of paper trails is often still necessary to ascertain the origin of suspicious medicines, particularly when those medicines have moved between Member States. The use of paper documentation is not

only costly and time-consuming compared to electronic records, but is also a weakness of the security of the supply chain, as paperwork is more easily forged than electronic records. The same inefficiencies affect the handling of other medicines that should be prevented from reaching patients, such as medicines which have expired or have been recalled.

2.2.1.1. Ineffective rules due to divergent coding structure and carrier

Some Member States have introduced codes on medicine packs (product coding) with the motivation, inter alia, to secure the supply chain. Even when present, these national product coding systems are, in most cases, not suited to efficiently preventing fake medicines from entering the legal supply chain because conceived for reimbursement purposes (e.g. Greece) rather than to identify single packs. In fact, codes on packs can be easily copied, as there is no system in place to single out packs carrying duplicate numbers. In addition, in the Member States with systems in place to identify single packs, it is not mandatory for a manufacturer to use the coding system (e.g. in Belgium) or for a pharmacy to authenticate a medicine pack before dispensing it to the patient (e.g. Italy).

The lack of harmonised requirements across Member States further limits the impact of such measures at EU level. Different standards of product coding are currently used at national level¹¹. The product number can contain from 7 to 13 digits and the information coded in the number varies widely (manufacturer product code, national reimbursement code, etc). In Germany, for example, pharmaceuticals are attributed a Central Pharmaceutical Number (PZN) by the organism IFA. This number is product-specific, not pack-specific.

The format of the data carrier also varies across Member States. For example, France introduced a traceability system that uses a two-dimension (2D) barcode to track batch numbers for recall purposes. In parallel, Belgium, Greece and Italy introduced a unique identifier with a one-dimension (1D) barcode for reimbursement purposes. In other Member States, a product number is labelled in Arab numerals (1, 2, 3...).

It is important that, upon introduction of the unique identifier, a product should not bear two different identifying codes on the outer packaging. This would complexify the system and lead to several potential problems:

- Potential errors due to system failure (for example, failure in the recognition of the coding system at pharmacy level)
- Obligation for the pharmacist to scan twice, once for reimbursement and a second time for authentication purposes;
- Additional costs of maintaining two identifiers.



Examples of barcodes

¹¹ e.g. PZN in Germany, CNK, in Belgium, GS1 in France, etc.

The 2008 impact assessment¹² estimated the costs of having non-harmonised coding systems in the EU Member States to be as high as 1bn EUR per year.

2.2.1.2. Ineffective rules due to non-connected national databases

In addition to the divergent coding and data carrier, Belgium, Italy and Greece have developed their own database to store the codes for the purposes of authentication, reimbursement or traceability. To date, these systems are not interconnected and do not recognise each other. It is impossible, for example, to electronically track a medicine pack that is produced in Greece and sold in Germany.

If each EU Member State develops its own database, the EU will have 28 different, non-communicating systems that may hinder, rather than facilitate, the traceability of medicines.

2.2.2. *Absence of verification along the supply chain*

The unique identifier should be secured by entering it into a repository system at the time of manufacture and deleting it from the system when the medicine is dispensed, so that any other pack bearing a copy of that identifier would be immediately recognised as illegitimate. It is clear from the above that a unique identifier will only be effective in identifying falsified medicines if there is an adequate system of verification at appropriate levels of the supply chain. Despite coding systems being in place in a limited number of Member States, most medicinal products are not systematically checked for authentication. For example, Belgium has a system of authentication in place but participation to the system is voluntary. This means that the authenticity of only a small number of medicines is verified before dispensing to the patients. In Italy and Greece, there is no verification of authenticity.

There are no authenticity checks at the level of the wholesale distributors so far. However, there have been incidents of falsification¹³ where fake medicines entered the legal supply chain at the wholesale level. In these cases, the lack of verification at the wholesale level means that fake medicines circulate for months in the EU market without being detected. For example, fake interferons, distributed by a Romanian wholesaler, were detected at first by a German parallel-distributor in September 2013 and two months later in Romanian pharmacies¹⁴. The longer fake medicines can circulate undetected, the more widely they can be distributed across the EU and the higher the chance that they might evade controls and reach patients. When eventually pharmacies or patients detect something suspicious (e.g. on the colouring or labelling of the product), usually months after the product transited through the premises of wholesale distributors, it is extremely difficult to know exactly when and where the fake medicines have been introduced in the supply chain. A check of the safety features by the wholesale distributors would allow detection of fake medicines at the point of entry and increase the probability to identify the source of the falsification, hence facilitating the fight against this illegal activity. It would also avoid having fake products circulating months in the legal supply chain.

The European association of wholesale distributors identified specific situations where fake medicines can enter their premises:

¹² The proposal for Directive 2011/62/EU had been supported by an impact assessment report of the Commission services published in 2008 (the "2008 impact assessment"). Where appropriate, the results and findings of the 2008 impact assessment are being referred to in this report.

¹³ See Annex 4, Tables of "Incidents of falsification", entry 29

¹⁴ See Annex 4, Tables of "Incidents of falsification", entries 13 and 45

- When the product is not obtained from either the manufacturing authorisation holder¹⁵ or the marketing authorisation holder;
- When the product is returned by another wholesale distributor or a pharmacy.

According to the European Association of Pharmaceutical Wholesalers, the above mentioned products represent 3.17% of the total volume of medicine packs handled by full-line wholesaler distributors.

The non-systematic electronic verification of medicines at the time of dispense also increases the probability that not only fake medicines, but also recalled or expired medicines are inadvertently supplied to patients.

2.3. Who is affected by the problems identified?

Patients are the group most severely affected by the overall problem of falsified medicines. The consequences of falsified medicines can be considerable and include death, injury, medical treatment, hospitalisation and long-term disability. Associated costs include not only the costs of the required medical interventions, but also the socio-economic costs caused by lost productivity (e.g.: absences from work). The inadvertent supply of recalled or expired medicines to patients may have similar consequences.

Falsified medicines represent a twofold risk for public health:

- patients not receiving the appropriate treatment for their condition;
- patients being harmed by receiving dangerous ingredients.

Pharmaceutical companies are also affected by the overall problem of falsified medicines in the legal supply chain. Falsified medicines harm the legal trade of genuine manufacturers, reduce their competitiveness, and damage the reputation of high-quality medicinal products legally available on the EU market.

Protecting the competitiveness of the pharmaceutical sector is critical as this sector plays an important role in the European economy. In this light, the proper functioning of the pharmaceutical sector is a clear precondition for smart, sustainable and inclusive growth and plays a crucial role in meeting the Europe 2020 targets¹⁶.

According to Eurostat, there were 3 800 manufacturers of medicines¹⁷ in 2009. Their turnover was € 192 523 million. The pharmaceutical industry is a profitable industry sector with a profit margin from 13% to 24%.¹⁸ EFPIA estimates the Europe's pharmaceutical trade surplus at €80 billion in 2012. Moreover, the pharmaceutical industry directly employs 700,000 people and generates three to four times more employment indirectly – upstream and

¹⁵ The manufacturing authorisation holders may include both original manufacturers and parallel importers engaged in repackaging the medicines. These operators are inspected by competent authorities and have an authorisation to conduct their tasks.

¹⁶ Positive effects include improving people's employability, generating high-quality employment, offering an effective safeguard against poverty, and beneficial spill overs from sustained research and development efforts. These knowledge-intensive areas have traditionally been associated with exported overall economic growth for the EU. Evidence suggests that the investments in R&D-intensive activities carried out in the sectors of pharmaceuticals, biotechnology, and healthcare equipment play a crucial role in contributing to reach the 2020 target of investing 3 % of GDP in R&D. In the EU, the economic value of R&D carried out in the pharmaceutical industry in 2010 amounted to € 27.8 billion.

¹⁷ Referred as manufacturers of pharmaceutical preparations by Eurostat.

¹⁸ ECORYS study *internet link to the report (to be completed at the date of adoption of the delegated act)*

downstream – than it does directly.¹⁹ The sector is composed of originator companies (selling brand medicines), generic manufacturers (selling generic medicines once the originator product's patent has expired) and parallel importers. The generic medicines industry represents about 50 % of the medicines dispensed in the European Union. Parallel importers repack the products bought at a low price in one country (e.g. Greece) and sell them at a higher price in another country (e.g. Germany, Denmark, Sweden). Parallel trade was estimated to amount to € 5 billion (value at ex-factory prices) in 2011. Intra-EU27 trade of medicines (export and dispatch) reached 105 billion euro in 2006²⁰. Pharmaceutical manufacture is particularly high in UK, IE, FR, DE, IT and BE who produce for the whole EU. The EU pharmaceutical sector has also a strong export activity to the US, Switzerland, Russia, and Japan.

The handling of products that have to be recalled from the market (e.g. because suspected falsified or due to quality defects) and products returned from distributors and retailers/pharmacists is currently very burdensome and costly for manufacturers due to the lack of electronic traceability and limited availability of electronic records.

Authorities and the European Commission

Incidents involving falsified medicines undermine the robustness of the entire European regulatory framework laying down harmonised rules for the authorisation, manufacture, distribution and labelling of medicinal products in the EU.

Wholesale distributors

Wholesale distributors bring medicines from manufacturers to pharmacies and hospitals.

Falsified medicines entering the supply chain at some point between manufacture and dispense to the patients not only harm the reputation and reliability of wholesaler distributors but are also source of economic loss. Whenever a wholesale distributor buys medicines which later result falsified, he is under the obligation to replace the falsified products with the genuine one and bear the full costs of this replacement. Wholesale distributors fall into two types: full-line wholesalers (who deliver all medicines that are used in their geographic area) and short-line wholesalers (who deliver a limited range of products). Short line wholesalers represent a very small (3-5%) share of the distribution market. Distribution of medicines is essentially ensured by full line wholesalers or by manufacturers directly distributing their own products. In particular, 75% of all prescription medicines in the EU are distributed through full-line wholesale distributors. The number of wholesale distribution plants is 2,019 for the EU 25 (excluding Malta, Cyprus and Croatia) plus Norway and Switzerland.

Wholesale distributors are also affected by not having the batch number in a machine-readable format: they are to record and store all batch numbers of products bearing the safety features²¹ and, in the absence of a machine readable batch-number, the information will have to be captured manually, resulting in a drastic slowdown of the workflow in the warehouse and increased labour costs.

Pharmacies/retailers²²/other points of dispense may be affected as the presence of falsified medicines in the legal supply chain may break the link of confidence with the patients. There

¹⁹ <http://www.efpia.eu/facts-figures>

²⁰ http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-CV-07-001/EN/KS-CV-07-001-EN.PDF

²¹ Article 80(e) of Directive 2001/83/EC.

²² In accordance with national legislation

are about 170 000 pharmacies in the EU that dispense 18 billion prescription medicines per year. Community pharmacies²³ are the key points for dispensing medicines, and are authorised and recognised in all 28 Member States. In addition, hospital pharmacies²⁴ exist in most EU Member States. There are approximately 154 000 community pharmacies and 21,000 hospital pharmacies in the EU. Some Member States authorise additional means of dispensing medicines to the patient, for example dispensing doctors in the UK.

The handling of recalled and returned products as well as the reporting of adverse events is currently quite burdensome also for retailers/pharmacists due to the difficulty of acquiring the information on the medicinal product in electronic format.

2.4. How would the problem develop, all things being equal? (baseline scenario)

All things being equal, fake medicines will continue to enter the legal supply chain in the EU, with the concrete risk that such medicines will reach the patients.

The 2008 impact assessment has extensively analysed the scale of the problem of falsified medicines in the European Union, all things being equal. It has shown that, today, annual costs resulting from counterfeit medicinal products in the legal supply chain have estimated direct²⁵ and indirect²⁶ costs of approximately € 950 million.

It should be noted that the introduction of the safety features is a mandatory requirement of the EU legislation following the adoption of Directive 2011/62/EC. The legislators chose to address the problem of falsified medicines by introducing harmonised, technology-based solutions.

Therefore, the non-introduction of the technology options (unique identifier, barcode, repository system) required by the legislation would not only maintain the current vulnerability of the supply chain to permeation of falsified medicines – it would also be illegal.

Equally important, the non-introduction of the safety features would impede the proper implementation of additional legal provisions improving the traceability of medicines:

- Directive 2011/62/EC introduces the obligation for wholesale distributors to keep record of batch numbers for products bearing the safety features. If the safety features are not introduced, this obligation cannot be enforced. In addition, if the unique identifier is introduced but does not contain the batch number in a machine-readable format, the wholesale distributors will be forced to record the batch number manually, with additional annual labour costs estimated at € 66.1 million²⁷.
- Directive 2010/84/EU as regards pharmacovigilance introduces the obligation to record the batch number for any biological medicinal product prescribed, dispensed, or sold which is the subject of a suspected adverse reaction report. Currently, originators claim that batch numbers are still not systematically recorded since the

²³ Community pharmacy is a pharmacy that supplies medicines to the public in the local area

²⁴ Hospital pharmacy can usually be found within the premises of a hospital

²⁵ A direct cost approach looks at the costs falling on the health sector in terms of prevention, diagnosis and treatment of disease

²⁶ Indirect costs typically measure the lost productivity potential of patients who are too ill to work or who die prematurely

²⁷ Estimated costs provided by GIRP.

manual recording is too time-consuming. This leads to confusion in the attribution of adverse events to the generic or the branded product. The introduction of the safety features, and in particular a unique identifier containing the batch number in a machine-readable format, would greatly facilitate the application of this provision.

In addition, the non-harmonisation of the technology options in the national legislations will maintain the existing fragmentation of labelling requirements for authentication and identification of medicines, leading to unnecessary high costs for manufacturers. The current global trend towards increased traceability of medicinal products should also be taken into account. California, Turkey, Argentina, India and China are introducing traceability measures²⁸. A bill to introduce similar requirements at federal level in the US, the Pharmaceutical Quality, Security and Accountability Act is currently being examined by the US Senate. Divergent labelling requirements, across the EU and at global level, would oblige companies to have multiple manufacturing lines depending of the country of destination, increasing the costs for the sector.

It should be noted that, since the introduction of the safety features is a mandatory requirement of Directive 2011/62/EU, the purpose of this impact assessment is not to assess the impact of the introduction of the safety features *per se*, but rather the cost effectiveness²⁹ of the different options that can be implemented to introduce the unique identifier (the anti-tampering device is excluded from the scope of this exercise, as previously mentioned).

2.5. Does the EU have the right to act and is EU added value evident?

Article 54a(2) of Directive 2011/62/EU obliges the Commission to adopt a delegated act setting out the characteristics and technical specifications of the unique identifier, the modalities for the verification of the safety features and the establishment and management of the repository system containing the unique identifiers. The Commission needs to define the modalities of verification of the safety features by the manufacturers, the wholesale distributors and all persons authorised or entitled to supply medicines to the public (e.g. pharmacies, hospitals).

The aim of introducing the safety features is to harmonise the security aspects of the outer packaging of medicinal products that will circulate in the internal market. This will ensure the equal protection of all European patients. Furthermore, harmonisation at EU level will facilitate the circulation of medicines taking into account the cross-border dimension of the pharmaceutical sector. Such objectives can only be achieved at EU level.

In the public consultation, the stakeholders and the national competent authorities also recognised the evident added value of an EU action in this field.

Equally important, the non-introduction of the safety features has an impact on the implementation of additional legal provisions of the pharmaceutical legislation, namely:

- Article 80 (e) of Directive 2011/62/EC introduces the obligation for wholesale distributors to keep a record of batch numbers for products bearing the safety features. If the safety features are not introduced, this obligation cannot be enforced.

²⁸ For example, California has introduced an obligation of serialisation for all products under prescription by January 2015 and all products by Jan 2016, Turkey and India have already introduced a unique barcode, while China is currently taking measures to introduce a unique identifier in the coming years.

²⁹ Art. 4 of Directive 2011/62/EU

- Article 102 (e) of Directive 2010/84/EU as regards pharmacovigilance introduces the obligation to record the batch number for any biological medicinal product prescribed, dispensed, or sold which is the subject of a suspected adverse reaction report. If the unique identifier does not hold the batch number, this information is not recorded systematically as it is a manual recording.

3. OBJECTIVES

3.1. General policy objectives

The general objective of this initiative is to improve the protection of public health while fostering the internal market and the competitiveness of EU pharmaceutical companies.

3.2. Specific policy objectives

The specific objectives of this initiative are to:

- establish a framework for the unique identifier and its verification that is simple, effective in safeguarding public health and protects personal and commercial information;
- limit the costs for all actors.

3.3. Operational objectives

The operational policy objectives to be achieved by this initiative are the following:

- to ensure efficient and effective characteristics and technical specifications of the unique identifier (objective 1);
- to introduce proportionate verification of the safety features in order to combat falsified medicines (objective 2);
- to ensure interoperability of the repository system, free movement of medicines and supervision by the competent authorities (objective 3).

4. POLICY OPTIONS

4.1. Policy options for achieving objective 1: To ensure efficient and effective characteristics and technical specifications of the unique identifier

The minimum requirement to identify a pack is to have a unique number on the pack. This number could either be not informative (i.e. a randomly-generated sequential number) or be based on specific product information such as a product code³⁰ and a serial number³¹.

³⁰ This uniquely identifies the medicinal product at global level. It may include the country prefix.

³¹ A unique code assigned for identification of a single pack. Typically serial numbers used for the purpose of securely and uniquely identifying a pack are randomised.

4.1.1. Policy option 1/1: Full harmonisation of the composition of the identifier and the data carrier to protect against falsified, recalled and expired medicines

This option proposes a full harmonisation of both the composition of the identifier and the standard/format of the barcode carrying it. The identifier includes additional product-related information (batch number and expiry date) in order to facilitate return and recall procedures, as well as pharmacovigilance activities. This option goes beyond the minimum requirements necessary to ensure the effective authentication of an individual pack.

Thus, the identifier would contain the following information:

- Product code.
- Serial number
- A national identification or reimbursement number, if required by Member States.
- Batch number (to facilitate recalls and pharmacovigilance activities)
- Expiry date (to facilitate returns of expired medicines).

This option also defines the type of "carrier", i.e. barcode that holds the unique identifier. Barcodes can have one or two dimensions (1D or 2D barcode), with 2D barcodes being able to contain a larger amount of information in a smaller surface.

As the amount of information requested to be included in the unique identifier is too large for a 1D barcode, a 2D barcode is a compulsory choice. The national reimbursement number will be added if required by the Member State of destination of the medicine.

4.1.2. Policy option 1/2: Partial harmonisation of the composition of the number to fight against falsified medicines

This policy option proposes a partial harmonisation of the composition of the identifier. It imposes the minimum requirements necessary to identify and authenticate a single pack, namely a unique identifier containing the product code and a serial number. It is left to the manufacturer to choose whether or not to add additional product-related information (e.g. batch number and expiry date) to the unique identifier, and to choose the most appropriate carrier (e.g. 1D barcode, 2D barcode or RFID (radio frequency identification device)).

In both options 1/1 and 1/2, the structure of the unique identifier, as proposed, complies with international standards such as ISO standards. The compliance with ISO standards will allow the identifier and the carrier on the pack to be scanned/read efficiently anywhere in the EU. Stakeholders including EFPIA support the exclusive use of ISO compliant symbology for the data carrier, i.e. the Data Matrix (see ISO/IEC 16022) and ISO standardised syntax and structure for the code (see ISO/IEC 15459, ISO/IEC 15418 and ISO/IEC 15434).

4.1.3. Other policy options

Many different options for the technical characteristics of the unique identifier can be envisaged, for example by varying the mandatory/non mandatory components of the identifier. For the purpose of this impact assessment exercise, priority was given to two options supported by stakeholders and competent authorities in the public consultation that

took into account systems already in place in the pharmaceutical sector and Member States – in order to minimise costs.

Consequently, options not proposed by stakeholders or Member States were not considered. These include, for example:

- The use of a non-informative, randomized sequential number as unique identifier;
- The harmonisation of the carrier but not of the composition of the number.
- The harmonisation of the carrier and the composition of the number to include the manufacturing code and serial number, but no additional product information (i.e. no expiry date, batch number or reimbursement number).

The no-action option is not proposed because Directive 2011/62/EU places the Commission under the obligation to act via a delegated act.

4.2. Policy options for achieving objective 2: To introduce proportionate verification of the safety features in order to combat falsified medicines

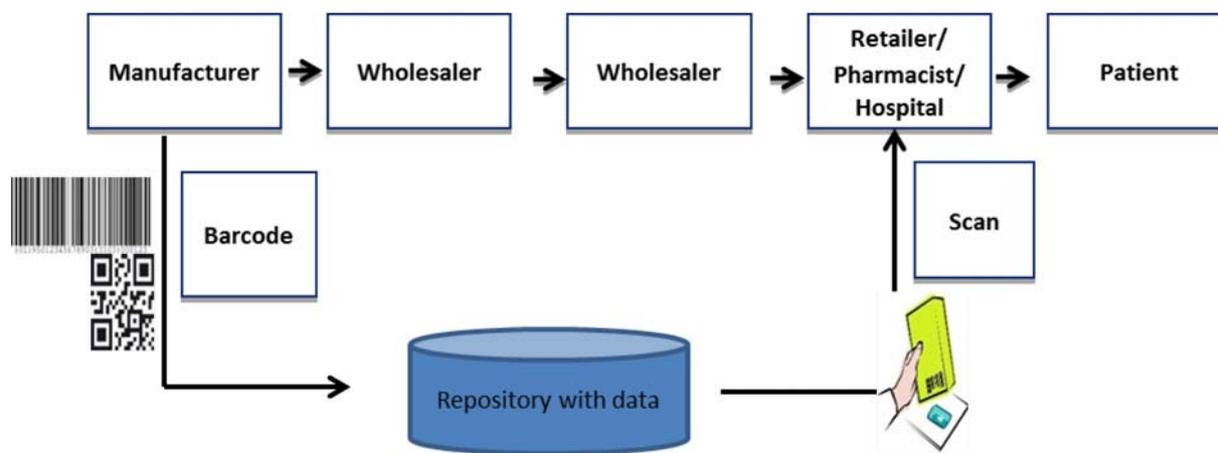
Directive 2011/62/EU does not *a priori* exempt any of the actors in the supply chain from the obligation of verifying the safety features but leaves to the delegated acts the responsibility to set the most cost-effective verification system.

It should be considered that the minimum requirements to verify the authenticity of a medicine pack are (i) entering the number uniquely identifying each pack (unique identifier) in a repository system at time of manufacture (“check-in”), and (ii) checking the unique identifier against the repository system at one or more points in the supply chain (“check-out”).

All options include the "check in" by manufacturer (or parallel importer) while different ways to implement point (ii), i.e. the "check out", are discussed below.

4.2.1. Policy option 2/1: Systematic verification of the unique identifier at the dispensing point — ‘end-to-end verification system’

In this option, the pack is verified and checked out of the repository system following the reading (scanning) of the unique identifier at the end of the supply chain, i.e. by the retailer, hospital pharmacy, community pharmacy or general practitioner. The wholesale distributor is not required to check out or verify the unique identifier. The reading given from the pack is instantly checked against the manufacturer’s record for that pack, via an electronic connection to a repository. If the pharmacist’s reading and the manufacturer’s records match, then the pack is genuine. If not, the product is likely to be a fake and an alarm would be triggered.



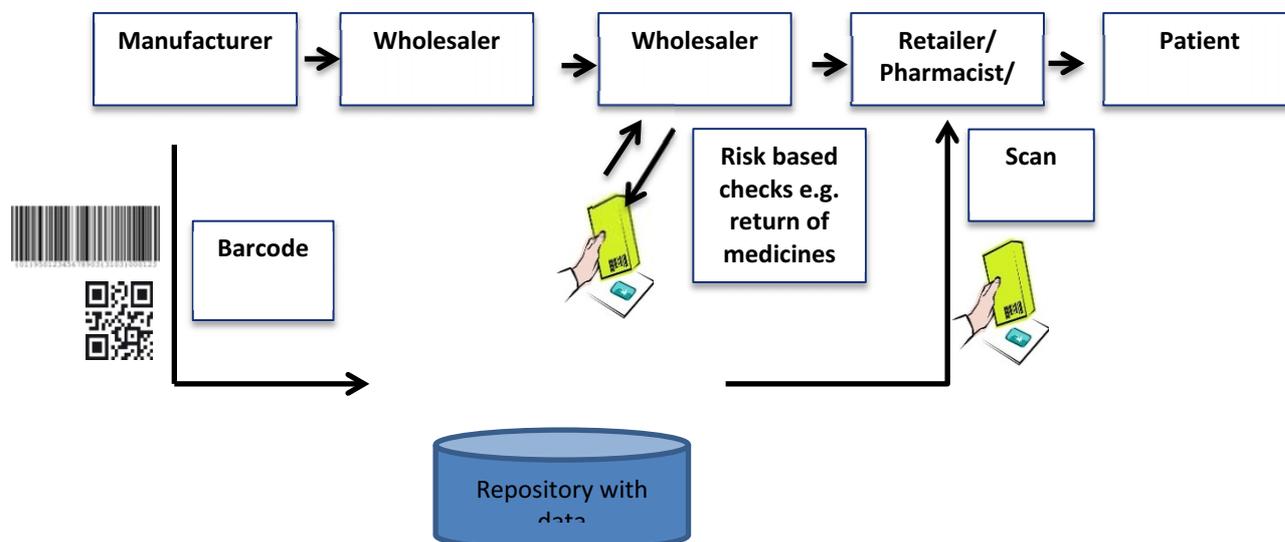
As stipulated in the Directive 2011/62/EU, the pack should also be scanned prior to repackaging by a parallel importer. A new unique identifier should then be generated, introduced in the repository system, and then placed on the new package to enable the product to be tracked in the event of falsification, recalls or other safety issues.

4.2.2. *Policy option 2/2: Systematic verification at the dispensing point and risk-based verification by wholesale distributors*

In this policy option, in addition to the systematic check-out at the dispensing point, wholesale distributors perform risk-based verifications of the serial number. In particular, wholesaler distributors would be required to verify the authenticity of the safety features when exposed to situations that could facilitate the entry of falsified medicines into the supply chain, such as when:

- the product is not obtained from the holder of the manufacturing authorisation or the holder of the marketing authorisation;
- the product is returned by another wholesale distributor or a pharmacy.

In their submission, GIRP estimated that 376 million packs/year would have to be scanned by wholesale distributors should option 2/2 be implemented. This represents 3.17% of the total volume of medicine packs handled by full-line wholesaler distributors.



4.2.3. *Other policy options*

The systematic check of all prescription medicines by wholesale distributors was one of the options ('track and trace verification system') discussed in the concept paper launched in public consultation. However, this option was received very negatively by stakeholders, in particular wholesaler distributors, due to the very high costs it would entitle. For this reason, this option has been discarded and will not be further discussed in this impact assessment.

4.3. ***Policy options for achieving objective 3: To ensure interoperability of the repository system, free movement of medicines and supervision by the competent authorities***

In order to verify the authenticity of the medicinal product, the unique identifier has to be checked against the repository system where the identifiers are stored. According to Directive 2011/62/EU, the delegated act must contain provisions on the establishment, management and accessibility of such repository system. In addition, Directive 2011/62/EU stipulates that the costs of the repository system have to be borne by the holders of manufacturing authorisations for medicinal products bearing the safety features.

4.3.1. *Policy option 3/1: Establishment and management by stakeholders with supervision by the relevant competent authorities*

This policy option provides for the establishment, management of and accessibility to the repository system by stakeholders (manufacturers, wholesale distributors, pharmacists/retailers). It defines the obligations of the manufacturers, but would leave to the relevant actors the choice of the appropriate infrastructure for the repository system, and to the national competent authorities the right to supervise the system.

Thus, the delegated act would ask the manufacturers and parallel importers to ensure that:

- the unique identifier is placed on the pack for authenticity checks;
- the serial number can be checked out at the dispensing point;
- the repository system is suitable to ensure authentication of medicinal products in the middle of the supply chain and at the dispensing point;
- the response from the repository system is virtually instantaneous;
- the repository system guarantees the protection of commercial, confidential and personal data; the only data contained in the repository should be for the purposes of the verification ("check in" or "check out" processes) of medicinal products. Personal or patient data should not be stored in the repository. Information generated during the verification checks by different actors in the supply chain (pharmacists, parallel importers, and possibly wholesalers) should only be accessible by the stakeholders

who generated the data or by competent authorities. The system should also safeguard the impartiality of the investigation of potential incidents of falsifications and the process of information sharing in case of fake medicines detected by the pharmacy.

- the concerned competent authorities have full access to the repository system and can supervise its functioning.

Stakeholders are currently running pilot projects at European level (e.g. the European Stakeholder Model³² (ESM), e-TACT³³) and national level (SecurPharm³⁴, Aegate³⁵). The Aegate system is operational. These pilots are testing a variety of different repository structures, from a centralised European repository to national interconnected databases. During the test phases, these pilot systems proved to be effective in identifying fake packs while allowing pharmacies to work at normal pace. The European Stakeholder Model (Annex 11), Securpharm and Aegate have confirmed that their pilot projects do not generate, process or store any personal or patient data. Pilot projects are also taking measures to protect commercially sensitive data. Securpharm, for example, uses separate databases for manufacturers and pharmacists, where stakeholders access and control only their own data. This means, for example, that manufacturers do not have access to pharmacy-specific information. The anonymity of the information is agreed by contract and guaranteed through technical measures.

4.3.2. Policy option 3/2: Establishment and management by a public authority at EU level

This policy option provides for the establishment, management and accessibility of the repository system by an EU body (the Commission or European Medicines Agency).

The delegated act would set up a single European repository system – managed by an EU body – to which all actors would connect. This system would provide a "one-stop shop" to check unique identifiers in and out. The manufacturers and parallel importers would have to place the unique identifier on the pack for authenticity checks, and feed the unique identifiers into the system. Pharmacies and wholesale distributors would access the repository to check the information.

The specifications of the system – such as possibility of authentication at the dispensing point, capacity for instantaneous reply, protection of commercial and personal data – and the access provisions would be defined by the European Commission. The national competent authorities would also be granted access to consult information on products placed on their market.

4.3.3. Policy option 3/3: Establishment and management by public authorities at national level

This policy option involves the establishment of individual repository systems, managed by national competent authorities at national level. The specifications of the system would be defined by the national competent authorities. The national databases will have to be interoperable and interconnected in order to allow intra-EU trade.

³² <http://www.esm-system.eu/home.html>

³³ <http://www.edqm.eu/en/eTACT-1466.html>

³⁴ <http://www.securpharm.de/international-sites/english.html>

³⁵ <http://www.aegate.com/>

All actors in a Member State, and actors supplying medicines to the territory of that Member State, will need to be connected to the specific repository system of that Member State. Stakeholders will have the same obligations as in option 3/2.

Summary

Problem	Causes	Objectives	Options
Increasing numbers of falsified medicines in the EU and no technology solutions in place to fight falsification	Ineffective rules for protecting EU citizens from falsified medicines and other inappropriate medicines due to divergent coding structure and carrier	To ensure efficient and effective characteristics and technical specifications of the unique identifier (objective 1)	1/1: Full harmonisation of the composition of the identifier and the data carrier to protect against falsified, recalled and expired medicines 1/2: Partial harmonisation of the composition of the identifier to fight against falsified medicines
	Absence of verification along the supply chain	To introduce proportionate verification of the safety features to combat falsified medicines (objective 2)	2/1: Systematic verification of the safety features at the point of dispense 2/2: Systematic verification of the safety features at the dispensing point and risk-based verification by wholesale distributors
	Ineffective rules for protecting EU citizens from falsified medicines and other inappropriate medicines due to non-connected national databases	To ensure interoperability of the repository system, free movement of medicines and supervision by the competent authorities (objective 3)	3/1: Establishment and management by stakeholders with supervision by the relevant competent authorities 3/2: Establishment and management by a public authority at EU level 3/3: Establishment and management by public authorities at national level

5. ANALYSIS OF IMPACT

For the purpose of this exercise, all options have a negligible environmental impact. Therefore, this impact will not be assessed in this impact assessment.

5.1. Policy options for achieving objective 1: To ensure efficient and effective characteristics and technical specifications of the unique identifier

5.1.1. *Policy option 1/1: Full harmonisation of the composition of the identifier and the data carrier to protect against falsified, recalled and expired medicines*

5.1.1.1. Social impact

This option introduces fully harmonised technical specifications for the unique identifier.

The harmonised code and data carrier will allow the use of one software and one scanner type, thereby facilitating the systematic check and identification of each pack before dispense to the patient. This will decrease the risk that fake medicines reach the patients.

The obligatory inclusion of batch number and expiry date in the unique identifier will enable the packs to be traced electronically, hence facilitating recall and return procedures.

This option goes beyond the minimum requirements of Directive 2011/62/EU with regards to the authentication of medicines. In addition to protection from fake medicines, this option provides the additional opportunity to protect patients from recalled products, expired products and involuntary administration of inappropriate medicines.

An additional social impact relates to the possibility of facilitating the traceability of biological medicines. The recent legislation on pharmacovigilance introduces the obligation to report any adverse event caused by biological medicinal products. These medicines are identified via their batch number. The encoding of the batch number within the unique identifier, and the possibility of machine-reading it and storing it in a repository will facilitate the tracing of the batch in case of reporting of an adverse reaction, hence strengthening public health protection.

If patients are protected against falsified medicines, recalled products, expired products and inappropriate medicines, we can anticipate a reduction in the direct costs falling on the health sector in terms of prevention, diagnosis and treatment of disease. The benefits would fall largely into these categories:

- reduced costs occurring during hospitalisation and lengthy hospital stays;
- reduced costs occurring in an outpatient setting (e.g; general practitioner visits) for dealing with the consequences of a treatment involving falsified medicines.
- Increased Quality-Adjusted Life Years³⁶ (QALY) and reduced Disability-Adjusted Life Years³⁷ (DALY) due to safer, more appropriate treatment reaching the patients
- Reduced costs linked to lost productivity (e.g. reduced absences from work).

In conclusion, this option offers a very positive social impact.

5.1.1.2. Economic impact

Manufacturers and parallel importers

The introduction of a unique identifier with harmonised specificities in terms of composition and carrier entails costs and therefore has a significant economic impact.

The costs of the unique identifier for manufacturers and parallel importers will arise from the need to adapt production lines or packaging lines (operating costs) and invest in software systems to upload the unique identifier information into the repository system. Currently, packaging lines print batch numbers on the package. In order to print a unique identifier, the packaging lines have to be upgraded with new printing and scanning software. According to

³⁶ Combined effect on life expectancy and quality of life, 1 QALY being equal to 1 year of life expectancy in full health

³⁷ Combined measure of lost years of life and lost quality of life resulting from a disease

the European Federation of Pharmaceutical Industries and Associations (EFPIA), the manufacturing costs of placing a unique identifier on the outer packaging are **€0,016 per package of medicinal product**. This estimation was confirmed by EDQM³⁸ and it is considered the most reliable value.

According to the evaluation of competitiveness proofing provided by ECORYS – which takes into account all stakeholders' estimates, annual costs per package could reach €0.033 per package of medicinal product in the worst-case scenario. In this case, the total investment costs for adapting 12 000 packaging lines for prescription medicines range from € 0.7 billion to € 3.2 billion. Considering a lifetime of 10 to 15 years for a packaging line, the total costs per year range from € 50 million to € 320 million for the whole sector. Total annual costs for originator companies would range from €20 million to €110 million, and total annual costs for generics companies from €30 million to €210 million (see Annex 8). Although the numbers vary widely, it can be expected that manufacturers and importers will strive to implement the required measures at the minimum costs. So the lower figures in the range are the most reliable.

Costs manufacturers (annual costs)

Costs for adapting production lines	Total costs sector (in € million)	Costs per manufacturer (in € 1,000)
<i>Originator companies</i>	20 – 110	7-39
<i>Generics companies</i>	30 – 210	30-210
<i>Parallel importer</i>	1 – 5	1 – 5
Total costs	51 – 325	

In addition to the above, the repackagers face specific costs since they will have the obligation to verify and check-out the safety features before repackaging. Consequently, repackagers have to bear the costs needed to modify their management software accordingly and buying scanning equipment. Estimated costs for repackagers are not available, but it is reasonable to assume that they will face the same investments as wholesaler distributors since they will have to perform similar activities. ECORYS calculates that the total costs for scanning/verification of the safety feature would be less than € 0.5 million a year.

The calculations above are based on the assumption that a large majority of prescription medicines will bear the safety features. Directive 2011/62/EU stipulates that prescription medicines might be exempted from bearing the safety features "by way of exception", so the contribution of these exceptions to the overall cost calculation was considered negligible.

The large difference in costs between originator and generics is explained by the fact that two third of all packaging lines operate in the generic sector. The generic sector would therefore be forced to update a higher number of manufacturing lines.

³⁸ European Directorate for the Quality of Medicines and Health Care of the Council of Europe

The costs estimates also differ widely due to the uncertainty about the equipment currently in use by the manufacturers, the level of automation of printers and cameras, or the number and type of packaging lines (single-country *vs* multiple-country lines with different requirements).

It is critical to note that the above-mentioned costs would be partially compensated by **potential savings** and benefits through:

- The replacement of different national product coding systems with a harmonised EU system, thus eliminating the need of having multiple manufacturing lines to comply with the specifications of individual national systems. The 2008 impact assessment extensively showed that a harmonised system of safety features would allow for important savings by all operators (innovators, generics and parallel traders). Industry estimates these savings to be as high as 1bn EUR per year³⁹. The recent public consultation also confirmed that the current fragmentation of the rules and techniques for product coding increases costs without bringing any added value;
- Reduction in falsified/counterfeit medicines. If less falsified medicines are sold, this translates into an increase in legitimate sales and profits for manufacturers. ECORYS estimates that for 2009, total gross operating surplus of reducing counterfeit medicines in the legal and the illegal supply chain would amount to approximately € 3 million a year.
- Reduction of costs, human resources and time needed to handle recalls and returns procedures. The number of recalls has more than doubled in the last 5 years. On average about 200.000 units are affected per medicine recall⁴⁰. Each product recall is estimated to cost € 2 million⁴¹ across the supply chain.

The impact of the costs linked to the unique identifier will depend on the size of the manufacturer/parallel importer. Although the pharmaceutical sector is dominated – in terms of revenues – by a limited number of large pharmaceutical companies, there is nevertheless a very large number of small and medium enterprises (SMEs). According to the impact assessment on the fees on pharmacovigilance (SWD (2013) 234 final), SMEs represent approximately 90% of the marketing authorisation holders in the EU. The micro enterprises represent 33% of the MAHs within the SMEs category. EGA, the European Generic Medicines Association, also confirmed that the sector of generic medicines has a high number of SMEs.

Due to their low production volume, SMEs could be potentially more affected by the costs of introducing the safety features than large pharmaceutical companies, which would benefit from economies of scale. However, Directive 2011/62/EU does not provide for exemption from bearing the unique identifier based on the size of the company, or on the classification as originator *vs* generic medicine, as this could compromise the protection of patients.

³⁹ Impact Assessment - Commission Staff Working Document Accompanying document to 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 (SEC(2008) 2674), p42

⁴⁰ McKinsey and Company, "Strength in unity: The promise of global standards in healthcare". October 2012.

⁴¹ Pharmaceutical recalls take man-hours at hospitals and pharmacies to check the shelves, process the recall and bring the product back to the manufacturer. Manufacturers may spend up to a few men-month in executing a recall. They also face losses due to product compensation.

As available data are partly qualitative and data from industry are uncertain, it is difficult to conclude at what extent the savings offset the costs. However, this option is the preferred option for the European Associations representing the pharmaceutical sector, wholesale distributors, parallel importers, pharmacies and the Member States for the following reasons:

- Harmonisation of the modalities for identifying products is crucial given the movement of medicines across national borders. This will allow information to be exchanged between manufacturers, parallel importers, distributors and retailers in the Member States and the free movement of medicines in the internal market to be improved. A fragmented system creates different standards and processes that are costly for all users;
- The use of a 2D barcode as the data carrier for the unique identifier is supported by most stakeholders. This carrier allows the storage of a large amount of information in a small surface, and is therefore suitable for small packs. The Data Matrix code (two-dimensional barcode) has been an ISO standard for 12 years and is widely used globally. Manufacturers have extensive experience in using it due to existing serialisation requirements. It is flexible, i.e. it can easily be adapted to respond to technical advances/changes in the future. It is considered a more reliable and affordable carrier than a 1D barcode or a RIFD;
- Respondents strongly recommended using internationally recognised standards for identifying all products in line with the systems in place in certain Member States. The use of ISO standards, is the safest approach to ensure compatibility across national systems as these are overarching, widely used, internationally-recognised standards. Internationally recognised standards are already used for serial numbers and their carriers in third countries, e.g. in Turkey and South Korea, and may also present an advantage at global level. It is known that other world regions are moving towards protecting their supply chain. The use of international standards could facilitate the international trade. Basing the approach on established international standards in line with systems currently in place will also help ensure alignment with national healthcare cost reduction initiatives;
- The integration of the reimbursement code in the unique identifier would avoid placing two sets of barcodes on the outer packaging, reducing costs. Certain Member States (FR, DK, SE, FI, AT) already require the reimbursement to be indicated on the packaging in a machine-readable format.

Authorities and the European Commission

This option will have no direct economic impact on European authorities (the European Commission and the European Medicine Agency). However, this option will have a positive effect on the robustness of the entire European regulatory framework laying down rules for the authorisation, manufacture, distribution and labelling of medicinal products in the EU.

At national level, it would harmonise national provisions and facilitate implementation, reimbursement and surveillance activities by national competent authorities. The need for investigations on falsified medicines and recalled products by national competent authorities will decrease, as will the budgetary and human resources needed to perform these tasks.

The overall economic impact for national authorities is therefore positive.

Pharmacies

The full harmonisation of the specificities of the unique identifier will have a positive economic impact on pharmacies for a number of reasons:

- The necessary investment will be lower in case of harmonised specificities as only one piece of software and one reader (i.e. scanner device for a 2D barcode) will be required. In case of non-harmonisation, the pharmacists will have to be equipped with different scanners and software to be able to read the different codes and data carriers; this was the most important argument put forward by many stakeholders during the consultation.
- A machine-readable batch number will facilitate recalls, thereby decreasing the man-hours needed to handle them. The recalls system currently relies on (i) information being relayed to pharmacies by email or fax and (ii) pharmacists manually checking their stocks. Despite the best efforts to avoid recalled products reaching patients, the system is currently inefficient. Percentages of medicines successfully recalled vary from 50% (in case of recalls associated with low medical risk) to 90% (for critical recalls)⁴².
- Reduce the costs and man-hours linked to the tracking of adverse events⁴³ caused by biological medicinal products⁴⁴ as required by the recent legislation on pharmacovigilance⁴⁵
- Reduce the amount of expired products being delivered to pharmacies and dispensed to patients, thereby significantly contributing to the efficient management of pharmacy stocks. This would be a consequence of the possibility of electronically checking expiry dates. This opportunity is highly valued by pharmacists in the Member states where such product coding systems is in place (e.g.: Belgium).
- Reduce the costs and man-hours linked to the handling of returns. Approximately 1 % of medicinal products are returned every year.
- Inclusion of the reimbursement code within the unique identifier will avoid the need to scan a pack multiple times to capture different information, simplifying the dispensing of medicines to patients and saving time.

Wholesale distributors⁴⁶

This option has a positive economic impact on wholesale distributors because it allows saving in terms of both time and labour costs. The European Association representing full line wholesale distributors, GIRP, strongly supports this option. According to GIRP, the inclusion of the batch number and the expiry date in the unique identifier in a machine-readable format will have a very positive impact on the administrative burden. In particular, having the expiry

⁴² McKinsey and Company, "Strength in unity: The promise of global standards in healthcare". October 2012.

⁴³ Adverse event: a response to a medicinal product which is noxious and unintended.

⁴⁴ Plasma derived medicinal products and vaccines, (Directive 2001/83/EC)

⁴⁵ Article 102 of Directive 2010/84/EU of the European Parliament and of the Council, as regards pharmacovigilance

⁴⁶ Short-line wholesale distributors were not taken into account when calculating costs estimations, as their market share is very limited (3-5%).

date in a machine-readable format is essential for the stock management process in the wholesale distribution facilities. It would facilitate the rotation of stock according to the FEFO (first expiry, first out) principle, as recommended by the EU good distribution guidelines. In addition, having the batch number in a machine-readable format would facilitate complying with the requirements of Article 80(e) of Directive 2001/83/EC. Indeed, the wholesale distributor will be required to record and store all batch numbers of products bearing the safety features once these will be introduced. If the batch number is not printed on the pack in a machine-readable format, the information will have to be captured manually. This would drastically slow down the workflow in the warehouse and increase labour costs. GIRP estimates that the wholesale distributors' annual labour costs for manually capturing batch numbers would be about €53 million for the EU-25 (excluding Malta and Cyprus). Furthermore, the costs for retrieving and recording batch numbers through a database are estimated at €13.1 million for the EU-25. The above costs could be avoided by requiring the manufacturers to introduce the batch number in the unique identifier

5.1.2. Policy option 1/2: Partial harmonisation of the composition of the number to fight against falsified medicines

5.1.2.1. Social impact

Partial harmonisation still provides the minimum requirements allowing pharmacies to systematically check the authenticity of the medicine pack before dispensing it to the patient. However, the benefits for the patients would not be as high as in option 1/1 for the reasons explained below.

This option would allow manufacturers to use different coding systems, i.e. different "carriers". This, in turn means that the pharmacists checking the unique identifier require different reading devices depending on the technology chosen. It will therefore be more difficult to ensure systematic pack verification by pharmacies and retailers. If packs are not systematically verified at dispensing points, the protection against falsified medicines will not be optimal and the best level of security for patients cannot be ensured.

In addition, this option allows manufacturers to choose 1D barcodes as carriers for the unique identifier. Due to their limited storage capacity, 1D barcodes cannot contain additional information such as batch number and expiry date. If the batch number and expiry date are not included in the machine-readable pack code, it would not be possible to use electronic reading to improve the accuracy of the recall, return and adverse effect tracking processes, leading to more inappropriate medication reaching the patients. This would limit benefits for the health of patients.

In conclusion, this option decreases the risks that fake medicines reach the patients and has a positive social impact on the health and safety of the EU population, although to a lesser extent than option 1/1.

5.1.2.2. Economic impact

Manufacturers

The costs required to upgrade the manufacturing lines and presented under option 1/1 are valid also for option 1/2.

The difference with option 1/1 is that the current option offers manufacturers the opportunity to:

- choose their preferred technical solution for the composition of the number and the data carrier. This flexibility may translate in cost-neutrality for companies which only manufacture medicines for the Greek, Belgian and Italian market, i.e. to Member States where a system of authentication is already in place. These companies will not be forced to upgrade their manufacturing lines to accommodate a different unique identifier.

- continue to use pre-printed cartons. From the public consultation, the European Generic Association raised that a limited number of companies currently order from third parties cartons which are pre-printed with barcodes (no figures were provided). Companies concerned are mainly small and medium size enterprises. Indeed, the use of pre-printed cartons⁴⁷ allows for simpler, cheaper packaging lines. Pre-printed cartons, however, are not compatible with 2D barcodes and the mandatory inclusion of batch number and expiry date in the carrier. Some companies argued that option 1/2, allowing some flexibility in both the number and carrier, would not require an upgrading of packaging lines, hence saving costs. However, others argued that, even in case of pre-printed cartons, the manufacturing line would still need to be equipped with a new camera, a reject ejection mechanism and packaging line controller software, regardless of the carrier and composition of the unique identifier, and savings would be marginal. In addition, according to GIRP, costs savings at the production site would be offset by higher costs incurred for wholesale distributors and pharmacies.

Wholesale distributors/Pharmacies

Allowing manufacturers to select their own coding technology would have a negative impact on the cost and technical efficiency of both wholesale distributors- and pharmacy-level authentication.

The necessity to recognise potentially different carriers would require for wholesale distributors and pharmacies to invest in multiple scanning devices and software systems, hence increasing the economic impact for these sectors.

Directive 2011/62/EC introduced the obligation for wholesale distributors to keep record of batch numbers. Should the manufacture choose not to introduce the batch number in the unique identifier; the wholesale distributors will be forced to record the batch number manually (rather than reading them directly from the carton). Wholesale distributors estimate the additional annual labour costs of capturing the batch number manually at € 66.1 million.

For the Member States where a national number already exists for reimbursement purposes, the non-inclusion of the reimbursement number in the unique identifier would likely mean that the presence of two barcodes on the box (one for reimbursement purpose and one for authentication). Such situation would lead to the need for a double scanning by wholesale distributors and pharmacies, reducing efficiency in distribution operations and increasing labour costs.

Authorities and the European Commission

⁴⁷ Outer packaging of a medicinal product

This option will have no direct economic impact on European authorities (the European Commission and the European Medicine Agency). However, a provision allowing the detection of fake medicines will strengthen the European regulatory framework and increase public health protection. Consequently, this option will have a positive effect on the robustness of the entire European regulatory framework if a suitable verification system is put in place.

At national level, the time and human resources needed for implementation, reimbursement and surveillance activities by national competent authorities will not decrease.

This policy option will not generate the savings achieved by option 1/1 through harmonisation of national product coding systems. The overall economic impact of this option is therefore neutral.

5.2. Policy options for achieving objective 2: To introduce proportionate verification of the safety features in order to combat falsified medicines

5.2.1. Policy option 2/1: Systematic verification of the unique identifier at the dispensing point

5.2.1.1. Social impact

This policy option has a positive social impact by ensuring a high level of patient protection. It ensures the minimum requirements guaranteeing that a falsified medicinal product is detected before it is dispensed to the patient.

Community and hospital pharmacies and other retailers are the last point in the distribution chain where the quality, security and authenticity of the medicines dispensed to the patient can be ensured. This option therefore has a positive impact on community and hospital pharmacies because it builds a relationship of trust between pharmacists and the patients by ensuring the safety of medicines dispensed to them.

5.2.1.2. Economic impact

The main economic impact of this option is for pharmacies.

Pharmacies

This option has an economic impact on this sector. In order to carry out the authentication check, this option entails the costs necessary to modify the pharmacy management software, buy scanners and verify authenticity by connecting to the repository system via the Internet. Finally, employees will have to be informed about and trained in the new working procedures. Modifying the software, buying scanners and the training of staff can be considered as one-off investment costs.

The consequences in terms of costs for community pharmacies are presented in Annex 7. The estimated total annualised investment costs (one-off cost) ranges from €17 to € 69 million. This translates into an annualised investment cost of €530 per pharmacy. Yearly costs for maintenance and operations of the pharmacy management will probably remain the same as before the introduction of the unique identifier. Hence, the costs consequences on community

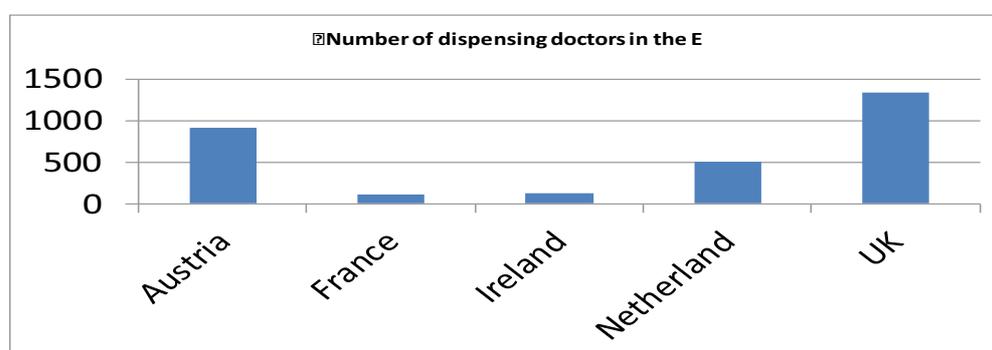
pharmacies can be considered of limited impact compared to the production value and the profit margin.

The costs incurred by hospital pharmacies are expected to be higher than the costs for community pharmacies. Hospital pharmacies currently do not have to scan medicines so they are not equipped with the necessary scanners and software. Total costs needed to buy the necessary equipment are estimated at € 2 to 4 million, with costs per hospital pharmacy up to € 750 (see Annex 7). These investment costs are relatively low and will not impact significantly on the total budgets of hospitals.

European Associations representing pharmacies and hospitals broadly supported this option.

Health care professionals

In a small number of Member States, doctors and other health professionals are authorised to dispense medicines to patients. They are responsible for only a small fraction of the medicines dispensed every year in the EU. In the interest of patient's safety, dispensing doctors should also authenticate the medicines they dispense. This option will entail costs as doctors and other health professionals may not be equipped with the necessary scanners and software. Estimated total investments costs amount to € 2 million, resulting in a maximum cost per dispensing doctor or health professional of €530. It is important to note, though, that: (i) the associations representing health care professionals have not expressed specific concerns; and (ii) rapidly evolving technology may induce doctors to buy scanners regardless of the need to verify the safety features (for example, to read electronic prescriptions, which are becoming widespread and will be even more so by the time the delegated act will enter into force).



Authorities and the European Commission

This option will have no direct impact on European authorities (the European Commission and the European Medicines Agency). However, adding provisions allowing the detection of fake medicines will strengthen the robustness of the whole European regulatory framework.

The economic impact on the Authorities and the European Commission will be equivalent in the three options.

5.2.2. Policy option 2/2: Systematic verification at the dispensing point and risk-based verification by wholesale distributors

5.2.2.1. Social impact

This option ensures a higher level of protection against falsified medicines than option 2/1 because it introduces an additional level of controls earlier in the supply chain. Checks of medicines at risk at the level of wholesale distributors would allow the detection of the falsified medicine at the point of entry. This would not only prevent the circulation of the fake medicine for months or years among the different actors in the supply chain, but also increase the probability of identifying the source of falsification and the responsible traffickers. The sooner a fake medicine is detected after entering the supply chain, the higher the probability to identify its point of entry and its source. This option therefore facilitates the fight against medicine falsification.

In addition, additional checks upstream of the dispensing point provide an additional security in case the medicine is, for whatever reason, not checked-out at the dispensing point.

Additional checks will also increase the traceability of medicines and management of stocks in case of shortages. For example, should the production of a particular medicine be interrupted due to quality issues, leading to recalls of defective batches and potential EU-wide shortages, scans at wholesale level would permit the rapid localisation and quantification of non-defective batches across the EU (where these stocks are located and how many units are available). This would facilitate a rapid redistribution towards Member States with lower stocks and allow a swifter resolution of the shortage.

Finally, scanning by wholesale distributors will facilitate the investigations and the recall of medicines in the supply chain, reducing the exposure of patients to inappropriate medicines.

This option therefore has a very positive social impact.

5.2.2.2. Economic impact

The economic impact described for pharmacies under option 2/1 is also valid for the current option. The main difference is the presence of an economic impact on the wholesale distributors.

Wholesale distributors

This option has a significant economic impact on the wholesale distributors as it requires investments to modify the management software, buy scanners and verify pack authenticity (based on risk) by connecting to a repository system via the Internet.

The costs for wholesale distributors are linked to:

- *modifying wholesale management software*
- *buying scanning equipment*
- *scanning time (labour hours per year to unpack pallets, scan the code, wait for response time of repository system)*
- *warehouse space.*

In the table below the main results of this section are presented for full-line wholesale distributors. Total investment costs are annualised at € 8 million for the entire sector. Additional annual costs of risk-based are estimated at € 25 million per year for the whole sector. The total burden (investments costs and annual costs) for wholesale distributors would be approximately € 33 million per year and around €43,000 per wholesaler distributor.

Table 3.2: Investment costs and annual costs for full-line wholesale distributors (annualised)

	Total costs for sector (in €)	Costs per wholesaler (in €)
<i>Investment costs ^{a)}</i>		
Modify wholesale software	8 000 000	10 000
Buy scanning equipment	Less than 500 000	Less than 500
<i>Total investment costs (one-off costs)</i>	<i>8 000 000⁴⁸</i>	<i>10 000</i>
<i>Annual costs</i>		
Scanning time	15 000 000	20 000
Warehouse space	10 000 000	13 000
<i>Total annual costs</i>	<i>25 000 000</i>	<i>33 000</i>
Total costs	33 000 000	43 000

In 2009, the total value added for wholesale of pharmaceutical goods was € 56.6 billion. The additional annual costs, € 25 million, represent less than 0.1% of the total value added.

As regards the costs of the scanning time, GIRP has based its calculation on the number of additional employees that would have to be hired.

The above-mentioned costs would be partly compensated by potential savings. When wholesalers inadvertently receive a falsified product, they have to replenish the stocks with genuine products, incurring in a net loss. Authenticity checks at the level of wholesalers would likely prevent the above scenario from happening.

Furthermore, we believe that certain investment costs mentioned above will have to be done automatically due to the obligation for the wholesaler distributor to record the batch number. For the purpose to record the batch number, wholesaler distributor will need to adjust the warehouse management software and buy a limited number of scanners. Even if point of sale verification by the pharmacy (option 2/1) will be the option chosen, GIRP confirmed that

⁴⁸ Using GIRP figure, it will cost approximately € 20,000 per warehouse equals a cost estimate of approximately € 50,000 per wholesaler. A wholesaler distributor may have several warehouses. Taking into account approximately 2,000 warehouses in Europe, this would mean a total investment of approximately € 40 million. Annualised and using a period of 5 years for the lifetime of software, the costs are € 8 million for the sector or € 10,000 per wholesaler.

wholesale distributors would need access to the system to at least be able to verify in case of doubt.

It is important to note that, in its submission, GIRP supports this option because it considers that product verification at the dispensing point complemented by risk-based checks at the wholesale distributor level is, despite the involved costs, the most cost effective and proportionate approach to verify the safety features and achieve supply chain and patient's safety.

5.3. Policy options for achieving objective 3: To ensure interoperability and performance of the repository system by laying down the requirements for the establishment and management of and access to repositories

5.3.1. Policy option 3/1: Establishment and management by stakeholders with supervision by the relevant competent authorities

5.3.1.1. Social impact

Based on the experience of the existing pilot systems developed by stakeholders (see option 4.3.1), a stakeholder-led repository ensures robust and efficient verification of individual packs, and an effective detection of falsified, expired and recalled products. This option consequently ensures a high level of protection of patients' health.

In addition, the supervision by the national competent authorities would introduce control over the system, increasing transparency surrounding the system and increasing the level of trust between the economic operators and the authorities. Some national authorities raised the possibility of a potential conflict of interest when companies both manage and own the data in a private repository system. The supervision by competent authorities eliminates such risk.

We can therefore expect this option to have a positive social impact.

5.3.1.2. Economic impact

The main impact of this option is on manufacturers and parallel importers.

Manufacturers/parallel importers

This option entails costs and therefore has a significant economic impact on both sectors.

To date, the main European organisations representing pharmaceutical companies (with the exclusion of generics manufacturers), parallel importers, wholesale distributors and pharmacies have developed a pilot project for authentication of medicines, the European Stakeholder Model. The European Stakeholder Model (ESM) is composed of a network of national data repositories linked via a hub (together forming the European Medicines Verification System, EMVS) serving as the verification platforms which pharmacies and other registered parties can use to check a pack's authenticity. The system will be interoperable across EU Member States with the necessary flexibility to account for national needs. The cost estimates⁴⁹ of the pilot project are broken into five main blocks:

⁴⁹ For a repositories system with the capacity of connecting more than 216000 users (154000 community pharmacies, 21000 hospital pharmacies, 37500 wholesalers, 3800 manufacturers and 100 parallel traders)

- Set-up costs
- Running costs (annual)
- Technical investments
- Administrative fees
- Stakeholder governance (annual)

The cost estimates are calculated on the basis of the unique identifier being placed on all prescription medicines.

Annual costs EU-wide for the manufacturers	Cost per pack
€ 120m to €205m	€0.013–0.022

These costs estimates stem from the direct experience of the pilot projects and are considered as the most reliable.

The cost estimates for the repository system vary widely, reaching in certain cases €400 million. In view of the divergences of the costs, Commission has asked ECORYS to analyse the data and to explain variability. ECORYS concluded that the difference stems from different designs of the system in terms of its engineering.

For the purpose of this impact assessment, the most conservative value (205m EUR) is going to be used for the assessment and comparison of the options.

The main advantage of running pilot projects is that they could easily and rapidly be scaled up and be made operational, should it be decided to implement this option. Scaling up an existing system will save time and be more cost-effective than creating a brand new system. Both the public consultation and contacts with stakeholders confirmed that this is considered by all associations representing pharmaceutical companies and parallel importers as the only option for putting an effective and efficient system of product authentication in place in a timely manner, for a number of reasons:

- Incorporating the expertise of key actors in the supply chain in the body governing the repository system is essential to ensure that needs of manufacturers, parallel importers, wholesale distributors, and pharmacies for operating the supply chain efficiently and smoothly are met;
- The experience of stakeholders would ensure that no unnecessary obligations are added in the system in addition to authentication requirements.

Authorities and the European Commission

This option will have no direct impact on European authorities (the European Commission and the European Medicine Agency).

Supervision by the national competent authorities may require the allocation of dedicated human resources; hence it may entitle an increase in personnel costs.

5.3.2. Policy option 3/2: Establishment and management by a public authority at EU level

5.3.2.1. Social impact

This option would offer a thorough supervision of the system by an official EU body. It would be the responsibility of the EU body to ensure that the system is safe and functional for all operators in the supply chain. The fact of being set up by an EU body would guarantee the independence of the system. This option would preserve the trust of patients in the regulatory framework for medicines.

The system would be independent and have the protection of public health as the primary objective.

Hence, the system would offer good protection for patients and therefore has a positive social impact.

5.3.2.2. Economic impact

The main difference with the previous option is the impact on the European Commission and the manufacturers/ parallel importers.

European Commission

This option requires the European Commission or another official body such as the European Medicines Agency to set up a new database. Directive 2011/62/EU does not provide a budget for the repository system and considers that the costs of the system are to be borne by the manufacturers. This means that the Commission would need to devise a scheme for charging fees to all actors in the supply chain. The fees would feed into a budget for setting up an EU database and hiring human resources. Such option would oblige the Commission to allocate a part of its EMA budget for this purpose. In terms of human resources, at least, 30 staff would be required to set up and to maintain the system. The cost of an IT consultant in Belgium costs about 700€ per day.

So far, the EU has never set up a database to which all pharmaceutical companies, distributors, pharmacies, retailers and general practitioners currently controlled at national level should connect and from which they would receive an instantaneous reply. Experience of European systems such as the Schengen Information system⁵⁰ or the food product tracing⁵¹ show that intensive financial and human resources are needed. Therefore, due to the limited experience in European interactive databases in the pharmaceutical sector, the development of such a system by an EU body could entail costs higher than in option 3/1.

During the public consultation, stakeholders raised the extreme complexity of the system. It would be a real challenge for a public authority to establish such system without the prior experience of pilot projects or comparable databases that take into accounts the specificities of all actors in the supply chain. Stakeholders doubted that an efficient and timely system could be put in place by an official body. This option would require a new central repository system storing all data from all actors in the supply chain, the simultaneous connection of thousands of actors at the same time, and the instantaneous authentication of individual packs. It would require setting up a brand new IT tool taking into account the knowledge of local

⁵⁰ The SIS is a Central System, EU States' national systems and a communication infrastructure (network) between the Central and the national systems.

⁵¹ <http://ec.europa.eu/food/animal/diseases/traces/>

distribution and pharmacy/retailer procedures. Such a system may be less responsive to specific regional market features such as local reimbursement practices and local dispensing practices. Difficulties would be encountered in setting up timely a secure and cost-effective system.

Manufacturers/parallel importers

Considering the most optimistic scenario, the costs of the final system could be the same than in option 3/1 if the functionalities of the system are exactly the same and if there is only one database. However, there is no pilot project for a EU-led repository, nor appropriate database that could be adapted/scaled-up. Initial costs to explore pilot projects will have to be added in comparison to option 3/2. Moreover, this option would generate additional "coordination costs" that can have great influence over the total costs of ICT system. These are the costs necessary to align the interests of all stakeholders, all European stakeholders' organisations and national and regional stakeholder's organisation into one single system.

5.3.3. Policy option 3/3: Establishment and management by public authorities at national level

5.3.3.1. Social impact

If all Member States were to set up a repository system on time, the advantages of this policy option would be that:

- The system would offer uniform protection for patients across the European Union and would therefore have a positive social impact. This option should offer good supervision of the system by an official body. It would be the responsibility of the Member States to ensure that the system is safe and functional for all operators in the supply chain.
- The system would be independent, with the protection of public health as the primary objective.

5.3.3.2. Economic impact

The main difference with the previous options is the impact on the national authorities and the manufacturers/ parallel importers. However, many of the disadvantages of option 3/2 also apply to this option.

Manufacturers/parallel importers

This option seems to have a significant economic impact on pharmaceutical companies, for the following reasons:

- The fragmented system that could emerge would be highly burdensome and expensive to run as each manufacturer (especially when serving multiple markets) would need to be connected to a multitude of national repositories rather than going through a centralised database. Manufacturers would have to pay multiple fees to access the individual repository systems;
- Development costs are likely to be much higher for 28 systems than for a central system (EU- or stakeholder-driven);

- During the public consultation, many stakeholders doubted that public authorities at national level would succeed in establishing such a complex and costly system.

On the other hand, the number of actors linked to each national repository system would be limited. This might reduce the complexity of the system.

National authorities

Member States can select the appropriate characteristics of the national repository system in view of their specific needs, such as processing medicine reimbursements.

Member States with a system in place could adapt it to fulfil the obligation to verify the authenticity of the medicinal product. This could result in a cost-efficient solution. However, these Member States represent a minority (3 out of 28).

A system led by national authorities would be independent from private organisations, thus avoiding potential conflicts of interest. National governance would present the advantage of guaranteeing local supervision whilst still ensuring an acceptable level of harmonisation to agreed common database standards.

Under this option, national authorities would need to introduce fees to manage the system and engage initial financing for setting up the system and for hiring staff. During the public consultation, two competent authorities favoured either EU or national governance while one authority called for national governance. The remaining competent authorities pointed to the high initial costs and human resources needed to set up such a system. As for option 3/2, stakeholders raised the extreme complexity of the system and the difficulty for national authorities to establish such system in a timely and cost-effective way.

5.4. Comparing the options

The policy options for the three problem areas are compared below against the criteria of effectiveness (i.e. to what extent they fulfil the objective), efficiency (i.e. at what cost they do so) and coherence with other EU policies. Given the qualitative and quantitative nature of the impact assessment, the following scores were chosen for illustrative purposes: low, medium and high. Coherence will be assessed according to the EU policies: protecting public health and ensuring the free circulation of goods.

Comparison of the options for objective 1: To ensure efficient and effective characteristics and technical specifications of the unique identifier		
OPTIONS	EFFECTIVENESS (to what extent they fulfil the objective)	EFFICIENCY (at what cost they fulfil the objectives)
Policy option 1/1: Harmonisation of the composition of the identifier and the data carrier to protect against falsified, recalled and expired	HIGH in harmonising the specificities of the unique identifier HIGH in protecting patients against the entry of falsified medicines and recalled and expired products HIGH in ensuring the free movement	HIGH as the fixed costs for the introduction of the unique identifier are mitigated by the reduced costs of verification equipment and reduced needs for country-specific

medicines	of medicines in the internal market	manufacturing lines.
Policy option 1/2: Partial harmonisation of the composition of the identifier and the data carrier to fight against falsified medicines	MEDIUM in protecting public health, ensuring harmonisation and protecting against falsified medicines due to the non-uniformity of the features and the data carrier	LOW as the fixed costs for the introduction of the unique identifier are aggravated by the necessity of buying multiple pieces of equipment to verify divergent number formats, and need for country-specific manufacturing lines.

Consequently, option 1/1 prevails in terms of both effectiveness and efficiency.

Comparison of the options for objective 2: To introduce proportionate verification of the safety features in order to combat falsified medicines		
OPTIONS	EFFECTIVENESS	EFFICIENCY
Policy option 2/1: Systematic verification of the safety features at the dispensing point End-to-end verification	LOW as this is the minimum verification to be performed in the supply chain to ensure detection of falsified medicines. Fake medicines may still circulate in the EU for months or years before being detected	HIGH as only pharmacies/retailers would be affected by the costs
Policy option 2/2: Systematic verification of the safety features at the dispensing point and risk-based verification by wholesale distributors	HIGH in ensuring a proportionate verification of the safety features. Additional verifications are performed only when there is an increased risk of falsification.	MEDIUM as wholesale distributors, in addition to pharmacies/retailers, would also be affected by the costs

Consequently, option 2/2 prevails in terms of both effectiveness and efficiency.

Comparison of the options for objective 3: To ensure interoperability of the repository system, free movement of medicines and supervision by the competent authorities		
OPTIONS	EFFECTIVENESS	EFFICIENCY
Policy option 3/1: Establishment and management by stakeholders with supervision by the relevant competent	HIGH in ensuring interoperability of the databases and interfaces HIGH in ensuring coordination of the various stakeholders	HIGH due to the low coordination costs and the possibility to rapidly scale-up existing pilot

authorities	HIGH in ensuring the free movement of medicines HIGH in ensuring supervision by competent authorities	projects
Policy option 3/2: Establishment and management by a public authority at EU level	HIGH in ensuring interoperability as there would be a single database with limited interfaces MEDIUM in ensuring coordination of the various stakeholders HIGH in ensuring the free movement of medicines HIGH in ensuring supervision by an official body	LOW due to additional costs to set-up a pilot project and the coordination costs necessary to align the interests of all stakeholders
Policy option 3/3: Establishment and management by public authorities at national level	LOW in ensuring interoperability of the systems in the EU MEDIUM in ensuring coordination of the various stakeholders HIGH in ensuring the free movement of medicines HIGH in ensuring supervision by competent authorities	LOW due to the extra costs of setting up 28 national systems

Consequently, options 3/1 prevails in terms of both effectiveness and efficiency.

Overall, the consultant ECORYS assessed the impact of introducing the unique identifier on the competitiveness of the pharmaceutical sector particularly on manufacturers, wholesale distributors, parallel importers and pharmacies (Annex 10). Total yearly costs estimates of the unique identifier for the entire sector range from € 200 to € 800 million per year. However, considering the production value (ex-factory) of the sector, the additional cost appears modest at less than 1%.

The cost impact of the unique identifier may be higher for generic companies and parallel importers. This difference can be explained for the following reasons: the number of packaging lines to upgrade is higher in the generic sector and the generic companies tend to be smaller than originators. Unfortunately, possible waivers of the unique identifier for certain sectors are not possible without compromising the identification of fake medicines.

Costs for prescription medicines

	Unique identifier	
	Total costs sector (in € million)	Costs per company
<i>Manufacturers</i>		(in € 1,000)
Originator manufacturers	20 – 110	7 – 39
Generics manufacturers	30 – 210	30 – 210 ⁵²
Repackagers / parallel importers	1 – 5	1 – 5
Total costs	51 – 325	-
<i>Wholesalers</i>		(in € 1,000)
Full-line wholesalers	33	43
Short-line wholesalers	Not available	Not available
Other	0	0
Total costs	> 33	-
<i>Retailers</i>		(in €)
Community pharmacies	17 – 69	270 – 530
Dispensing doctors	2	270 – 530
Hospital pharmacies	2 – 4	390 – 750
Other retailers	?	?
Total costs	21 – 75	-
<i>Repositories system</i>		
Stakeholder governance	100 – 400	
EU governance	100 – 400	
National governance	> 100 – 400	
Total costs	100 – 400	-
Total costs sector	205 – 833	-

The ECORYS study also drew conclusions on the impact on the price of medicines. The direct effect on prices depends on whether pharmaceutical manufacturers will absorb the costs of the unique identifier by reducing their profit margins or whether they will increase prices to cover for the additional costs. The European Generic Association claims that reducing the profit margin may be unsustainable for some generics companies, forcing them to increase the price or exit the market. Generic medicines could then become less competitive. On the other hand, a Mc Kinsey study⁵³ shows that the generic industry is performing well (+11.6% growth), particularly so in comparison to originator pharmaceutical companies (-1.9%). A

⁵² The number of generic companies is estimated to be around 1,000 companies

⁵³ http://www.mckinsey.com/insights/health_systems_and_services/a_wake-up_call_for_big_pharma. Chart on Growth relative to industry.

reduction in the profit margins would also affect originators, as they need to invest in research and developments to discover and bring to the market new medicines. Consequently, it cannot be proven that the implementation of the unique identifier will affect the competitiveness generic manufacturers more than that of the originators. In the worst case scenario, some companies may increase the price of medicines by a few euro cents. Overall, however, the direct effect on the prices for consumers is expected to remain limited: the potential price increase is not only small in absolute terms, but its impact will be further diluted by the time needed for the full implementation of the delegated act in all Member States (not before 2020). In real terms, other factors, such as variations of taxation regimes (e.g. TVA) could have a much more significant impact on medicine prices.

Moreover, ECORYS conducted an in-depth comparison of the three policy options of repository system and their conclusions are presented in Annex 9.

The implementation of the unique identifier will bring major benefits to protect patients from falsified medicines in the legal supply chain, although it will also generate costs for the pharmaceutical sector. The most cost-effective options to mitigate these costs are:

- harmonising the composition of the number and the data carrier;
- verifying the unique identifier at the pharmacy and, for medicines at higher risk of falsification, at the level of wholesale distributors
- using a repository established and managed by stakeholders, under the supervision of the relevant competent authorities

6. MONITORING AND EVALUATION

Monitoring is already provided for in Directive 2011/62/EU of the European Parliament and of the Council on preventing the entry into the legal supply chain of falsified medicinal products. It requires the Commission to monitor and evaluate the measures it takes. At the latest five years after the date of application of the delegated acts referred to in the Directive, the Commission must submit a report to the European Parliament and to the Council containing the following:

- (a) a description, where possible including quantitative data, of the trends in the falsification of medicinal products in terms of: categories of medicinal products affected, distribution channels including sale at a distance to the public by means of information society services, the Member States concerned, the nature of the falsifications, and the regions of provenance of these products; and
- (b) an evaluation of the contribution of the measures provided for in the Directive regarding the prevention of the entry of falsified medicinal products in the legal supply chain. That evaluation should in particular assess the rules related to the safety features.

To this end, the Commission will consult the Member States to collect the above mentioned data. The Commission fixes an indicator to collect every year the incidents of fake medicines reported by the EU Official Medicines Control Laboratories and from the rapid alert system for quality defects. All this should be sufficient to ensure an effective monitoring of the functioning of the proposed action.

As far as implementation is concerned, the Member States shall apply the provisions related to the safety features from three years after the date of publication of the delegated act setting out the characteristics and technical specifications of the unique identifier, the modalities of verification of the safety features and the establishment and management of the repository system containing the unique identifiers. Member States having a system in place shall apply the provisions at the latest from nine years after the date of publication of the delegated act.

7. ANNEXES

Annex 1: Glossary

EAEPCC - European Association of Euro-Pharmaceutical Companies representing Europe's licensed parallel distribution industry comprising licensed wholesalers who supply ("export") and/or purchase ("import") and repackage legitimate European medicines in free circulation.

EDQM European Directorate for the Quality of Medicines and HealthCare of the Council of Europe

EFPIA: European Federation of pharmaceutical industries and associations

EGA: European Generic Associations

EMA European Medicines Agency

Falsified medicines are medicines with false identity, history or source, while counterfeit medicines are products infringing intellectual property rights.

A falsified medicinal product has a false representation of:

- (a) its identity, including its packaging and labeling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;
- (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or
- (c) its history, including the records and documents relating to the distribution channels used.

Directive 2011/62/EC introduced a definition of falsified medicines in order to distinguish falsified medicines from counterfeit medicines which infringe the rules on intellectual property rights of a company.

Full line wholesale distributors: wholesale distributors who deliver to the pharmacies all medicines that are used in their geographic area

GIRP: European Association of Pharmaceutical Wholesalers

MAH – Marketing Authorisation Holder: for the purpose of this document, holder which is responsible for marketing the medicinal product. The MAH is responsible for the quality, efficacy and safety of its products.

Manufacturing authorisation holder: for the purpose of this document, this term includes both manufacturers and parallel importers engaged in repackaging to the exclusion of contractors and subcontractors involved in the manufacturing process but not responsible for putting pharmaceutical products on the market. For the avoidance of doubt, a manufacturer

engaging contractors or subcontractors to produce on its behalf shall be considered the manufacturing authorisation holder.

OTC medicines ‘Over-the-counter medicines’, i.e. non-prescription medicinal products

PGEU - Pharmaceutical Group of the European Union representing community pharmacists.

Pharmacovigilance is the process and science of monitoring the safety of medicines (adverse events of medicines) and taking action to reduce the risks and increase the benefits of medicines

Repository system: system/database which contains the data on the unique identifier

RFID: Radio-frequency identification device

UI: Unique identifier

Annex 2: Summary of responses following the public consultation

1. In 2011, the Commission submitted to public consultation a concept paper on the delegated act on the detailed rules for a unique identifier for medicinal products for human use, and its verification. The concept paper put forward various ideas for implementing the unique identifier and identified various policy options to address a defined problem/objective. This public consultation was also used as a means of gathering further quantified information on the costs and effectiveness of various policy options.
2. The consultation period was from 18 November 2011 to 27 April 2012. The contributions received in reply to the public consultation were published on the website of the European Commission.
3. In a nutshell, all stakeholders expressed their full support of the Commission's initiative, on the grounds that the unique identifier would create better protection for European patients against falsified medicines.
4. Overall, European Associations representing branded medicines, wholesale distributors, parallel importers and pharmacies presented a joint position supporting full harmonisation of the unique identifier, a risk based verification system and a repository managed by the stakeholders.
5. As regards the **characteristics of the unique identifier**, the Commission proposed either to leave the choice of the technical specifications to the individual manufacturer or to regulate the composition of the number. Most respondents except generics support harmonising the technical specifications of the unique identifier through a regulation. This would be the only option for ensuring interoperability between different manufacturers and different EU Member States. Manufacturers, wholesale distributors and pharmacies would only need to invest in one piece of software and one reader (i.e. scanner device). Different standards and processes would be costly for all users. Respondents strongly recommend using internationally recognised standards for identifying all products in line with the system in place in certain Member States. The use of ISO standards, which are overarching standards, e.g. GS1, could be the best and most neutral approach. The serial number element of the UI could be generated by the manufacturer or by a national registry.
6. Most stakeholders would like to see the batch number and the expiry date included in the composition of the number. This would allow wholesalers to record, in a cost-effective way, the batch number as required under Article 80(e) of Directive 2011/62/EU. Wholesale distributors estimate that the additional annual labour costs of capturing batch numbers in a database (them directly from the carton) would be around €13.2 million per year. Wholesale distributors estimate that labour costs of capturing the number from the cartons are much higher. In addition, information on the batch will facilitate the recall of products to the benefit of patients.
7. As regards the reimbursement code, certain Member States (FR, DK, SE, FI, AT) require this number to be present on the packaging in a machine-readable format. The integration of the reimbursement code in the unique identifier would avoid two sets of barcodes on the outer packaging. The suggestion is to integrate the reimbursement code, when available, in the product code, rather than have it as a

separate element. Some stakeholders propose either keeping this information optional or introducing it in the database only. According to EGA, the composition of the serial number should not be harmonised through regulation but should be adjustable to national requirements. Different standards of product coding are used at national level (e.g. PZN in Germany, CNK in Belgium, and GS1 in France). An open code will be required to make the system cost-effective and has no effect on the inter-operability of the system.

8. With the exception of some associations, all stakeholders including the European pharmaceutical Association and association representing wholesalers, pharmacies and consumers support the use of a 2D barcode as a data carrier for the unique identifier. This carrier allows the storage of a large amount of information and is suitable for small packs. It is considered a more reliable and affordable carrier. If the carrier is a 2D barcode, community pharmacies and hospital pharmacies will need to be equipped with new scanners.
9. In parallel, the European Association of Generic Industry calls for a cost-effective and cost-proportionate solution, taking the form of a 1D barcode containing only a minimal amount of the information prescribed by the legislation. This would allow for the continued pre-printing of the UI on cartons. On the other hand, most stakeholders believe that the 1D barcode cannot hold enough information. With regard to the RFID (radio frequency identification device), all stakeholders consider it inappropriate, given the current state of technology and its cost (€ 0.10-0.15 per tag; € 3 000 per reader device).
10. Some stakeholders have provided estimates of the possible costs:
 - Manufacturer costs for the UI: €0.016 per pack (source EFPIA);
 - Upgrade of pharmacy management systems: € 50-200 per pharmacy;
 - Pharmacist costs for the reading devices: € 250-300 per scanner;
 - Costs for scanners by wholesale distributors: € 1 200 per scanner.

Estimate of the costs/benefits of the possible options:

		<i>1D</i>	<i>2D</i>	<i>RFID</i>
<i>Costs</i>	<i>Manufacturers</i>	+	++	+++
	<i>Wholesale distributors</i>	+	+	+++
	<i>Pharmacies</i>	+	++	+++
<i>Benefits</i>		+	++	++

0= neutral in terms of costs + = costs. The software used in pharmacies and wholesale distributors will need to be upgraded independently of the choice of the data carrier (1D, 2D or RFIF). Even a 1D barcode will create costs for the actors in the supply chain.

11. As far as **verification of the unique identifier** is concerned, most stakeholders support an end-to-end authentication system. This means that the manufacturer stamps the unique number on each individual box, and the number is stored in a repository system. The number is then authenticated before the product is dispensed to the patient. In most cases, this check will take place in pharmacies. This practice also allows the number to be checked in the system. The authentication should be instantaneous to avoid delays in the workflow of pharmacies. Due to the specifications of some Member States, stakeholders suggest clarifying how the UI will be checked for dispensing points other than pharmacies (general practitioners dispensing medicines, hospital pharmacies, other outlets, etc.). The disadvantage of this option is that there would be no checks between the manufacturer and the dispensing point. As a result, packs of falsified medicines could circulate for months in the Union before they are detected. However, complementing verification at the point of dispensing with a systematic check by the wholesale distributor is estimated to cost about €636 million annually without offering any real additional patient safety. Instead, there is general agreement among most of the stakeholders that any **additional verification** at the level of wholesale distributor should be done **following a risk-based assessment**. This is considered the most cost-effective way to improve patient safety. Situations where falsification could present a risk and which could benefit from additional checks by the wholesale distributor are when:

- (a) the product is not obtained by the wholesaler from the manufacturing authorisation holder or the marketing authorisation holder;
- (b) the product is returned to the wholesaler from another wholesaler or person authorised to sell medicines to the public.

The former option may limit the cost to € 36 million for the wholesale distributors. Stakeholders stress that the authentication of the UI should be instantaneous to avoid delays in the workflow of wholesale distributors.

Estimate of the costs/benefits of the possible options:

		2/1 Check-out by the pharmacies	2/1 + risk-based checks	2/1 +systematic check
<i>Costs</i>	<i>Manufacturers</i>	0	0	0
	<i>Wholesale distributors</i>	0	+	+++
	<i>Pharmacies</i>	+	+	+
<i>Benefits</i>		+	++	+++

0: neutral in terms of costs; + = costs

12. **As regards the repositories system**, the Commission put forward, in its concept paper, several options for the establishment, management and accessibility of the repositories system which will contain the information on the safety features. The first option is that the objective of the repositories and the obligations of the relevant actors (e.g. manufacturers) with respect to the repositories should be laid down in the delegated act. In parallel, the relevant actors in the supply chain should set up the

appropriate infrastructure for the repositories system (stakeholder governance, option 3/1). The second option is a pan-European repositories system to which all actors are connected and which is governed by an EU body (EU governance, option 3/2). The third option is to establish national repositories to which all actors in the Member State, and actors supplying medicines to the territory of that Member State, are connected. The national repositories would be governed by official national bodies (national governance, option 3/3).

13. Pharmaceutical companies and some competent authorities (UK) support stakeholder governance for putting a timely, effective and efficient system of product authentication in place. The system would integrate the expertise of the key users of the system, namely the marketing authorisation holders, the wholesalers and the pharmacies, and should avoid adding unnecessary obligations (goldplating). With the exception of the European Association of generics (see below), the European associations representing manufacturers, wholesale distributors and pharmacies strongly support this policy option, as a similar system is currently being developed. The system proposed by EFPIA (European Federation of Pharmaceutical Industries and Associations), GIRP (European Association of Pharmaceutical Full-line Wholesalers), PGEU (Pharmaceutical Group of European Union) and AESGP (Association of the European Self-Medication Industry) comprises national data repositories that serve as the verification system which pharmacies and other registered parties can use to check a pack's authenticity. The national system may be established by the stakeholders locally and adapted to local specifications. The national repositories would have to be linked by a European hub that would store product master data and would be a single entity from which national systems could receive new/revised serialisation data. If the option of stakeholder governance were to be chosen, manufacturers of generics would support a plurality of IT providers of stakeholder models to ensure competition and decrease the price of the repositories (EGA's position). A big manufacturer should be able to set up its own system. Competent authorities stress the need to pay particular attention to the protection of information where the database is managed by or on behalf of stakeholders. There is a potential conflict of interest between those holding the information and those using it. The competent authorities recommend supervising the system. An alternative proposal could be that the systems are developed in partnership with governments and relevant actors in the supply chain. One authority proposes that the repository is developed by stakeholders and managed by a public body.
14. Two competent authorities favour EU or national governance while one authority calls for national governance.
15. EU governance could provide the advantage of providing harmonisation across Member States. However, most stakeholders are against one repository having EU governance due to the complexity and the cost of such a system. The EU-wide traffic volume could be very intense and national requirements (e.g. language requirements) of distribution and dispensing systems could be disregarded.
16. Some competent authorities point out that national governance provides independence of the system, local insight and guarantees the confidentiality of data. However, the costs to be borne by manufacturers for setting up 27 separate systems and the limited human resources available to national authorities should also be taken into account.

17. Other public bodies suggest a mixed system comprising national repositories with a centralised system under EU governance.
18. Furthermore, stakeholders stress that the supply of medicinal products should not be dependent on the reliability of any computer network in which the repository is based.
19. As regards the protection of data, stakeholders recommend that all stakeholders having access to the system should own the data they generate in the system. The system requires a high degree of data security and should not store patients' data. The European Consumer Organisation stresses that the repository system should not contain any personal data.
20. Some stakeholders have provided costs estimates:
 - Italy: Repository: € 1 800 000 for setting up the repository system; maintenance costs: € 500 000 per year; € 0.01 per pack
 - Stakeholder model: € 120 000 000-205 000 000 (including European hub: € 12 000 000); € 0.013-0.022 per pack
 - Germany: Packaging and running of the repository: less than € 0.10 per pack
 - European Generics Association: Implementation costs (adapt packaging lines to 2D barcode + adapting software + uploading code in repositories+ anti-tamper evidence): € 1 billion
 - Verification of authenticity (for generics industry): € 200 000 000 per year
 - Overall cost for EU generics industry: € 500 000 000 per year
 - Generics industry provides 10 billion packs per year. Commission concludes that the costs are about € 0.05 per pack.
 - EDQM: Setting up and maintaining the repositories, storing the items and transactions data: 0.01 per pack.
21. Stakeholders stress that the price will depend on the number of national databases in the final system and also the number of packs in the system.
22. In the case of repackaging, stakeholders stress that it is crucial to ensure traceability between old and new codes in the system.
23. The concept paper also lays down topics related to the **lists of products that should bear the safety features (black list) or not bear them (white list)**. Stakeholders support the quantitative approach to identifying products to be exempted from bearing the safety features.
24. Stakeholders recommend having substances classified by Anatomical Therapeutic Chemical code (ATC of the WHO), active substance (e.g. International Non-proprietary Names), brand name or a flexible approach on a case by case basis.

25. With regard to the white list, associations representing generic medicines call for a robust weighted risk assessment to identify high-risk products, taking into account the characteristics of generics, EGA stipulates that there are no reports of counterfeit generic medicines in the EU at all and especially not in the legal supply chain. Generic medicines should even be considered as preventing the falsification of medicines as they trigger competition, resulting in lower prices, and fragmenting the market into multisource volumes, which are unattractive for counterfeiters.
26. The most important risk factor for falsification should be previous incidents of falsification and the price of medicines. Furthermore, € 2 cannot be considered a high price for a medicine. The criteria of high price should be adjusted and increased to € 100 ex-manufacturers' gross price excluding VAT.
27. Most stakeholders regard price and demand for medicinal products as being the major driving factors for falsification.
28. In parallel, many stakeholders acknowledge the difficulty of screening the thousands of prescription medicines available on the market. Some stakeholders believe that exempting a large number of medicines would make the UI system ineffective and reduce patient protection. Indeed, it would encourage traffickers to target unprotected medicines with a view to falsification. Finally, it does not prevent the competent authorities imposing the unique identifier anyway for other purposes, e.g. reimbursement.
29. As regards the black list of over-the-counter medicines (OTC medicines) bearing the safety features, associations recommend switching to a qualitative assessment driven by the incidence of falsified medicines in the European Union. In the case of a quantitative approach, only OTC products that accumulate more than 25 points should be listed. The assessment should be performed by a panel of experts based on clear evidence of falsification.
30. Some authorities suggest moving forward with a model which is refined as experience is acquired.
31. Regarding the notification process, stakeholders suggest putting in place a **rapid system** to **notify** medicinal product at risk of falsification.
32. Finally, some stakeholders have put forward additional ideas, e.g. the possibility for patients to check/scan the authenticity of their medicines. The association of hospital pharmacies calls for every single dose of medicine used in hospitals to include an individual barcode to reduce medical errors. Moreover, the European Consumer Organisation highlighted the importance of ensuing cost-efficient measures that do not have a negative impact on access to treatments and on health care budgets.

Annex 3: ECORYS Report

Competitiveness proofing of a unique identifier for medicinal products for human use, and its verification - Ex ante evaluation of competitiveness impacts of the Commission's policy proposal Delegated act(s) on the detailed rules for a unique identifier for medicinal products for human use, and its verification.

The report is available at the following address:

http://ec.europa.eu/health/files/falsified_medicines/ecorys_report.pdf

Annex 4: Scale of the problem – Increased number of falsified medicines

The Commission's Annual Report on customs actions to enforce intellectual property rights (IPR) (July 2012) gives statistics on the type, origin and transport method of IPR-infringing products detained at the EU's external borders. The top categories of articles stopped by customs were medicines (24 %), packaging material (21 %) and cigarettes (18 %). The increase in the number of detained postal packages continued in 2011, with 36 % of instances concerning medicines. Equally important, the official medicines control laboratories in the Member States confirm the increasing number of requests to test unknown products received from customs, police and public health authorities (see below). Most of them are medicinal products that are unauthorised in the EU or unlabelled medicinal products with unknown composition. In 2011 alone, some 350 requests related to counterfeit medicines in the legal supply chain (e.g. pharmacies operating legally in an EU Member States). The substances concerned were anabolics (in particular testosterone), slimming agents (sibutramine), stimulants and phosphodiesterase type 5 inhibitors (used in the treatment of erectile dysfunction, such as sildenafil). For example, the National Institute for Public Health and the Environment (RIVM) in the Netherlands confiscated about 538 erectile dysfunction products between 2007 and 2010. Among them, 17 % were counterfeit Viagra (Sildenafil), Cialis (Tadalafil) and Levitra (Vardenafil) and 69 % were illicit generics of erectile dysfunction products. The laboratories also received an enormous amount of unknown products found in the illegal supply chain. Taking the example of the Polish laboratory, 4250 samples were tested in 2011. In reality this includes a big number of products sampled from smart shops, which at the time of confiscation were legal shops and have then been forbidden. The Commission will introduce the unique identifier on medicines in the legal supply chain and not on illegal products sold in smart shops or illegal websites on internet. In the latter situation, the Commission will introduce by the end of 2013, a logo on all legally operating pharmacies. This will allow for the public to clearly distinguish a legal and illegal website.

Among the more severe incidents of fake medicines in the last few years, a contaminant in heparin — a blood thinner — has been connected to dozens of deaths worldwide in 2008. The counterfeit heparin reached patients in the US and in the EU.

Among the most recent incidents is the spread of fake Avastin (bevacizumab for the treatment of metastatic colorectal cancer), Casodex (used to treat prostate cancer), Plavix (used to treat heart complaints) and Zyprexa (used to control the symptoms of schizophrenia). In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has recorded ten cases of counterfeit prescription-only medicines reaching patients through the legal supply chain in the UK since 2004. Prior to that, the last known counterfeit medicines case in the UK was over ten years ago. So, counterfeit concerns not only lifestyle medicines but also medicines essential for survival.

According to the World Health Organisation (Fact sheet No 275), all kinds of medicines have been counterfeited, both branded and generic, ranging from medicines for the treatment of life-threatening conditions to inexpensive generic versions of painkillers and antihistamines (see table).

Table: Examples of SFFC medicines from the WHO

Spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines	Country and year	Report
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Spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines	Country and year	Report
Avastin (for cancer treatment)	United States, 2012	Affected 19 medical practices in the US. The drug lacked the active ingredient
Viagra and Cialis (for erectile dysfunction)	United Kingdom, 2012	Smuggled into the UK. Contained undeclared active ingredients with possible serious health risks to the consumer
Truvada and Viread (for HIV/AIDS)	United Kingdom, 2011	Seized before reaching patients. Diverted authentic product in falsified packaging
Zidolam-N (for HIV/AIDS)	Kenya, 2011	Nearly 3 000 patients affected by falsified batch of their antiretroviral therapy
Alli (weight-loss medicines)	United States, 2010	Smuggled into the US. Contained undeclared active ingredients with possible serious health risks to the consumer
Anti-diabetic traditional medicine (used to lower blood sugar)	China, 2009	Contained six times the normal dose of glibenclamide. Two people died, nine people were hospitalised
Metakelfin (antimalarial)	Tanzania, 2009	Discovered in 40 pharmacies. The drug lacked sufficient active ingredient

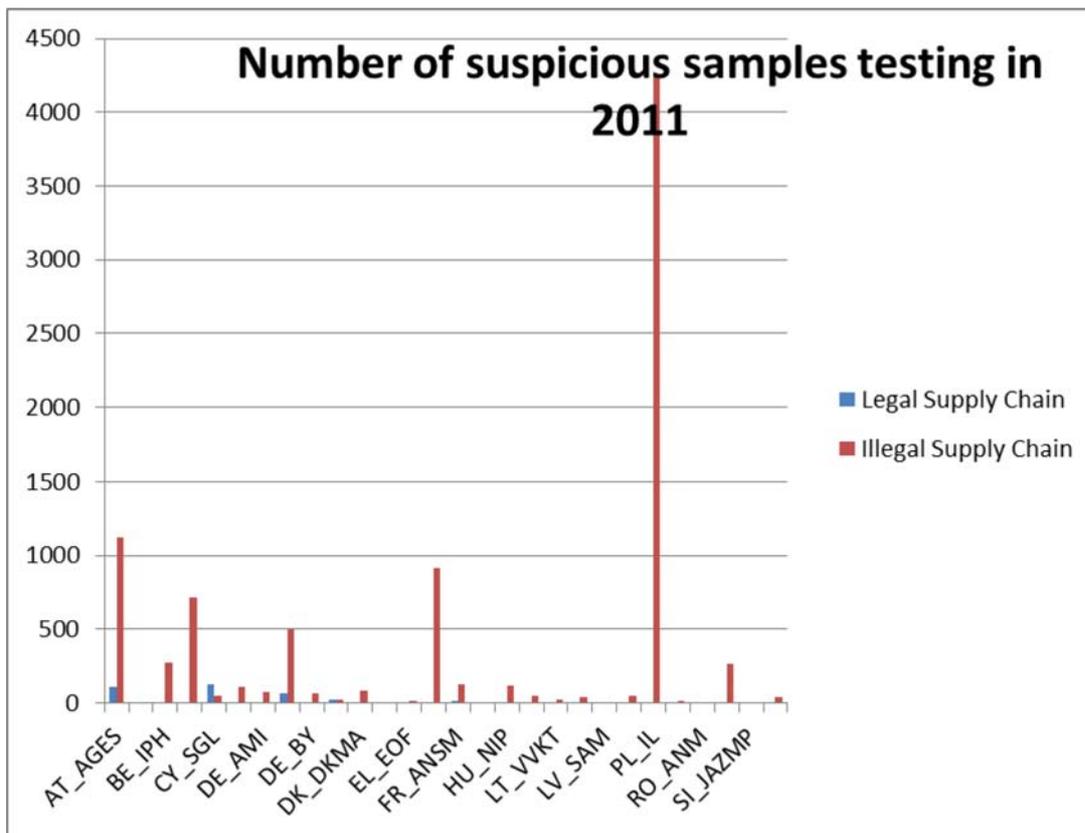
The internet, which offers new opportunities for businesses and individuals alike, has also facilitated the spread of falsified medicines across the EU. According to the WHO, in over 50 % of cases, medicines purchased over the internet from illegal sites that conceal their physical address have been found to be counterfeit. The importance of the internet in selling such products has increased sharply over the past years, illustrating the growing availability of and demand for the products. Further incidents involving counterfeit medicines of which the Commission has been made aware are presented in Annex 4.

However, the figures reflect only a small part of the problem. Due to the illegal nature of counterfeiting, it is only possible to provide data on what has been discovered and it is very difficult to obtain accurate statistics. The techniques employed by traffickers have become so sophisticated that detection may require testing or expert visual examination of the product.

Chart of incidents from Official Medicines Control Laboratories (OMCL) in the EU and further incidents of falsified medicines

OMCL	Legal Supply Chain	Illegal Supply Chain
AT_AGES	110	1122
BA_IMQC		2
BE_IPH		275
CH_SWISSMEDIC		715
CY_SGL	125	51

CZ_SUKL		107
DE_AMI	2	77
DE_BW	63	502
DE_BY		64
DE_LLBB	25	23
DK_DKMA		87
EE_SAM		3
EL_EOF	6	15
ES_AGEMED		911
FR_ANSM	11	122
HU_DVMP		1
HU_NIP		115
IT_ISS-H	4	52
LT_VVKT		20
LU_LNS		42
LV_SAM	1	
NO_NOMA		51
PL_IL		4250
PT_INFARMED	1	15
RO_ANM		4
SE_MPA		264
SI_JAZMP	8	
UK_NIBSC		42



Product group N° of Reports in 2011:

Anabolics 75

Antibiotics_Antiviral_Antimicrobial agents 5

Biologicals 19

Cancer therapy 2

Dermato therapeutics 7

Heart diseases 6

PDE-5 inhibitors 222

Slimming agents 78

Stimulants 85

Other psychotropics 4

Other life-style drugs 3

Other drugs 23

Placebos 20

Incidents of falsification of medicines for human use notified through the press or other public sources									
Incident	Product concerned	Active Substance	Side effects	Where it was seized	When it was reported	Manufacturing place	Detection in legal or illegal supply chain	Source of information	
1	72,000 packs of counterfeit drugs entered the UK supply chain in 2007 but 25,000 remain untraced. MHRA successfully seized 40,000 packs before they were distributed to pharmacies, 25,000 reached chemists across the UK and were dispensed to patients. A further 7,000 were recovered following a recall. The counterfeit medicines contained only just 50% to 80% of the correct ingredients (a fraction of the correct dosage).	Among others: - Casodex - Plavix - Zyprexa	Bicalutamide Clopidogrel Olanzapine	Not believed to have caused any fatalities or adverse reactions.	Wholesalers in UK	Spring 2007	China	Legal supply chain: authorised UK wholesalers	BBC News http://www.bbc.co.uk/news/health-16760513
2	MHRA reports a case of counterfeit Stillnox	Stillnox (zolpidem)	Contained 10 mg Melatonin instead of 9 mg Zolpidem	UK	6 July 2011		unknown	MHRA http://www.mhra.gov.uk/PrintPreview/PressReleaseSP/CO/N123137	

3	<p>Non authorised abortion pills were sold by online sale through an illegal online pharmacy site (eurodrugstore.eu). The dispatching site was located in Canada whilst the call centre was based in Cyprus.</p>		<p>Mifepristone Misoprostol</p>		<p>France</p>	<p>4 October 2011</p>		<p>illegal online pharmacy</p>	<p>Belgian newspaper (Le Soir) http://www.lesoir.be/lifestyle/sante/2011-10-04/une-pilule-abortive-met-les-femmes-en-danger-867500.php</p>
4	<p>Two containers from Asia with 10 tonnes of counterfeit drugs were seized in the customs of the Havre harbour (France). Counterfeit drug samples were showed to be dangerous as they were over-dosed, under-dosed or non-sterile.</p>	<p>Muscular anti- inflamma- tory drugs Auricular collyriums Vitamin supplements Solutes against hair loss</p>			<p>Customs of Port du Havre (north west, France)</p>	<p>8 December 2011</p>	<p>Asia</p>		<p>http://www.lexpress.fr/actualites/1/societe/saisie-record-de-faux-medicaments-sur-le-port-du-havre_1059482.html</p>

<p>5</p>	<p>Fake Avastin containing a variety of toxic chemicals (a mix including benzoic acid, acetone, propandiol and a phthalate compound) but no active ingredient.</p> <p><u>Supply Chain:</u> Manufactured in Turkey → through sold by a Syrian Businessman to an Egyptian distributor not registered in the National health Ministry → Swiss Distributor (Hadicon AG) → Danish licensed distributor → British licensed distributor → USA</p>	<p>Avastin</p>	<p>The genuine product contains Bevacizumab</p>		<p>Oncology practices, USA</p>	<p>28 February 2012</p>	<p>Turkey (Roche's Genetech division)</p>	<p>Legal supply chain in US: It is presumed that 19 oncology practices might have purchased counterfeit Avastin.</p>	<p>FiercePharma web site: http://www.fiercepharma.com/story/phony-avastin-vials-contained-chemicals-no-drugs/2012-02-28</p>
<p>6</p>	<p>Illegal, unauthorised medicinal product sold as food supplement and sexual-enhancement product.</p>	<p>Name of the product unknown</p>	<p>Glibenclamide</p>	<p>Four men hospitalised with dangerously low blood-sugar levels</p>	<p>Singapore</p>	<p>6 Feb 2012</p>	<p>Asia</p>	<p>The patients got the products from makeshift stalls in the red lights districts of Geylang or Desker Road</p>	<p>Media reports</p>

7	A new batch of fake Avastin containing no active ingredient was seized in USA. They were labelled as Altuzan (Avastin's brand name in Turkey). Supply chain: A Turkish supplier sold 120 packs of counterfeit medicines to a British wholesaler who shipped them to the USA	Injectable Avastin vials	Bevacizumab		USA	4 April 2012	Turkey (Roche's Genentech division)	Legal supply chain in US and the EU	http://www.reuters.com/article/2012/04/04/avastin-fake-idUSL6E8F45K820120404
8	116 counterfeit drugs from China and India were seized in Zaventem (Brussels, Belgium) and Bierset (Liege, Belgium) Airports	No info			Belgian airport customs	April 2012	China and India		http://www.lesoir.be/lifestyle/sante/2011-10-04/une-pilule-abortive-met-les-femmes-en-danger-867500.php
9	The fake versions of the generic drug Omeprazole were discovered by Ratiopharm, a subsidiary of Teva after being alerted from a patient in Germany, who noticed spelling mistakes on the label of the packaged drug	Omeprazole	Omeprazole		DE	April 2013		Legal supply chain: sold by authorised pharmacy	http://www.theferranigroup.com/supply-chain-matters/2013/04/29/incidents-of-counterfeit-heartburn-treatment-drugs-discovered-in-europe/

10	<p>Half a million pounds of unlicensed sex, diet and hair loss drugs was seized by the MHRA in a west London raid. Around 150,000 tablets were discovered with the majority being generic versions of erectile dysfunction drugs, with others being for hair loss and slimming.</p>	<p>Sex, diet and hair loss drugs</p>		<p>West London</p>	<p>23 April 2013</p>	<p>India</p>	<p>Illegal supply chain</p>	<p>MHRA website</p>
11	<p>The MHRA seized a record £12.2 million of counterfeit and unlicensed medicines in the UK. This was part of a week-long international crackdown on the illegal internet trade of medicines that seized over £26.8 million globally.</p> <p>This activity resulted in more than 3.7 million doses of unlicensed medicines, including 97,500 doses of counterfeit pills worth £525,000.</p>	<p>Falsified medicines were for slimming, hair loss and erectile dysfunction</p>		<p>UK</p>	<p>27 June 2013</p>		<p>Illegal internet websites</p>	<p>MHRA website</p>

12	Swiss intercepted 400kg of counterfeit Xanax en route to Egypt	Xanax	contained no active ingredient. The genuine product contains alprazolam	Swiss Airport Customs	18 October 2013	Unknown	Between China and Egypt	http://www.in-pharmatechnology.com/Regulatory-Safety/Swiss-intercept-400kg-of-counterfeit-Xanax-en-route-to-Egypt/
13	Tens of boxes of counterfeit medicines discovered in Romanian pharmacies	Pegasys	Peginterferon alfa-2a	Romanian pharmacies	8 Nov 2013	Unknown	Legal supply chain (pharmacies)	Romania Libera: <i>Distilled water instead of Interferon in Romanian pharmacies</i> by Jeles Alexandra page: 1, Nov 8, 2013
14	Counterfeit versions of Roche's cancer drug Avastin – shipped to UK, Denmark, Switzerland	Altuzan (Avastin)	The genuine product contains bevacizumab	Turkey, US	19 February 2014	Turkey	Legal supply chain – authorised wholesalers and parallel importers	http://www.securingindustry.com/pharmaceuticals/fake-avastin-reached-europe-as-well-as-us/s40/a1966/

15	Fake aspirin and anti-diarrhoeal medicines seized by customs in Le Havre. The fakes contained sugar instead of active ingredients	Aspegic, Smecta	Acetylsalicylic acid Diosmectite	Le Havre, France	14 April 2014	Unknown	shipped to a person in Belgium, for subsequent export outside the EU	http://www.in-pharmatechnology.com/Regulatory-Safety/Sugar-in-place-of-APIs-discovered-in-EU-s-largest-fake-drug-seizure/
16	Law enforcement authorities from Austria, Belgium, Cyprus, France, Hungary, Slovakia, Spain and the United Kingdom, supported by Europol and Eurojust, contributed to simultaneous operations to stop the distribution of prescription-only counterfeit medicines (mainly erectile dysfunction pills) in the European Union.	Mainly erectile dysfunction medicines		Several Member States	1 Sept 2014	China and India	Austria, but probably sold also to France, Spain and UK.	https://www.europol.europa.eu/content/international-law-enforcement-action-against-fake-medicines http://www.eurojust.europa.eu/press/PressReleases/Pages/2014/2014-09-01.aspx
17	<p>^{3rd} RIVM¹ report on Illicit Erectile Dysfunction (ED) products in the Netherlands (2007-2010). During this period, 538 ED products were confiscated. Among them, 17% were counterfeit Viagra (Sildenafil), Cialis (Tadalafil) and Levitra (Vardenafil) and 69% were Illicit generics. There are high indications of the presence of counterfeited illicit generics, but it could not be confirmed due to the lack of reliable reference material.</p> <p>¹ RIVM : National Institute for Public Health and the Environment</p>							

Incidents of falsification of medicines for human use notified through the rapid alert notification system

	Incident	Product concerned	Active Substance	Side effects	Where it was seized	When it was reported	Manufacturing place	Detection in legal or illegal supply chain	Source of information
18	A pharmacy complained about a package of Combivir which contained an empty blister. The material was investigated at the manufacturer laboratory and ascertained to be counterfeit.	Combivir 150mg / 300mg tablets	Lamivudin 150mg Zidovudin 300mg		DE	25 Aug 2009		Legitimate German supply chain	Rapid Alert Notification System
19	Unauthorised medicinal product sold as food supplement. It contains significant amounts of the active substances sibutramin and rimonabant. The competent authority in Germany that has issued the notification is the 1 Capsule contains about Sibutramine and about Rimonabant	Ultra Effect	20 mg Sibutramin and 16 mg Rimonabant		Germany	03 Sept 2009	Boston, USA	Illegal supply chain	Rapid Alert Notification System
20	The test on the label and the carton of this product was in Spanish neutral (official language in Haiti is French) The batch number VS61971 is a genuine Novo Nordisk batch number for Dominican Republic. The shelf life period and manufacturing date were not correct. The appearance of the product did not look right.	NovoLin 30/70 Also registered under the name: Mixtard	Insulin		Bought in a pharmacy in Haiti	11 Sept 2009	Dominican Republic	Bought in a pharmacy in Haiti	Rapid Alert Notification System

												release http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/ucm237980.htm
23	Unauthorised medicinal product sold as food supplement. FDA analysis determined that U-Prosta samples contain terazosin (the active ingredient in an FDA-approved drug used to treat Benign Prostatic Hyperplasia (enlarged prostate))	U-Prosta Natural Support for Prostate Health capsules	terazosin			USA		FDA, March 2011	Changsha Huakang Biotechnology Development Co., Ltd.; CHINA	Distributed nationwide in USA via retail stores, internet sales, and mail order	Rapid Alert Notification System FDA press release http://www.fda.gov/Safety/Recalls/ucm248116.htm	
24	Counterfeit Clenbuterol did not contain any active ingredient	Clenbuterol Sopharma	The genuine product contains Clenbuterol			Seized from a private residence in Cyprus		10 Nov 2012	Bulgaria	Unknown	Rapid Alert Notification System	
25	Unauthorised medicinal product sold as dietary supplement for male enhancement	Rock-it Man,	Hydroxythiohomosildenafil			US		4 Jan 2013	Unknown	Nationwide in the US	Rapid Alert Notification System	

26	A German parallel distributor informed of falsified Truvada.	Truvada	tenofovir disoproxil and emtricitabine 200 mg / 245 mg		UK	5 February 2013	Unknown	Legal: Authorised parallel distributor in Germany.	Rapid Alert Notification System
27	Counterfeit Omeprazole Hexal (generic medicine) found in Germany	Omeprazole 20 mg and 40 mg, hard capsules	Omeprazole		Munich (DE)	20 March 2013	Salutas Pharma GmbH	Legal supply chain: Wholesalers pharmacies	Rapid Alert Notification System
28	Batches intended for the Turkish market were irregularly re-imported into the Union with falsified labels and leaflets without knowledge of Marketing Authorisation holder.	Viread	tenofovir disoproxil			22 March 2013		Distributed by several Bulgarian wholesalers	Rapid Alert Notification System
29	A German wholesaler received, from a UK wholesaler, a product from the Romanian market where the batch number on the outer packaging was not identical with the batch number on the vial.	Remicade	Infliximab		UK	10 April 2013	Romanian market	Legal supply chain	Rapid Alert Notification System

30	Medicine shipment imported as "car tyres"	Deca-Durabolin	Nandrolone decanoate Clomiphene citrate	Bulgaria	8 May 2013	Unknown	The Shipment was addressed to a recipient in Bratislava who was not an authorised wholesaler	Rapid alert Notification System
31	Falsified packs of Viartril-S Capsules 250 mg were seized by Hong Kong Customs from a community pharmacy in Hong Kong. The capsules contained glucosamine sulphate content substantially below the labelled amount	Viartril	glucosamine sulphate	Hong Kong	4 June 2013	Unknown	seized from a community pharmacy in Hong Kong	Rapid Alert Notification System
32	AIFA withdrew three lots of Ozopulmin G suppositories, one for adults and two for children, from the market due to being falsified by the manufacturer itself, the Italian company Geymonat. Left without the active ingredient for Ozopulmin due to a disagreement with the active ingredient supplier, Geymonat decided to use a different active ingredient to manufacture a falsified Ozopulmin.	Ozopulmin suppositories (for adults and for children)	The active ingredient in the drug sold by Geymonat was substituted with a similar substance normally used in cosmetics and food	Italy	20 June 2013	Geymonat Italy	Legal Supply Chain	Rapid Alert Notification System + AIFA Press Release

37	Unauthorised medicinal products sold as dietary supplements	Healthy Life Chemistry B-50 Healthy Life Chemistry Multi-Mineral Healthy Life Chemistry Vitamin C	Methast- rone Dimethyl- testosterone		US	5 August 2013	Purity First Health Products. N.Y. US	distributed nationwide in the US via the internet, retail and through retail stores between July 2012 and June 2013.	Rapid Alert Notification System
38	Unauthorised medicinal products sold as dietary supplements	Ginseng-Max Vigomax Vgmx Forcex	Tadalafil Nortadalafil Deacety-lated pretadalafil Tadalafil		unknown	07 August 2013	New Zealand Portugal	distributed through the internet or in health food shops	Rapid Alert Notification System
39	Confirmed counterfeit Biviol	Biviol	genuine product: Ethinylestradiol		Germany	20 August 2013	Unknown	Wholesalers community and hospital	Rapid Alert Notification System

49	Unauthorised medicinal products sold as dietary supplements.	Virilis Pro, PHUK and Prolifta Dietary Supplement	Sildenafil		US	18 Nov 2013	Unknown	via internet sales	Rapid Alert Notification System
50	Unauthorised medicinal products sold as dietary supplements	a) Rhino 5 Plus b) Maxtremez c) Extenzone	desmethyl carbodenafil and dapoxetine		US	18 November 2013	Unknown	Distribution is in the U.S.	Rapid Alert Notification System
51	Unauthorised medicinal product sold as dietary supplement	Vigour 300	Sildenafil		Spain	27 March 2014	US	Sold through several websites.	Rapid Alert Notification System
52	Unauthorised medicinal product sold as dietary supplement	Dymeth-aberry Steel Crushers	Dymethazine	No adverse reactions have been notified	Spain	28 March 2014	Unknown	Sold through multiple websites and retail body-building shops.	Rapid Alert Notification System

53	Falsified products, labeled as Herceptin 150mg vials, have been seized in the UK, Germany and Finland. The batch numbers on most vials do not match batch numbers on the outer package.	Herceptin	The genuine product contains trastuzumab	UK, Germany and Finland	11 April 2014	Unknown	The affected vials had been stolen from hospitals in Italy.	Rapid Alert Notification System
54	Falsified Remicade packages.	Remicade 100 mg	Infliximab	Germany	17 April 2014	Unknown	Legal supply chain: distributed by Pharmacia Internazionale, Italy to a DE parallel importer.	Rapid Alert Notification System
55	Falsified Herceptin 150 mg	Herceptin 150 mg	Trastuzumab	Czech Republic	23 May 2014	Romania	Legal supply chain: found in Orifarm Supply s.r.o., Czech Republic	Rapid Alert Notification System

56	Counterfeited medicinal product Kaletra	Kaletra	Lopinavir 200mg / Ritonavir 50mg		Germany	13 June 2014	Unknown	Legal supply chain: detected at a German parallel distributor.	Rapid Alert Notification System
57	Gardasil of falsified origin	Gardasil	Vaccine (for use in the prevention of certain strains of human papillomaviru s, HPV)		Paul- Ehrlich- Institute (Germany)	1 July 2014	Unknown	purchased by Pharma- TRADE SPA (IT) from an unauthorise d wholesaler in Hungary.	Rapid Alert Notification System
58	Falsified packs of Viartril®-S Capsules 250mg	Viartril®-S Capsules 250mg	glucosamine sulphate		Taiwan	5 August 2013	Unknown	On the Taiwanese market.	Rapid Alert Notification System
59	Ipsyl of falsified origin	Ipsyl	Lanreotidacet at		Norway	11 August 2014	Unknown	Initially distributed by an unauthorize d Hungarian wholesaler, entered the legal supply chain and travelled	Rapid Alert Notification System

								through several countries to reach the Norwegian market.	
60	One falsified pack of Panadol Extra Tablets was identified at retail level in Colombia.	Panadol Extra Tablets (Dolex Forte)	The genuine products contain 500mg Paracetamol and 65mg Caffeine		Colombia	14 August 2014	Unknown	The falsified pack was detected in a retail shop in Cali, Colombia.	Rapid Alert Notification System
61	Falsified product sourced from an illegal wholesaler	Abilify	Aripiprazole 1mg/ml		Part of ongoing investigations by the Italian Medicines Agency, AIFA	27 August 2014	Unknown	Legal supply chain: Repacked by Europharma DK and delivered to the German and Danish market	Rapid Alert Notification System
62	Several falsified products - suspected to be stolen medicinal products	Several, e.g. Mab Thera, Clexane, Sandostatin			Detected by Orifarm, Germany	28 Aug 2014	Unknown	Probably stolen from Italy and imported to Germany.	Rapid Alert Notification System

								Distributed to pharmacies, hospital pharmacies and wholesalers	
63	Several falsified products - suspected to be stolen medicinal products	Viramune 400 mg Celebrex 200 mg	Nevirapine celecoxib		Detected by the parallel importer CC-Pharma in Germany	28 Aug 2014	Unknown	The products were stolen from Italy and imported to Germany.	Rapid Alert Notification System
64	The unauthorised medicinal product Runaway was found to contain undeclared sildenafil	Runaway	Sildenafil		Customs in Bremen, Germany. Imported from Turkey	2 Sept 2014	China	Distributed through internet.	Rapid Alert Notification System
65	The product "Pepper Time New" was found to contain undeclared Sibutramin and Sildenafil	Pepper Time New	Sibutramin Sildenafil		Germany	2 Sept 2014	Unknown	Via internet from supplier in Turkey	Rapid Alert Notification System

66	Unauthorised medicinal product sold as dietary supplement	Slyn Both	Fluoxetine		Germany	2 Sept 2014	Thailand	Via internet	Rapid Alert Notification System
67	Falsified Mabthera was discovered in a hospital pharmacy in Germany.	Mabthera	The original product contains Rituximab		Germany	3 Sept 2014	Romanian origin	Legal supply chain: delivered by a wholesaler in Romania to a German hospital.	Rapid Alert Notification System
68	Zonegran and Ipstyl of falsified origin (sourced from an illegal wholesaler).	Zonegran, Ipstyl	Zonisamide (Zonegran) 50 mg Lanreotide acetate (Ipstyl) 120mg		Part of ongoing investigations by the Italian Medicines Agency, AIFA	9 Sept 2014	Italy	Legal supply chain: Repacked by 2Care4, DK and delivered to the Danish market (Zonegran) and the Norwegian market (Ipstyl)	Rapid Alert Notification System

69	Falsified Avastin	Avastin	Bevacizumab 400mg/16ml	Germany	18 Sept 2014	Romania	The counterfeit product was identified at a parallel distributor in Germany.	Rapid Alert Notification System
70	Truvada of falsified origin (non-compliant Italian source).	Truvada 200 mg / 245 mg	tenofovir disoproxil emtricitabine "	Finland	25 Sept 2014	Italy	Legal supply chain: distributed to hospitals and pharmacies	Rapid Alert Notification System
71	The product Zetra was found to contain undeclared sildenafil.	Zetra capsules	Sildenafil	Spain	29 Sept 2014	China, as declared on the label (not verified)	A sample of the product was taken from a retailer	Rapid Alert Notification System

72	Illegally traded Abilify	Abilify	Aripiprazol 15 mg	Recalled in Germany	2 Oct 2014	Romania	Sourced from an unauthorise d wholesaler, repacked in Germany (legal supply chain).	Rapid Alert Notification System
73	Falsified units of Fucidin Ointment and Fucidin Cream. The genuine active substances were not identified in samples of the falsified ointment and cream upon testing.	Fucidin Ointment, Fucidin Cream	The genuine product contains: 1. Sodium fusidate 2. Fusidic acid	Recalled in China	2 Mar 2015	China	detected at a manufacture r in China which is not the authorised manufacture r	Rapid Alert Notification System
74	Unauthorised medicinal product sold as dietary supplement	Yohimbine	Yohimbine	Seized at retailer in Spain	28 Jan 2015	US	Illegal supply chain	Rapid Alert Notification System

75	Unauthorised medicinal product sold as dietary supplement	Mega-Sten Extreme	Methylstenbolone	No adverse reactions have been notified	Seized at retailer in Spain	28 Jan 2015	US	US	Illegal supply chain	Rapid Alert Notification System
76	Unauthorised medicinal product sold as dietary supplement	Halo-Plex Xtreme	Chlorodehydro methyltestosterone	No adverse reactions have been notified	Seized at retailer in Spain	28 Jan 2015	US	US	Illegal supply chain	Rapid Alert Notification System
77	Unauthorised medicinal product sold as dietary supplement	Ultra-Sten	dymethazine	No adverse reactions have been notified	Seized at retailer in Spain	28 Jan 2015	US	US	Illegal supply chain	Rapid Alert Notification System
78	Falsified anti-malarial medicine circulating in West Africa. It contains no active ingredient.	Artemether/Lumefantrine	Artemether, Lumefantrine		Cote d'Ivoire, Togo	Feb 2015	Unknown		purchased in a street market in Abidjan, Côte d'Ivoire and in a drug store in Lomé, Togo	WHO Notification System

79	Counterfeit OMNADREN 250	Omnadren 250	mix of testosterone esters		Poland	27 Feb 2015	unknown	Mail shipment, internet order	Rapid Alert Notification System
80	Unauthorised medicinal product sold as dietary supplement	Vigoraxia	thiosildenafil	No adverse reactions have been notified	Seized at retailer in Spain	2 Mar 2015	Argentina	Illegal supply chain	Rapid Alert Notification System
81	Unauthorised medicinal product sold as dietary supplement	Man Power	Dapoxetine Dithiodesmet hylcarbodena fil Desmethylear bodenafil		Sweden	4 March 2015	unknown	Illegal supply chain: Bought in store in Sweden	Rapid Alert Notification System
82	Unauthorised medicinal product sold as dietary supplement	Maximum	Sildenafil, Tadalafil		Sweden	4 March 2015	unknown	Illegal supply chain: Bought in store in Sweden	Rapid Alert Notification System

83	Unauthorised medicinal product sold as dietary supplement	PowerCaps	Dithiodesmet hylcarbodena fil, Desmethyicar bodenafil		Sweden	4 March 2015	unknown	Illegal supply chain: Bought in sex-shop in Sweden	Rapid Alert Notification System
84	Unauthorised medicinal product sold as dietary supplement	PowerStrips	Tadalafil		Sweden	4 March 2015	unknown	Illegal supply chain: Bought in store in Sweden	Rapid Alert Notification System
85	Unauthorised medicinal product sold as dietary supplement	PowerTabs	Dithiodesmet hylcarbodena fil, Desmethyicar bodenafil		Sweden	4 March 2015	unknown	Illegal supply chain: Bought in store in Sweden	Rapid Alert Notification System
86	Falsified Viread 245 mg film-coated tablets	Viread 245 mg	Tenofoviridis oproxil		Lithuania, Germany	31 March 2015	unknown	Legal supply chain: found at LT wholesaler and on the DE market (parallel distributor)	Rapid Alert Notification System

87	Falsified Humira	Humira 40 mg/0.8 ml solution for injection in pre-filled syringe	Adalimumab	detected by a DE parallel importer during the check of incoming goods	13 April 2015	Goods were shipped from Poland	Legal supply chain: detected at a parallel importer	Rapid Alert Notification System
88	Falsified Actonel film-coated tablets (manipulated packaging and expiry date)	Actonel plus Calcium, film-coated tablets	Risedronate 35mg + Calcium carbonate 500mg	Detected at a DE pharmacy	15 April 2015	unknown	Legal supply chain (pharmacy)	Rapid Alert Notification System
89	Falsified Norditropin® SimpleXx containing less than half the stated amount of active ingredient	Norditropin® SimpleXx® 15 mg/1,5 ml solution for injection	Somatropin	detected by a DE patient	5 May 2015	unknown	Illegal supply chain (medicine not authorised in DE)	Rapid Alert Notification System
90	Falsified Botox	BOTOX Vacuum dried Powder for Injection 100U/vial	Botulinum toxin type A	Ukrainian market	7 May 2015	unknown	Detected at Ukrainian doctors. Investigation ongoing	Rapid Alert Notification System

Annex 5: Increase of counterfeit in the legal supply chain in the future: estimations and calculations (extract of the 2008 Impact Assessment)

Recent figures allow a rough estimation of the extent of counterfeit in the legal distribution chain: In 2007, approx. 72 000 packs of counterfeit drugs were confiscated in the legal distribution chain by the UK authorities.

One may argue that these detected counterfeit products in the legal supply chain are just ‘tip of the iceberg’⁵⁴. For the sake of this assessment, a conservative assumption is that these were 30 % of all counterfeit packs in the UK supply chain. In the UK, approx. 1/7 of all drugs in the EU are dispensed to the consumer. Therefore, for the purpose of this calculation, it shall be assumed that there are in 2007 approx. 1.5 m counterfeit medicinal products in the legal supply chain in the EU (a₂₀₀₇), i.e. approx. 0.005 % (i.e. 1 product out of 20 000) of all medicinal products.

On the basis of this, a baseline for the timeframe until 2020 shall be developed:

The ‘optimistic’ baseline of non-action shall be that these are all counterfeit medicinal products in the legal supply chain and that this figure remains stable. In view of the de-facto increase of the volume of the market, this baseline is *de-facto* a decrease in counterfeit in the legal supply chain.

This means that, as of 2008 until 2020, **19.5 m packs** in the legal supply chain will have been counterfeit.

The ‘realistic’ baseline assumes an increase of counterfeit medicinal products by 10 % per year (**i_r**) compared to the previous year.

One can thus model the realistic scenario for 2020 (**a₂₀₂₀**) the total number of counterfeit packs made available until then through the legal distribution chain as follows:

$$a_{2020} = \sum_{k=0}^{n-1} a_{2007} (1+i_r)^k = \mathbf{42\ m\ packs}$$

This would mean that, by 2020, 0.01 % of all medicinal products dispensed via the legal supply will have been counterfeit.

A ‘pessimistic’ baseline scenario of non-action shall be an increase by 30 % per year (**i_p**). A pessimist scenario for 2020 (**a₂₀₂₀**) would be:

$$a_{2020} = \sum_{k=0}^{n-1} a_{2007} (1+i_p)^k = \mathbf{192\ m\ packs}$$

This means that, by 2020, 0.05 % of all prescription medicinal products dispensed through the legal supply chain will have been counterfeit products.

⁵⁴ In particular, this number does not include products considered to be counterfeit in view of a counterfeit active ingredient. Here, figures are rare.

Annex 6: Direct/indirect costs and other costs attributable to counterfeit in the legal supply chain: estimations and calculations (extract of the 2008 Impact Assessment)

On the basis of the estimations above (Annex 5), one can establish the costs associated to non-action.

These costs depend as to whether the ‘optimistic’, the ‘realistic’ or the ‘pessimistic’ baseline apply.

It has to be stressed that the policy options discussed in this impact assessment which aim at attaining the objective would only be effective once adopted by the co-legislator, transposed by Member States applied by economic operators, and enforced by competent authorities. This can be expected as of 2011.

Therefore, the costs are linked to the following scenarios:

- ‘optimistic scenario’: $a_{20} = \sum_{k=0}^{n-1} a_{20} (1)^k = \mathbf{15 \text{ m packs}}$
- ‘realistic scenario’: $a_{20} = \sum_{k=0}^{n-1} a_{20} (1+0.1)^k = \mathbf{35 \text{ m packs}}$
- ‘pessimistic scenario’: $a_{20} = \sum_{k=0}^{n-1} a_{20} (1+0.3)^k = \mathbf{183 \text{ m packs}}$

Costs:

At the outset, it shall be stressed that the monetised benefits are expected to mount in line with inflation.

Direct costs:

- Costs for hospitalisation as consequence of treatment involving counterfeit medicines: Costs for hospitalisation are on average 480 EUR per day in the EU⁵⁵. The causality between counterfeit medicines and hospitalisation is largely unexplored. However, as set out above (2.2.), counterfeiters target increasingly life-saving drugs which are typically administered precisely in order to avoid hospitalisation. Examples of the past include medicines for treatment of:
 - thrombosis prevention;
 - heart attacks and strokes;
 - influenza;
 - prostate cancer⁵⁶.

⁵⁵ WHO (2005).

⁵⁶ Cf. chapter 2.2.

Therefore, it is a rather conservative approach to assume for the purpose of this impact assessment that 5% of the counterfeit packs in the lawful supply chain prolonged hospitalisation in average by 5 days. This means that the projected baseline until 2020 of costs of non-action with regard to avoidable hospitalisation in the EU can be estimated to lie **between € 1.8 bn and € 22 bn**.

- Costs occurring in an ambulatory setting for treating the consequences of a treatment involving counterfeit medicines: These costs are essentially based on general practitioner ('GP') consultations caused by counterfeit medicines which were toxic or of lower or too high efficacy. The average hourly wage rate for a GP across the EU is €31⁵⁷. One can assume that 20% of all counterfeit medicinal packs in the legal supply chain require additional ambulatory treatment by a GP of 3 sessions of 20 minutes each. This means that the projected baseline until 2020 of costs of non-action with regard to avoidable medical treatment by a GP in the EU can be estimated to lie **between €93 m and € 1.1 bn**.

Indirect costs:

To quantify and monetise impacts on human health, the concept of Quality-Adjusted Life Years ('QALYs'), which is widely employed for estimating the cost-effectiveness of pharmaceuticals, shall be used⁵⁸. QALYs combine effects on life expectancy and quality of life within a single measure, with 1 QALY being equal to one year of life expectancy in full health. Note, that Disability-Adjusted Life Years ('DALYs') are a similar concept and represent a combined measure of lost years of life and lost quality of life resulting from disease. For the purpose of this assessment the value of DALY shall be considered as similar to the QALY⁵⁹.

There are no studies available on the average change of QALY due to counterfeit medicines. This would be anyhow difficult, as very different medicines are affected. In recent impact assessments of the Commission related to wrong prescriptions, an average change of QALY for each instance of -0.170 was assumed on the basis of case studies⁶⁰. Concerning counterfeit medicines, it shall be assumed that the relevant instance - just as for (prolonged) hospitalisation - would be 5% of packs of counterfeit medicines in the legal supply chain. For the purpose of this impact assessment, account shall be taken of a recent study assuming a medium value of QALY of € 60 000⁶¹.

On the basis of these assumptions, it can be estimated that the indirect costs of counterfeit medicines based on QALY are approx. €765m per year. This means that the projected baseline until 2020 of indirect costs of non-action based on QALY can be estimated to lie **between € 7.65 bn and € 93 bn**.

Other quantifiable burdens:

⁵⁷ Based on OECD and Eurostat. Cf. also Impact Assessment Report on Commission proposal for a Directive amending Directive 2001/83/EC on information to patients (SEC(2008)), Annex 2, point A1.32.

⁵⁸ Cf. Impact Assessment Report on Commission proposal for a Directive amending Directive 2001/83/EC on information to patients (SEC(2008)), Annex 2, point A1.17 ff.

⁵⁹ Cf. WHO Burden of Disease data, <http://www.who.int/healthinfo/bodestimates/en/index.html>.

⁶⁰ Cf. Impact Assessment Report on Commission proposal for a Directive amending Directive 2001/83/EC on information to patients (SEC(2008)), Annex 2, point A1.17 ff.

⁶¹ Mason et. al., Estimating a monetary value of a QALY from existing UK values of prevented fatalities and serious injuries (2006).

- The exact costs depend on the quantity of products concerned and the depth of percolation of the product into the supply chain. With regard to the former, it is crucial to stress that recalls usually involve a larger quantity of products than only the counterfeit ones. Industry sources estimate that for one Member State of the size of the UK the recall of 30 000 products of three different batch-numbers which have reached the retail/pharmacy level has direct costs of approx. € 10 m. This would mean that a recall in the entire EEA-area costs business approx. € 60–80 m.
- Costs for destroying seized counterfeit products which at present fall on the rightholder.

Annex 7: Costs of the unique identifier for pharmacies – (extract of the ECORYS report)

Where possible, we distinguish between the 154 000 community pharmacies, 8 000 dispensing doctors⁶² and 5 000 hospital pharmacies⁶³.

The total annualised investment costs for pharmacies range from € 17 million to € 69 million. In addition, total costs for dispensing doctors are approximately € 2 million and total costs for hospital pharmacies are at least € 2 to € 3.5 million. In relative terms, the costs for hospital pharmacies are higher than for community pharmacies as hospital pharmacies currently do not scan individual medicine packages.

Table 3.3 Investment costs for pharmacies (annualised)

	Total costs for sector (in million euros)	Costs per pharmacy (in euros)
<i>Community pharmacies</i>		
Modify pharmacy software	3–11	<100
Buy scanning equipment (2D)	10–50	70–330
Scanning time	0	0
Connect to repository system	0	0
Staff training & support	4–8	<100
Total costs	17–69	270–530
<i>Dispensing doctors</i>		
Modify pharmacy software	.	<100
Buy scanning equipment (2D)	1	70–330
Scanning time	0	0
Connect to repository system	0	0
Staff training & support	.	<100
Total costs	2	270–530
<i>Hospital pharmacies</i>		

⁶² Informa UK Ltd. (2007), *European pharmaceutical distribution: Key players, challenges and future strategies*.

⁶³ EDQM (2012), *EDQM Response to delegated act on the detailed rules for a unique identifier for medicinal products for human use, and its verification — Concept Paper submitted for public consultation*.

Modify pharmacy software	.	>100
Buy scanning equipment (2D)	1–3	140–500
Scanning time	PM(+)	PM(+)
Connect to repository system	0	0
Staff training & support	.	150
Total costs	2–4+PM(+)	290–750+PM(+)

. stands for total annual costs less than € 500 000.

The average production value per community pharmacy is approximately €260 000 per pharmacy per year and most of them are SMEs. Profitability in the sector was 8.6 per cent in 2010. The additional annual costs for the unique identifier as a percentage of the production value in the sector shows a percentage of less than 1 %. This means that the cost consequences for community pharmacies are relatively limited compared to their production value and profit margins. As the pharmacies already use to scan medicines, this option does not increase the administrative burden.

For hospital pharmacies the costs per pharmacy are higher than the costs for community pharmacies. The costs presented here are a minimum value. These investment costs are relatively low compared to the total budgets of hospitals.

Annex 8: Costs of the unique identifier for manufacturers– (extract of the ECORYS report)

Several stakeholders have provided estimates of the average costs of adapting production lines. The EDQM estimates⁶⁴ that total investment costs range from € 60 000 to € 200 000. In the 2008 impact assessment⁶⁵ an average of € 150 000 was used for adapting packaging lines. EFPIA⁶⁶ has also provided an average figure for the investment costs, comparable to the lower bound of the EDQM estimate. The EGA⁶⁷ has also provided some detailed calculations for an average generic manufacturer leading to estimated investment costs of € 265 000 per production line. Given these differences in the estimates we have used a range of € 60 000 to € 265 000 per packaging line as the figure for investment. Annualised, these costs are € 12 000 to € 53 000 each year.

Next, it is important to consider how many packaging lines have to be adapted. The number of packaging lines is not exactly clear. In the 2008 impact assessment⁶⁸ it was estimated that 15 000 packaging lines operate for the EU market, of which 10 000 operate in the generics sector and 3 000 in the non-prescription sector.

Given these figures it is estimated that the total investment costs for adapting 12 000 packaging lines for prescription medicines range from € 0.7 billion to € 3.2 billion. Annualised, using a lifetime of 10 to 15 years for a packaging line, the total costs per year range from € 50 million to € 320 million for the whole sector.

In total, annual costs per package range from **€ 0.005 to € 0.033 per package of medicinal product.**

Around two thirds of all packaging lines operate in the generics sector which increases the costs for this sector. If we use the same percentage for prescription medicines packaging lines too, we can split the costs into costs for originator companies and those for generics companies. In that case total annual costs for originator companies would range from € 20 million to € 110 million, and total annual costs for generics companies from € 30 million to € 210 million.

It is not exactly clear what share of these packaging lines belongs to repackagers, so it is not possible to calculate the costs for parallel importers precisely. To provide some insights we calculated the costs under the assumption that the costs per package are the same for regular manufacturers as for parallel importers. In that case, the total annualised investment costs for repackagers range from € 1 million to € 5 million.

⁶⁴ EDQM (2012), *EDQM Response to delegated act on the detailed rules for a unique identifier for medicinal products for human use, and its verification — Concept Paper submitted for public consultation.*

⁶⁵ European Commission (2008), *Commission Staff Working Document. Accompanying document to 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. Impact Assessment.*

⁶⁶ Interview EFPIA.

⁶⁷ Interview EGA.

⁶⁸ European Commission (2008), *Commission Staff Working Document. Accompanying document to 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. Impact Assessment.*

Repackagers have to check out the safety features before repackaging. In addition to adapting their packaging lines, they also have to install equipment to verify the safety features. Estimates of the costs for repackagers are difficult to estimate, but it sounds reasonable that repackagers will face the same investments as wholesalers for checking medicine packages (see below).

Repackagers face additional costs for modifying management software, buying scanning equipment, scanning time and additional warehouse space. We calculated these costs under the assumption that the costs per package are the same for wholesalers as for parallel importers. Given the total annual costs for all wholesalers in the sector of € 33 million per year, this would mean that the total costs for scanning/verification of the safety features would be less than € 0.5 million a year.

The impact assessment covers only the costs of the unique identifier.

Costs manufacturers (annualised)

	Total costs sector (in million euro)	Costs per manufacturer (in euro)
Originator companies		
Adapting production lines	20 – 110	
Total costs	20 – 110	
Generics companies		
Adapting production lines	30 – 210	
Total costs	30 – 210	
Repackagers		
Adapting production lines	1 – 5	1,000 – 5,000
Scanning/verifying safety features	.	..
Total costs	2 – 10	10,000
Total costs (manufacturers)	52 – 330	

. stands for total annual costs less than € 500,000.

.. stands for costs less than € 500.

**Annex 9: In-depth comparison of the three policy options for the repository system–
(extract of the ECORYS report)**

For any repository system, costs have to be incurred in setting up the system and for maintenance and operations.

The most important factors affecting the costs are:

Functionalities of the repository system: The costs of any ICT system depend largely on its functionalities. The most essential functionalities of the repository system are of course checking in, verifying and checking out the unique identifier. Some other functionalities are data protection, security, performance, traceability of repackaged medicine packs or functionalities relevant for reimbursement purposes. The costs of the system increase with the number of functionalities.

Number of databases: One important factor for the level of the costs is the number of databases that have to be set up and maintained.

Number of interfaces: All actors in the chain have to communicate with each other. To that end, interfaces are needed between these actors' systems (so system A can communicate with system B). The interfaces have to be created and maintained (as ICT systems are updated and changed each year). The stakeholders are already thinking about a cost-efficient solution by setting up an EU hub⁶⁹. Many-to-one-to-many connections lead to fewer interfaces than many-to-many connections.

Use of existing system: At this moment some systems that are more or less comparable to a repository system do exist, e.g. national systems in Belgium, Italy, Turkey and France. Stakeholders have also developed promising pilot projects. If these systems can be adapted, fewer new systems would have to be developed. Normally, it is cheaper to design an add-on or to update a system than to design and build a new system.

Coordination costs. Coordination costs can have great influence over the total costs of ICT systems. The number of stakeholders is one factor; the alignment of their interests is another important one. In the case of this repository system, with such a large number and variety of manufacturers, wholesale distributors, pharmacies and governments, coordination costs are a factor to be taken into consideration.

Cost-efficiency of different policy options

	Stakeholder governance	EU governance	National governance
Functionalities of the repository system			
Risk of gold plating	++	+/-	-- (!)
Flexibility in adding new	--	--	+

⁶⁹ EAEP, EFPIA, GIRP & PGEU (2012), *Coding & serialisation. Delegated act on the detailed rules for a unique identifier for medicinal products for human use, and its verification. Concept Paper submitted for public consultation. Joint response (EAEP-EPPIA-GIRP-PGEU). 26 April 2012.*

functionalities			
Number of databases	+ / -	++	- (!)
Number of interfaces	+ / -	+ (!)	- (!)
Use of existing systems	+	--	+
Coordination costs	++	--	-

* ++ / + means that this system performs better/well on cost-efficiency, -- / - means that this option performs less well/below average on cost-efficiency, ? means that the effects on cost-efficiency are not yet clear, and ! means that cost-efficient solutions do exist and can be implemented (potential leading to higher cost-efficiency).

The remainder of the section presents the rationale of the differences between the three policy options.

Functionalities of the repository system

The functionalities of the repository system are considered the same in each of the three policy options. However, the risk of gold plating by adding other functionalities is lowest in the stakeholders option. This risk is highest in the national governance model and present in the EU governance model.

Number of databases

The number of databases can differ for the three policy options. For the EU governance option it is assumed that a single central EU database will be used and therefore the number of databases is lowest in this option. On the one hand, this means that this option is more cost-efficient than the other two options (reducing fixed costs per database)⁷⁰. On the other hand, the size and complexity of a single large central EU database leads to another level of costs for the database.

For the national governance option information about the number of databases is not available. Taking into account the fixed costs per database and thus trying to reduce the number of databases can lead to more cost-efficient solutions.

Number of interfaces

The number of interfaces depends on the number of databases, the use of existing systems and whether common industry-wide standards are chosen. As the EU option has only one database, this leads to the lowest number of interfaces.

The stakeholder model probably leads to a slightly less cost-efficient solution (compared to the EU model) as the number of databases is higher, but at the same time industry standards will be used, resulting in a fewer number of interfaces. The number of interfaces is probably highest in the national governance model, although this can be improved through taking into account industry standards and clever design of the system (with as few databases as possible).

Use of existing systems

⁷⁰ See for example the old but still interesting study: Booz, Allen & Hamilton (2003), *XML.gov registry/repository. Business case.*

The EU database performs less well than the other two systems on the use of existing systems as a new EU database is set up. In the stakeholder governance and the national governance options the use of current industry systems and current national systems is possible, resulting in more cost-efficient solutions.

Coordination costs

The stakeholder option performs better in terms of cost-efficiency than the EU and the national governance options⁷¹. Another reason for this difference is that most industry stakeholders have already set up a basic repository-type system. Coordination costs are probably highest in the EU governance option. Coordination costs are likely to differ for the three policy options. The stakeholder governance model performs better as some of the most important industry stakeholders have already agreed on the basic design of the system.

Estimates on costs for the repository system

Some stakeholders have provided estimates on the costs of the repositories system in their responses to the public consultation. Basically the costs for the repositories system can be split up into costs for setting up databases, costs for connectivity of the different systems and governance organisations. For the repositories system these cost estimates range widely. We have a) analysed these differences, and b) compared the figures with figures of other ICT systems. Our conclusion is that the single most important reason for differences in estimates of the costs is caused by differences in design brief of the systems (what is the ICT system supposed to do?). The devil is in the details – especially in ICT projects – and for this reason cost estimates range widely. As long as more detailed information is unavailable on the design brief, it will be difficult to estimate the plausibility of the different cost estimates.

Estimates from stakeholders of the total annual costs of the repositories system range from € 100 million to € 400 million a year. Some estimates have been provided specific for one of the policy options, others were more in general (regardless of the policy option chosen).

Given the differences in table 3.4 it is estimated that the costs of the stakeholder governance and the EU governance model will be more or less comparable. Probably the costs of the national governance option will be higher than the other options.

⁷¹ See for example: SEO (2004), *Goed(koop) geregeld: Een kosten-baten analyse van wetgeving en zelfregulering (A cost-benefit analysis of regulation versus self-regulation)*.

Annex 10: Overall Impacts of the safety features– (extract of the ECORYS report)

The costs of introducing a unique identifier increase the production costs for the manufacturers, wholesalers and retailers. In the table below the costs of unique identifier are presented for all actors directly affected in the pharmaceutical supply chain.

Table 3.6 Costs prescription medicines sector

	Unique identifier		Safety feature	
	Total costs sector	Costs per company	Total costs sector	Costs per company
	(in € million)	(in € 1,000)	(in € million)	(in € 1,000)
Manufacturers		(in € 1,000)		(in € 1,000)
Originator manufacturers	20 – 110	7 – 39	24 – 175	9 – 63
Generics manufacturers	30 – 210	30 – 210	38 – 340	38 – 340
Repackagers / parallel importers	1 – 5	1 – 5	2 – 10	1 – 10
Total costs	51 – 325	-	64 – 525	-
Wholesalers		(in € 1,000)		(in € 1,000)
Full-line wholesalers	33	43	33	43
Short-line wholesalers	?	?	?	?
Other	0	0	0	0
Total costs	33 + ?	-	33 + ?	-
Retailers		(in €)		(in €)
Community pharmacies	17 – 69	270 – 530	17 – 69	270 – 530
Dispensing doctors	2	270 – 530	2	270 – 530
Hospital pharmacies	2 – 4	390 – 750	2 – 4	390 – 750
Other retailers	?	?	?	?
Total costs	21 – 75	-	21 – 75	-
Repositories system				
Stakeholder governance	100 – 400		100 – 400	
EU governance	100 – 400		100 – 400	
National governance	> 100 – 400		> 100 – 400	
Total costs	100 – 400	-	100 – 400	-
Total costs sector	205 – 833	-	218 – 1,033	-

Total yearly costs estimates of the unique identifier for the entire sector range from € 200 to € 800 million a year and for the safety features from € 200 million to € 1 billion a year. This is a considerable amount that will be added to the production costs. Looking at the production

value (ex factory) of the sector the cost addition appears modest at less than 1%⁷². A better reference would be the impact in terms of share of the gross operating surplus generated by the manufacturing sector. The additional costs of the unique identifier would equal 1 to 2 percent of this operating surplus. However, gross operating surplus does not take into account the cost of capital and taxes. When taxes and capital costs would be taken into account it is tentatively estimated that the additional costs of the unique identifier would be measured between 2 and 4 percent of the net operating surplus.

Looking beyond these very broad sectoral averages, the cost increases are different for the different actors in the pharmaceutical supply chain.

For wholesalers (with a possible exception for short-line wholesalers) and for retailers the effects still appear limited.

For pharmaceutical manufacturers the average figures only tell part of the story. The cost impact of the unique identifier is higher for generic companies than for originator companies. Estimates of the additional yearly costs for the unique identifier excluding tamper evidence range from € 7,000 to € 39,000 for an originator company and from € 30,000 to € 210,000 per generics company. Including tamper evidence increases these differences between originators and generic companies as most packages produced by originators already include tamper evidence, while this is not the case for generics⁷³. The most important reasons for these costs differences between originator manufacturers and generic manufacturers are the relative number of packaging lines (relatively higher for generics). In addition, generic companies tend to be significantly smaller than originator companies⁷⁴ indicating that the impact of the cost increases will be relatively smaller for originator companies.

The additional cost estimates for parallel importers / repackagers seem limited, but the impact is underestimated as this is a relatively small sector comprising many SMEs and they face double investments compared to other actors in the pharmaceutical sector (both the costs for manufacturers and the costs for wholesalers).

Therefore the impact on cost is expected to be relatively larger for two actors in the chain: the generics manufacturers and the parallel importers.

⁷² This is the case both including and excluding the costs for tamper evidence in the composition of the costs of the unique identifier.

⁷³ Respectively € 9,000 to € 63,000 for originators and € 38,000 to € 340,000 when looking at the additional costs for the unique identifier and tamper evidence.

⁷⁴ European Commission, Competition DG (2009), *Pharmaceutical sector inquiry. Final Report*.

Annex 11: The European Stakeholder Model (ESM)

Extract of the joint response of EAEPC, EFPIA, GIRP and PGEU

The European Stakeholder Model (ESM), proposed by EAEPC, EFPIA, GIRP and PGEU, is composed of a series of national data repositories (linked via a European Hub and together forming the European Medicines Verification System, EMVS), that serve as the verification platforms which pharmacies and other registered parties can use to check a pack's authenticity. The system will be interoperable between EU Member States with flexibility to account for national needs.

European Medicines Verification System (EMVS)

ESM working in Partnership with National Governments

Importantly, and in line with the FMD, the European Stakeholder Model will be developed in partnership with governments and public agencies – as well as all other relevant actors along the supply chain. As a fundamental principle, the stakeholder governance at national level will *always* run in partnership with national public authorities.

The national system may be established by the stakeholders and procured to local specifications through a tender process. Alternatively a ready-made system will be available to implement at national level based on a standard blueprint developed together with the European Hub. This option is the “National Blueprint” (nBPS) in the diagram above and will under certain circumstances generate economies of scale and thus a more cost-effective system versus each EU Member State creating its own national repository.

