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COMMISSION OF THE EUROPEAN COMMUNITIES

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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

{COM(2008) 668 final}
{SEC(2008) 2675}

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List of acronyms

API	Active pharmaceutical ingredient
CoCP	Compilation of Community Procedures on Inspections and Exchange of Information
CoE	Council of Europe
EDQM	European Directorate for the Quality of Medicines and HealthCare of the Council of Europe
EEA	European Economic Area
EMEA	European Medicines Agency
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
MHRA	UK Medicines and Healthcare products Regulatory Agency
OTC medicines	"Over-the-counter medicines", i.e. non-prescription medicinal products
QP	Qualified Person (requirement for manufacturers, importers)
RP	Responsible Person (requirement for wholesalers)
U.S. FDA	United States Food and Drug Administration
WHO	World Health Organization

1. PROCEDURAL ISSUES

A proposal for a Directive of European Parliament and Council amending Directive 2001/83/EC[1] ("**Medicinal Products Directive**") as regards the prevention of the entry into the legal supply chain of medicinal products which are illegal in view of false identity, history or source was announced in early 2008 by Vice-President Verheugen. It is scheduled in the Commission's agenda planning under ref. n° 2008/ENTR/038.

1.1. Consultation of other Commission Services and agencies

Five meetings of the Inter-Service Steering Group were held on the following dates: 31 May 2007, 3 December 2007, 17 January 2008, 29 February 2008 and 21 May 2008. Representatives from Directorates-General SANCO, COMP, TRADE, TAXUD, MARKT, INFSO, DEV, RELEX, JLS, EMPL and from the Legal Service, as well as the Secretariat-General, were invited. To gain additional expertise, there were close contacts with the European Medicines Agency ("**EMEA**") on this file.

1.2. Consultation of Member States, fact-finding missions

Apart from informal contacts with officials from the competent authorities of the Member States, the file was discussed with Member States' representatives at the Working Group of Enforcement Officers on 28 April 2008, in the GMP/GDP Inspectors Working Group on 22 May 2008 and at the Pharmaceutical Committee on 20 May 2008. Moreover, DG ENTR undertook three fact-finding missions - to Germany, the UK and the Netherlands - to gain a better understanding of the matter and to discuss issues of "counterfeit" medicinal products with practitioners, including customs authorities.

1.3. Stakeholder consultation

A stakeholder consultation was held from 11 March 2008 to 9 May 2008 on the basis of a public consultation document. All the standards laid down in the "General principles and minimum standards for consultation of interested parties by the Commission"[2] were met. The main results of the public consultation are addressed in sections 2.-5. of the impact assessment report. A summary of the responses to the consultation is annexed to this impact assessment.[3] The responses themselves have been published on the "pharmaceuticals" website of the Commission.[4]

1.4. External studies contracted by the Commission

To acquire additional expertise, the Commission had contracted, already in 2007, a study looking into the safety of the supply chain of medicinal products. The study looks *inter alia* into aspects of "counterfeit" medicines. The final study is scheduled for autumn 2008. However, in view of this ongoing work, it was agreed with the

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1 OJ L 311, 28.11.2001, as amended.
2 COM(2002) 704.
3 Annex 9.
4 http://ec.europa.eu/enterprise/pharmaceuticals/counterf_par_trade/counterfeit_key.htm

contractor that useful "raw data" obtained so far would be used for this impact assessment report. This applies in particular to the data referred to in Chapter 5.3.1. and Annex 4.

1.5. Contacts with third country authorities

In the run-up to the impact assessment, the Commission consulted the authorities of several third countries (including the U.S., Canada, Japan, Russia, China and India) as well as with the World Health Organisation ("**WHO**") and the Council of Europe ("**CoE**"). The respective contact persons were specifically invited to submit comments during the public consultation.

1.6. Impact assessment board

The impact assessment was submitted to the impact assessment board ("**IAB**") for scrutiny.[5] In its opinion (which is publicly available on the EUROPA-server[6]), the IAB stressed the need to

- Strengthen further the assessment of the impact on parallel traders of various policy options discussed;
- Look more closely at interactions with other policy areas, such as customs control, fight against organised crime, awareness campaigns etc.;
- Differentiate more clearly compliance costs from administrative costs; and
- Clarify how the regulation of wholesale distributors impacts on importation and third-country manufacturing.

Moreover, in the "quality checklist", the author-DG was requested to set out more clearly the baseline for modelling of costs and benefits and to provide an easy-to-read overview.

The author-DG has amended the respective parts of the impact assessment report in line with the suggestions.

2. PROBLEM DEFINITION

2.1. Introduction – "setting the scenery"

The pharmaceutical sector is a strategic sector for Europe as it contributes to public health, generates positive effects on the EU economy and improves the general level of welfare. The approx. 3 700 pharmaceutical companies in the EU have a turnover of 170bn EUR; they employ more than 634 000 people.[7] Of these companies, approx. 1000 companies are producing generic, i.e. non-patented medicinal products. Approx. 1 000 companies are active in the non-prescription sector (often referred to as "over-the-counter medicines", "**OTC" medicines**)

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5 http://ec.europa.eu/governance/impact/practice_en.htm

6 http://ec.europa.eu/governance/impact/cia_2008_en.htm

7 Eurostat (2005).

It is crucial to bear in mind from the outset that the "pharmaceutical sector" in the broad sense includes a variety of other actors, ranging from suppliers of medicinal products ingredients (in particular the active pharmaceutical ingredient, "**API**"), importers, wholesalers (including parallel traders), retailers/pharmacies, and other traders (brokers, etc.). An overview of these actors, and their role and functions, is given in Annex 1.

Concerning pharmaceuticals, reduced safety, quality, or efficacy can be life-threatening. In this respect, pharmaceuticals are distinct from many other consumer products.

2.2. Problem identification

2.2.1. Increase in "counterfeit" medicinal products in the legal supply chain

At the outset, it has to be highlighted that the term "counterfeit medicines" in the context of this initiative is not restricted to violations of trade mark rights. Rather, in the context of this initiative "counterfeit" medicines are medicinal products which are false representations with respect to their identity, history or source. Such products usually do not include the correct or any active ingredient or include ingredients with a lower quantity ("identity"). In many cases such products are not manufactured in the declared sites ("source"). Such medicines may have been diverted in distribution chain thus not fulfilling obligations related to safe transport and storage, e.g. by respecting cold chain requirements ("history").[8]

A recent analysis of the current situation has revealed that counterfeit medicines have become a growing threat to public health over the past few years.

The Commission has observed the following worrying trends in particular:

- A sharp increase in seizures of counterfeit medicines by customs: EU Statistics report the seizure of a total of 2 711 410 medicinal products (articles) at EU customs borders in 2006. This is an increase of 384% compared to 2005.[9] Figures for 2007 confirm this trend with over 2.5m counterfeit medicines ceased at EU borders.[10] The responsible expert-group of the WHO estimates that, in industrialised countries, counterfeit medicines have a market share of up to 1%.[11] Industry estimates that the volume of counterfeiting medicines increases by 20%-100% per year.[12]

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8 For the purpose of this document, reference shall be made to „counterfeit medicines" in the larger sense otherwise indicated otherwise.

9 http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/counterf_comm_2006_en.pdf

10 "Counterfeit" as defined in Council Regulation (EC) No 1383/2003 of 22 July 2003 concerning customs action against goods suspected of infringing certain intellectual property rights and the measures to be taken against goods found to have infringed such rights (OJ L196, 2.8.2003, p. 7); http://ec.europa.eu/taxation_customs/customs/customs_controls/counterfeit_piracy/statistics/index_en.htm

11 http://www.who.int/mediacentre/factsheets/fs275/en/

12 Mike Muller, Director of global anti-counterfeiting operations, Eli Lilly, www.scriptnews.com, 27 June 2008.

Example: In Bulgaria, those investigations followed up by ordinances have increased from just five (in 2005) to over 15 (in 2007).

- A trend towards counterfeiting of life-saving drugs: Counterfeit medicines in the EU used to be mainly 'lifestyle' medicines, including erectile dysfunction and weight loss medicines. Now, criminals are increasingly targeting life-saving medicines, including medicines to treat cancer and heart disease, psychiatric disorders, and infections.

Example: In 2007, counterfeit medicines reached the legal chain of supply to patients. These medicines were prescription drugs for the treatment of conditions such as heart disease and psychiatric disorders. They contained a significantly lower quantity of the active ingredient than declared.

Treatment with such medicines could have fatal consequences. This trend may increase, as the main driving factors are high value, high turnover and total disregard for patient health.

Example (to be removed for the final - public - version): in 2007 Bulgarian authorities detected 1 050 packs of Tamiflu, which were shipped through Sofia airport. Subsequent analysis revealed that the counterfeit product contained only sugar and no active pharmaceutical ingredient.

- A trend towards targeting the classical supply chain: Recently, there has been alarming evidence that, besides the internet, counterfeiters are increasingly targeting the licensed distribution chain, including authorised wholesalers, parallel traders and pharmacies. A Commission survey amongst Member States competent authorities conducted in spring 2007 showed that, out of 13 Member States who had data, seven reported incidences of counterfeit medicinal products in the legal supply chain.

Example: The UK Medicines and Healthcare products Regulatory Agency ("**MHRA**") reported a steady increase in incidents affecting the regular distribution chain. Since 2004, there were nine separate cases of counterfeit medicines reaching patients, which necessitated batch recalls; counterfeit medicines were also discovered at the wholesale level on a further five occasions.[13] Prior to 2004, counterfeit products in the legal supply chain were practically unknown in the UK.

- A blurring of the line between counterfeit and sub-standard active pharmaceutical ingredients ("**API**"): The counterfeiting of finished medicines is compounded by the risks stemming from counterfeit and sub-standard API. While not every sub-standard API is necessarily a counterfeit, there is a link as a counterfeit API is most likely to be also sub-standard thus posing a risk to human health.

[13] MHRA Anti-Counterfeiting Strategy 2007-2010 http://www.mhra.gov.uk/home/groups/ei/documents/websiteresources/con2033156.pdf

Examples: In 2007/8, medicinal products for blood-thinning which contained counterfeit heparin reached patients in the U.S. and in the EU. According to the U.S. Food and Drug Administration ("**U.S. FDA**"), at least 81 deaths have occurred in the last 15 months which could potentially be related to the administration of heparin and the contaminant.[14] Although reports from the EU have mentioned only three side-effects and no deaths, the EU could have been equally affected.

In the early 2000s, numerous deaths and side-effects in the U.S. were connected with antibiotics containing gentamicin as an active substance. These effects are assumed to be related to faulty manufacture and impurities of the active substance.[15]

The figures above show only the "tip of the iceberg". This is due to the illegal nature of counterfeit, which leads to insufficiencies of official statistics. To this adds that, in practice, it has become extremely difficult to detect counterfeit products: The techniques employed by counterfeiters have become so sophisticated that detection of fakes may require chemical analysis of the product and/or expert judgement of highly sophisticated (overt or covert) safety features on the packaging.

Addressing this threat is part of the Community strategy for safe, innovative and accessible medicines, as presented by the Commission in its Communication to the Council, the European Parliament and the European Economic and Social Committee on a Renewed Strategy for the Pharmaceutical Sector.[16] Addressing these risks is also part of the Commission's strategic objective to protect citizens from health threats has also been set out in the Commission White Paper "Together for Health: A strategic approach for the EU 2008-2013".[17]

Indeed, counterfeit drugs represent a two-fold risk for public health: First, counterfeits that do not contain the proper active ingredient in the proper quantity result in the patient's condition going untreated. Secondly, counterfeits may contain toxic materials that result in the patient being poisoned.[18] The health risks through counterfeit drugs are a major concern. An overview of some of the counterfeit medicinal products detected in the legal supply chain in 2006 and 2007 alone illustrates this:

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14 http://www.fda.gov/cder/drug/infopage/heparin/

15 Wiener, Deubner, Holzgrabe: Composition and Impurity Profile of Multisource Raw Material of Gentamicin – a Comparison; Pharmeuropa Vol 15, No. 2, April 2003.

16 COM(2008) […] final.

17 COM(2007)630 final.

18 Products with correct ingredients/components or with fake packaging may also be considered as counterfeits.

Counterfeit medicines: Examples of cases reported in 2006/07, potential threats and players involved

Counterfeit Cases	Reporting MS	Medical Indication	Type of counterfeit	Concrete health threat
Heparin	BE, DE	Acute treatment of blood clots and prevention of thrombosis	Counterfeit "heparin-like" contaminant added to Heparin	Allergic reactions. Possibly caused deaths in 81 cases and side effects hundreds of patients.
Clopidogrel	UK	Prevention of heart attacks and strokes	Level of active ingredient only 70-80%	Thousands of patients received the product. Low level of active substance can lead to insufficient protection and subsequent heart or brain strokes.
Olanzapine	UK	Treatment of psychiatric disorders including schizophrenia and bipolar disorders (mental illness with alternating periods of high mood and depressions)	Level of active ingredient 60%	Thousands of patients received the product. Treatment with Olanzapine is particularly dose-sensitive! In case of under dosing risk of early occurrence of manic episodes.
Bicalutamide	UK	Treatment of prostate cancer	Level of active ingredient 75%	Inappropriate levels of active ingredient may impair the treatment of prostate cancer..
Various	MT	Various		Hundreds of packs relating to several diseases
Amoxicillin (Penicillin)	BE	Treatment of various types of infections, e.g. respiratory infections	Level of active ingredient 75% In addition stored under inappropriate storage conditions in customs which could impair active substance	Up to hundreds of thousands of packs are likely to have been transited through EU. Low level of active substance can lead to sub-potent antibiotic levels leading to a persistence of the infection. This can lead to long-term side effects (disabilities) and death
Oseltamivir	BG	Treatment of influenza	No or low level of active substance. Product was processed through customs.	More than 1000 packs were identified at customs, no information how many products have reached patients. Persistence of infections, potential long-term side-effects (disabilities) and death
Metamizole	BG	Pain Killer (for acute and chronic pain, in particular sever pain e.g. tumour pain), in particular used in hospitals and clinics	No active substance.	More than 1000 packs were placed on the market and received patients. Persistence of pain. Therefore possible switch to a stronger pain killer, e.g. opioids which have a different risk profile and may cause specific
Indapamide	BG	Diuretic, anti-hypertensive medication	Product was declared to be slow release but was in fact no slow release product	2000 packs have reached patients. No medical effect. Consequences of no medical effect of antihypertensive medication can be manifold, e.g. heart attacks.

The table above shows that public health consequences can be considerable: these include death, additional medical interventions, and prolonged hospitalisation and

long-term disabilities (e.g. after strokes, loss of hearing). There are also related costs in the form of treatment, absence from work, etc.[19]

Apart from these obvious health risks and their associated costs, there can be more far-reaching consequences in terms of the patient's trust in the legal supply chain, in particular the supply of medicinal products through pharmacies. The impacts on public trust are difficult to quantify. They may well be disastrous and could potentially become comparable to the consequences during the food-and-feed-crisis in the 1990's.

Both the public health risk and the loss of trust have major adverse economic impacts for industry and social security systems.[20] The assessment that the problem is critical has also been confirmed by several expert groups on national level, Community level and international level. For example:

- In a **Commission survey amongst Member States competent authorities** conducted in spring 2007 showed that, out of 13 Member States who had data, seven reported incidences of counterfeit medicinal products in the legal supply chain.

- The **responsible expert-group of the WHO** estimates that, in industrialised countries, counterfeit medicines have a market share of up to 1%.[21]

- A report issued by the **expert group of the Organisation of Economic Co-operation and Development** ("**OECD**") confirmed that "a worrisome trend is that counterfeits are increasingly being detected as having entered the supply chain of some of the most regulated jurisdictions" and that the magnitude and economic efforts of counterfeiting and piracy are of such significance that they compel strong and sustained action from government, business and consumers.[22]

- The **Council of Europe, in an expert study published 2006** highlighted the increasing threat of counterfeit – also in the legal supply chain – and recommended *inter alia* a "legislative framework at European level dealing specifically with medicines counterfeiting" and "regulatory measures particularly applicable to the security of the distribution chain and packaging/labelling of medicinal products."[23]

- Finally, **specialised pharmaceutical literature** has repeatedly and increasingly highlighted the problem.[24]

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19 Cf. chapter 2.3

20 Impacts are considered in depth below (cf. chapter 2.3.)

21 http://www.who.int/mediacentre/factsheets/fs275/en/

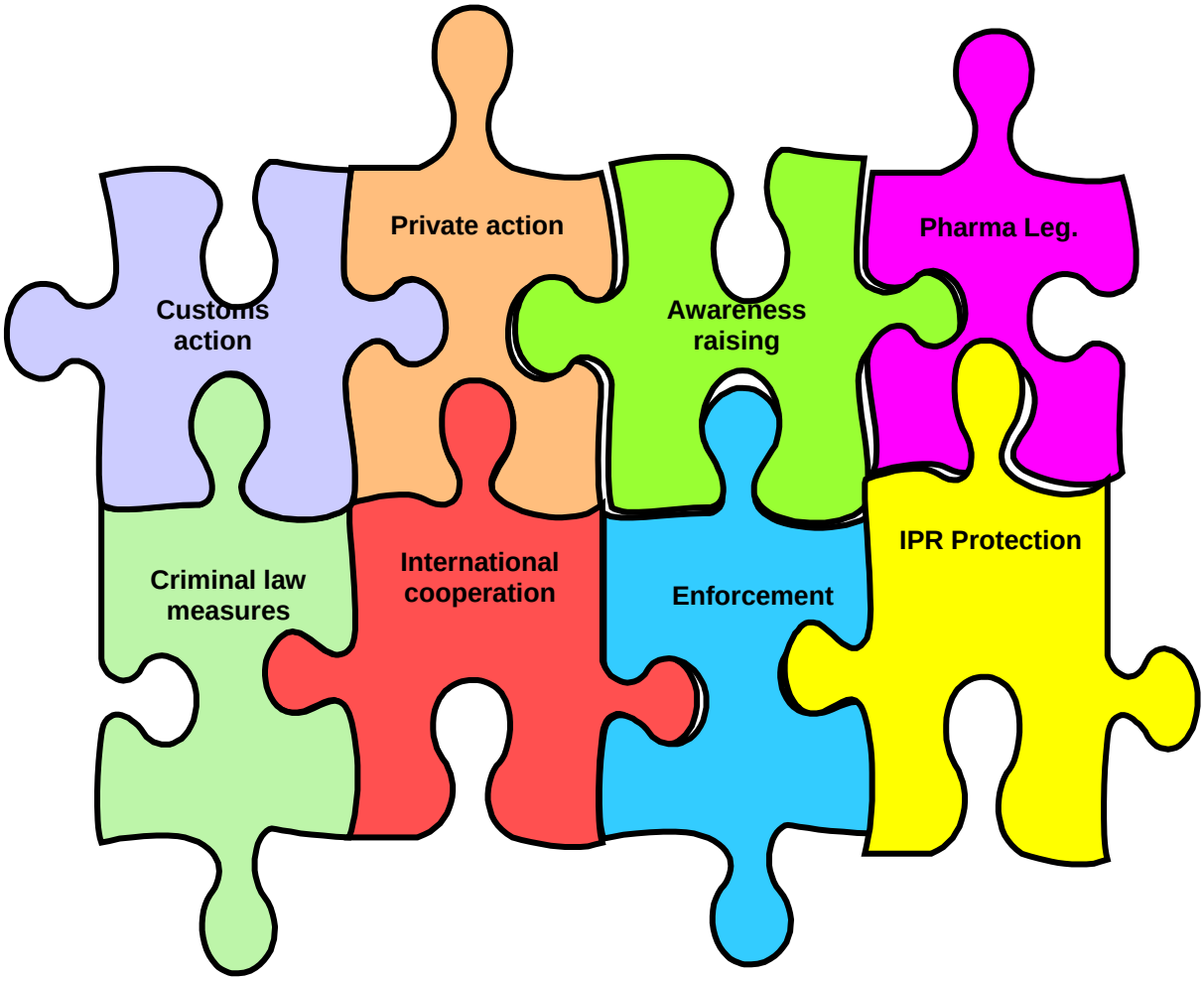
22 http://www.oecd.org/dataoecd/36/34/39543417.pdf

23 Council of Europe, Counterfeit medicines, Survey report (2006)

24 Cf. for example: *Schäfer*, Sicherheitsanforderungen zum Schutz von Produkt und Marke in der Pharmaindustrie, Pharm. Ind. 70 Nr. 3, p. 350; *Jung*, Gefälschte und illegale Arzneimittel – Einschätzung der Bedrohungslage und Darstellung aktueller Entwicklungen aus Behördensicht, Pharm. Ind. 70, Nr. 5, p. 659.

2.2.2. Underlying causes of the problem as regards pharmaceutical legislation and its enforcement

The causes of the problem are manifold and relate to a variety of different areas. These areas may range from a lack of awareness (of industry, authorities, pharmacies and end-users, i.e. health professionals or patients) to weak control mechanisms of infringements of intellectual property (in the EU and abroad) and insufficient deterrents in criminal law (in particular in view of organised crime). It is noteworthy that these are different "horizontal" aspects of activity which do not relate to pharmaceutical legislation as such. Rather, pharmaceutical legislation is one element in a multi-facetted effort. The situation can thus be presented as follows:



It is noteworthy that the Community, as well as Member States and stakeholders are currently working in order to address these many different elements. This relates to horizontal and sectoral, as well as to Community and international activities. Examples for **Community activities in an international setting** are:

- **Strengthening IPR**: The WTO-agreement on trade related aspects of intellectual property rights ("**TRIPS**") provide for requirements of effective tools to enforce substantive intellectual property rights. The Commission is, in accordance with its Strategy for the Enforcement of Intellectual Property

Rights in Third Countries,[25] currently working on ensuring that these requirements are properly implemented and applied.

- **Cooperation with regulators in third countries**: The Commission has actively contributed to the work of WHO in the framework of the International Medical Products Anti-Counterfeiting Taskforce ("**IMPACT**"). The "Principles and elements of national legislation against Counterfeit medical products" were agreed by representatives of non-governmental and governmental institutions in a conference in December 2007. Moreover, the Commission is in regular contact with the competent authorities of the major pharmaceutical markets. For example, in May 2008, the Transatlantic Economic Council ("**TEC**") agreed on conducting **joint inspections** by EU and U.S. Authorities in order to combat manufacturing of counterfeit medicines.[26]

- The EU is a main driver of a group of countries working towards an **Anti-Counterfeiting Trade Agreement** ("**ACTA**").[27] This stand-alone Treaty, which is outside of WTO, aims at increased international co-operation, best practice for enforcement, and a more effective legal framework. It is envisaged to finalize negotiations by the end of 2008.

As regards **Community activities at Community level**, examples are:

- **Strengthening enforcement at the outer border by customs**: The Council has adopted, in 2003, a Regulation aiming at strengthening the customs control of food suspected to infringe intellectual property rights.[28] The need of strong customs enforcement has also been highlighted in the Commission Communication on a customs response to counterfeiting and piracy adopted on 11 October 2005.[29] Currently, the Commission is working on establishing common risk criteria and standards for security and safety risk analysis for the harmonised, strengthened, application of certain customs controls.

- **Strengthening and harmonising criminal law**: The Commission has adopted, on 26 April 2006, an amended proposal for a Directive of the European Parliament and of the Council on criminal measures aimed at ensuring the enforcement of intellectual property rights.[30]

- **Supporting new technologies**: The Directorate-General Research of the European Commission has sponsored a project designated as 4IPR (for Intellectual Property Respect) to assist Brand Owners identify sources of authentication and security devices to protect their products.[31]

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25 OJ C 129, 26.5.2005, p. 3.

26 http://ec.europa.eu/enterprise/pharmaceuticals/international/intercoopbi.htm#usa

27 http://ec.europa.eu/trade/issues/sectoral/intell_property/fs231007_en.htm

28 Council Regulation (EC) No 1393/2003 of 22 July 2003 concerning customs action against goods suspected of infringing certain intellectual property rights and the measures to be taken against goods found to have infringed such rights, OJ L 196, 2.8.2003, p. 7.

29 COM(2005) 479 final.

30 COM(2006) 168 final.

31 http://www.4ipr.net/

- **Awareness raising**: For example, the Commission has issued, in March 2006, a press release warning of counterfeits of the slimming medicines "rimonabant".[32]

As regards **activities by other stakeholders**, there is a wealth of examples of initiatives taken. For example, pharmaceutical companies are **exchanging information** in the framework of the non-for-profit Pharmaceutical Security Institute (PSI).[33] Moreover, several national pharmacy associations have launched **initiatives to raise awareness** amongst health professionals and patients.[34]

The Commission has analysed past cases in order to assess whether the underlying causes of the problem also relate to sectoral pharmaceutical legislation. Several aspects, which have also been discussed in the public consultation, shall be explained below:

2.2.2.1. Product protection measures are insufficient or inefficient

The main underlying cause of the problem is that, today, it is technically relatively easy to fake the inner and outer packaging of medicinal products. This major weakness has also been highlighted in the public consultation.

As regards obligatory authenticity/traceability features (hereinafter "**safety feature**"), Member States have introduced in the past product codings of which some were motivated *inter alia* to fight counterfeit. This unilateral action was lawfully possible as, presently, rules for identification and authenticity of medicinal products are exempted from the general rule of exhaustiveness of Community legislation for labelling of medicinal products.[35] This policy has lead to a high degree of fragmentation of product coding in the EU.

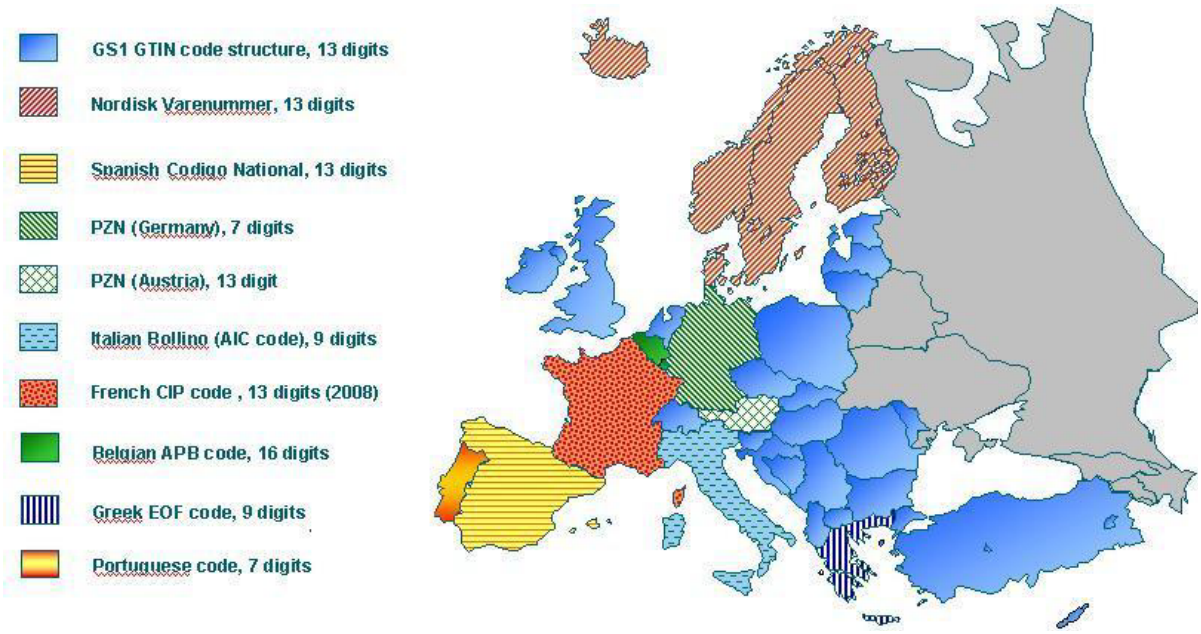
32 http://europa.eu/rapid/pressReleasesAction.do?reference=IP/06/375&format=HTML&aged=1&language=EN&guiLanguage=en

33 http://www.psi-inc.org/index.cfm

34 Cf., for example, in Germany: http://www.aponet.de/topthema/0804_amfaelschungen/0804_amfaelschungen_2.html

35 Cf. chapter 2.4.

Fragmentation of coding requirements for medicinal products in the EEA:



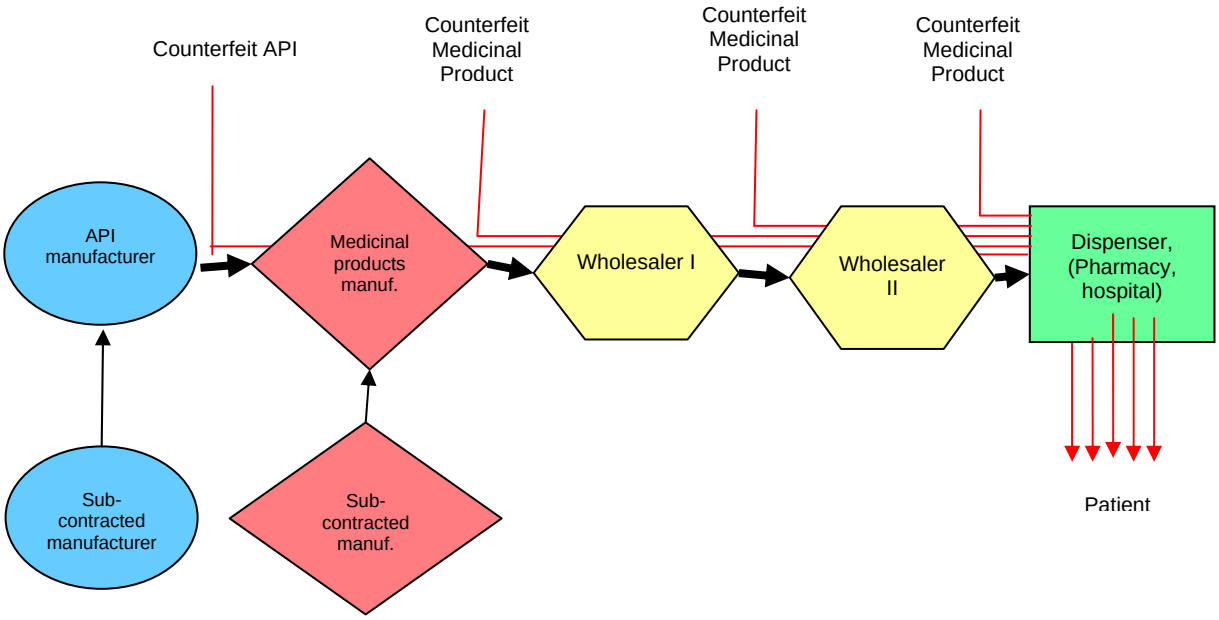
It was repeatedly highlighted in the public consultation that these product coding systems are mostly not suited to efficiently combat counterfeit products in the legal supply chain, as they can be too easily faked.

To respond to this, some companies have taken action and provide some of their products with safety features. However, in the subsequent distribution chain, these features are often discarded, removed, or covered ("manipulated"). Today, these manipulations are, from the point of view of the pharmaceutical legislation, not illegal, provided this is done under a manufacturing authorisation. However, these manipulations remove the usefulness of safety features and are a disincentive for industry to develop additional techniques.

2.2.2.2. Many potential "points of entry"

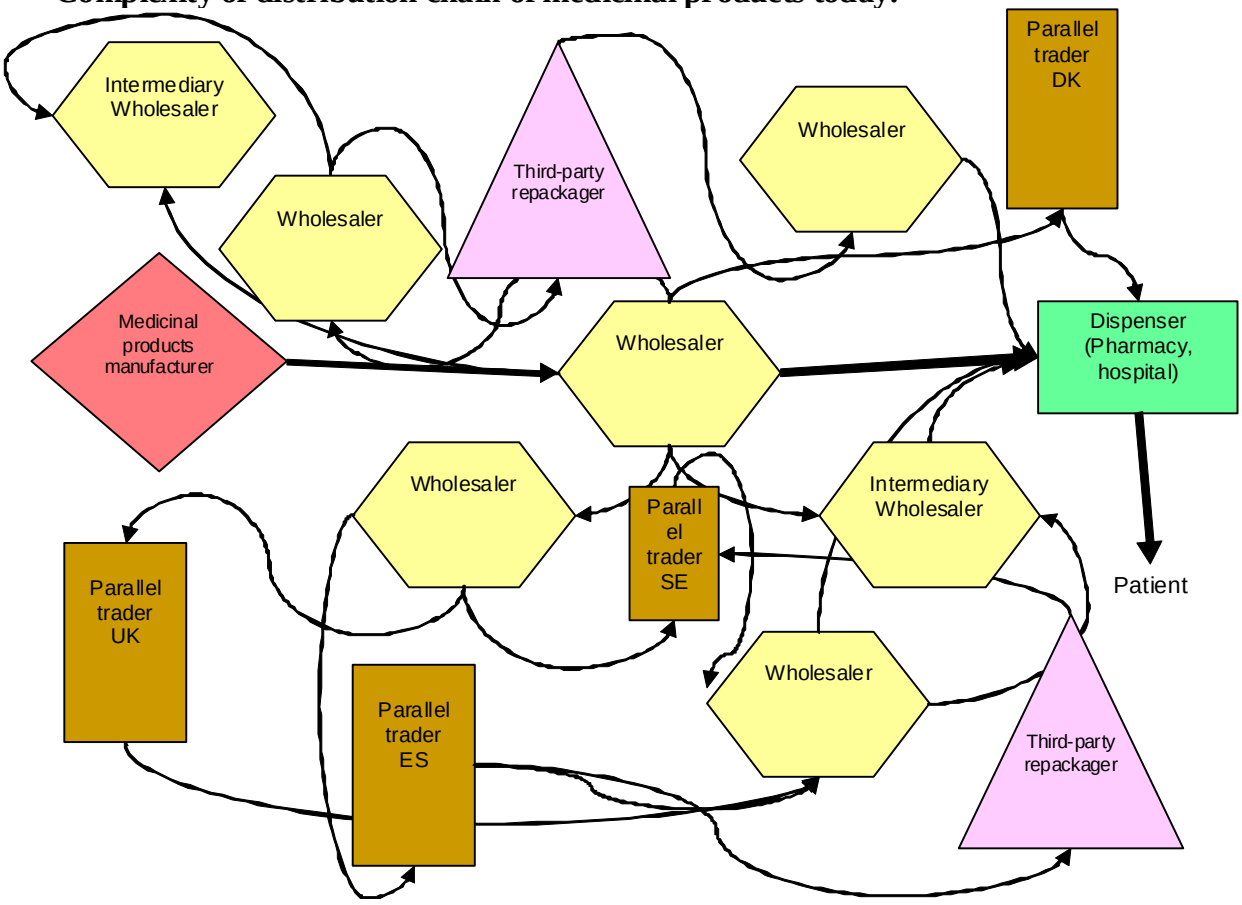
Counterfeit medicinal products can enter the legal production and supply chain at various stages:

Potential sources of counterfeit medicinal products in the legal distribution chain



This overview is in fact overly simplistic: Today's distribution system for medicinal products is highly complex. In the public consultation, manufacturers pointed out that their products may pass through up to 20 pairs of hand before reaching the retailer/pharmacist. While this may be an exaggeration, it is certainly more realistic to describe the distribution chain as follows:

Complexity of distribution chain of medicinal products today:



The distribution chain is only "as strong as its weakest link". In order to infiltrate it with counterfeit products, it is sufficient that *one* distributor purchases from unreliable sources. Once the fake product "is in the system" and supplied-on by good faith actors, it becomes difficult to detect it.

2.2.2.3. Counterfeit products are brought into the EU as "import for export"

Counterfeit pharmaceuticals are often produced outside the EU and subsequently imported.[36]

Owing to the political, legal and practical obstacles, it is difficult for regulators and enforcing authorities to pursue the producers concerned in third countries. Instead, in order to effectively tackle this problem, the point of *physical entry* of the product into the Community also has to be considered.

This applies in particular when products which allegedly are not placed on the market enter the Community customs territory under transit rules and undergo further minor processing (hereinafter "**import-for-export**").

Experience shows that once these products are physically on Community territory they can be redirected into the Community and made available there. This state of affairs is being exploited by counterfeiters and allows them to channel counterfeit products into the legal distribution chain.

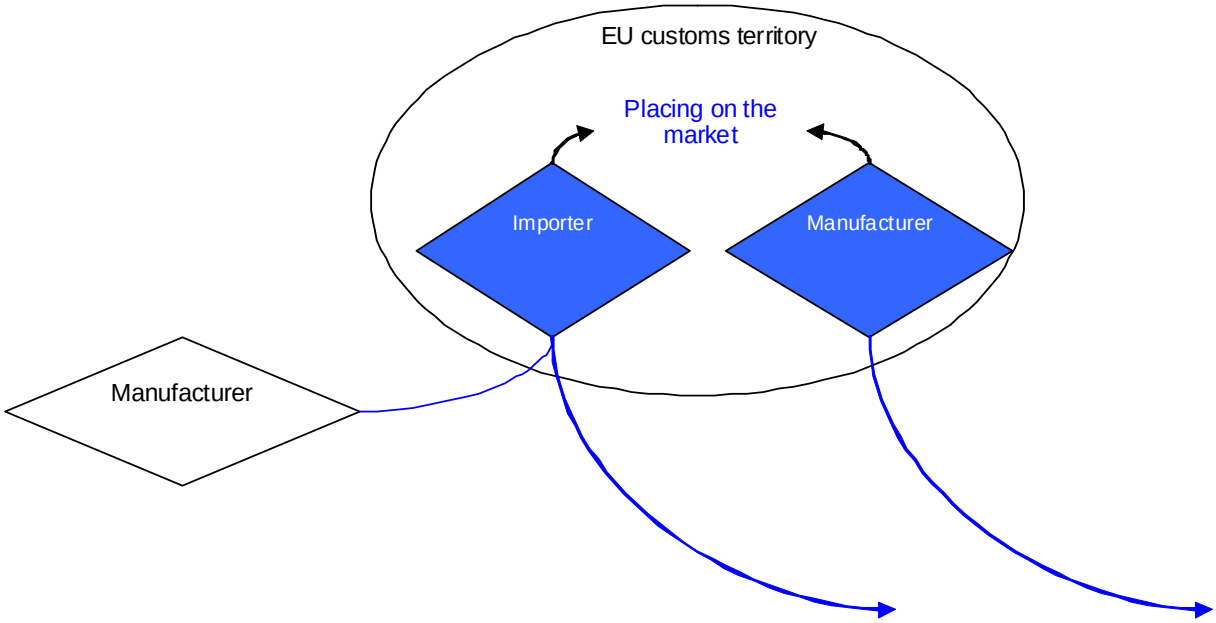
Example: Counterfeit drugs are frequently detected in T1 transit, for example in customs territory where non-Community goods are stored and handled. This has been the case most recently in the UK, Malta and Bulgaria.

The scope of EU legislation on medicinal products includes the importation of medicinal products into the EU. This scope not only includes importation for the purpose of placing the product on the market, but also importation for the purpose of export, i.e. **the physical introduction of the medicinal product into the Community.**[37]

[36] With regard to regional provenance, in 2006 31% of the fake medicines seized at EU borders came from India, 31% from the United Arab Emirates and 20% from China.

[37] Art. 2(3), 40(1) and (3) Directive 2001/83/EC.

Overview: Scope of EU pharmaceutical legislation



However, consultation with Member States has shown that there is **uncertainty as to the precise extent and content of the rules for products imported for the purposes of exportation**. For example, several provisions on imports seem not suited for this constellation.[38]

These uncertainties have created "loopholes" in supervision and enforcement, which can be used (and have been used) to channel counterfeit products into the legal supply chain. Moreover, other legal requirements (for example, conditions of storage) can be violated.

Example: One Member State reported problems in inspecting activities in T1 transit due to legal uncertainties. When access was finally granted, counterfeit medicinal products were found. Nevertheless, the case is now in judicial review.

2.2.2.4. Products contain counterfeit, or sub-standard API

The API is the primary factor that determines the safety and efficacy of a medicinal product and affects its quality. Practice shows that counterfeit medicinal products are also the result of manipulations higher up in the value-chain, i.e. at stage of production of the API (cf. 2.2.1.). Counterfeit API can have the same consequences as counterfeit medicinal products. A medicinal product containing a counterfeit, sub-standard API is, from the point of view of public health protection, to be considered as a counterfeit medicinal product.

The manufacturing of API is subject to Good Manufacturing Practices ("**GMP**").[39] As highlighted above (cf. 2.2.1.), GMP compliance of API play an important role in

[38] Cf. Art. 51(1)(b) Directive 2001/83/EC.

[39] Currently, the Community GMP for API are guidelines, i.e. non-binding. One could consider turning them into binding provisions. This, however, would be merely a question of legal *technique* and not change the substance.

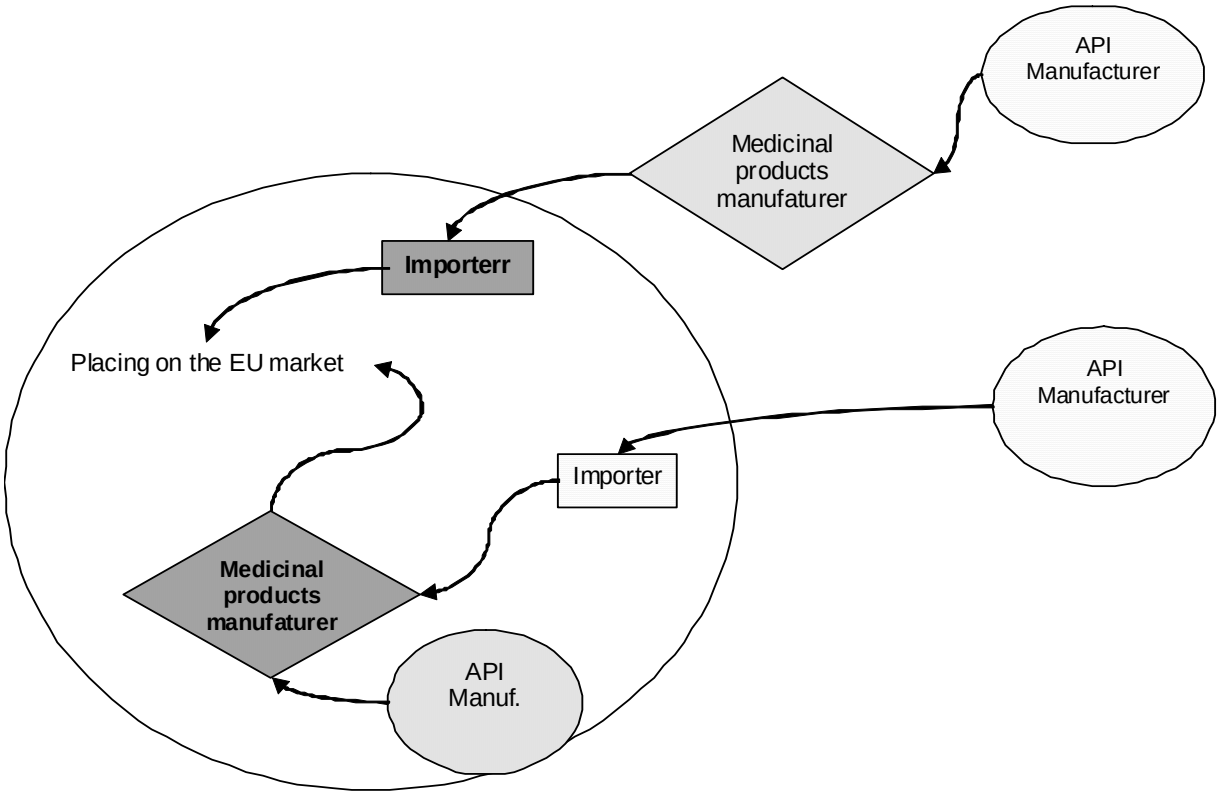
the context of counterfeit. Therefore, compliance and its scrutiny is crucial. This applies in particular to third countries, where the large majority of API are produced.

Currently, compliance with GMP by the manufacturer of active ingredients – both in the EU and abroad - is controlled via the manufacturer[40]/importer[41] of the medicinal product. Controls by EU competent authorities are rare. In the public consultation, it was stressed that even large Member States only control approx. 20 API plants in third countries per year.[42] On the other hand, in certain third countries controls are weak, and standards - compared to the EU – are low. Moreover, certain third countries have only a limited scrutiny of exported API.

This was confirmed during inspections by the Council of Europe's European Directorate for the Quality of Medicines and HealthCare ("**EDQM**"), which point to a striking difference in GMP compliance between API manufacturers based in the EU and those based outside. This was also highlighted in the public consultation.

Example: Following the heparin incident (above 2.2.1.), the Chinese authorities for medicinal products stressed that "safeguarding the legality, safety and quality of raw materials imported for use in pharmaceuticals is the responsibility of the importing country" and that they had no authority over the plant concerned.[43]

Globalisation of manufacturing and density of supervision by EU authorities



40 Art. 46(f) Directive 2001/83/EC.
41 Art. 51(1)(b) Directive 2001/83/EC.
42 The EU market is supplied by approx. 20 000 plants located in third countries, cf. Annex 1.
43 Press release of the Chinese State Food and Drug Administration on 26 February 2008.

2.2.2.5. Importance of enforcement

With regard to all four preceding underlying causes, a "horizontal" issue is the important role of enforcement activities by Member States. Enforcement is crucial: As counterfeit is by definition illegal, counterfeiters are only affected by legislation if it is rigorously enforced. Only enforcement ensures that provisions are applied by *all* economic actors. This, in turn, is important as a way to:

- Ensure the maximum effect of legal provisions; and
- Ensure a level playing field between competitors: if rules are not applied by all economic actors, non-compliant firms may have a competitive advantage over those firms that do comply.

Member States are responsible for enforcing Community rules. However, it would be completely wrong to point only at Member States for the increase in counterfeits. Rather, it is the Community (through its exhaustive regulatory competence) who has to support Member States in this task for three reasons:

- First, enforcement depends on clear and proportionate rules. These rules are set by the Community (cf. chapter 2.4.). Therefore, the Community is under an obligation to enact rules which are sufficiently clear and unambiguous to allow enforcement. Certain policy options discussed (cf. for example, policy options n°2/1 and n°3) seek to clarify legal provisions, thus facilitating enforcement.
- Secondly, while enforcement is primarily the task of Member States, there are a number of Community provisions related to coordination of enforcement by the Community. For example, the "Compilation of Community Procedures on Inspections and Exchange of Information" ("**CoCP**") provides guidelines to harmonise inspections of manufacturing plants by the different national competent authorities and to facilitate their cooperation (cf. below, 4.3.2.). This aspect is particularly important in order to avoid discrepant approaches to enforcement in Member States which could be exploited by counterfeiters.
- Thirdly, and more generally, enforcement alone cannot be considered as sufficient policy option to address the problems set out above. This is best demonstrated by the fact that Member States have actually stepped up enforcement in recent years.[44] However, rather than putting a stop to counterfeit in the legal supply chain, the increased supervision and enforcement has primarily helped in *detecting the problem*. The number of detected counterfeit products seems to rise with the increase in awareness, company checks and Member States' control.[45]

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[44] For example, some Member States have established or are considering mobile laboratories at customs controls, for an *ad hoc* chemical analysis of imported API and medicinal products.

[45] Interestingly, there is a parallel here with the "food-and-feed crisis" in the Community in the 90's where the number of detected infected animals increased with an increase of inspections.

2.3. Assessment of baseline – consequences of non-action

This chapter shall assess the baseline, i.e. the consequences of non-action. These consequences are already today considerable (below 2.3.1.). It has to be expected that they aggravate further if no Community action is taken now (below 2.3.2.).

2.3.1. Costs (direct and indirect) created by counterfeit medicinal products

It is evident that robust figures of the number of counterfeit products cannot be realistically attained. Estimations can only be based on extrapolation from existing figures. For example, one could extrapolate the figures available from some Member States to the EU: This would mean that today, approx. 1.5m packs 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 of out 20 000 packs would be a counterfeit.

On the basis of this extrapolated estimation, one can move on and consider the direct costs, indirect costs, and other qualifiable burdens:

A direct cost approach looks at the costs falling on the health sector in relation of prevention, diagnosis and treatment of disease. This involves issues of safety (for example, toxic effects) and efficacy (i.e. non-effect of a fake medicine). The costs fall largely into two categories:

- costs occurring during hospitalisation and resulting in prolonged hospital stays;
- costs occurring in an ambulatory setting for treating the consequences of a treatment involving counterfeit drugs.

Indirect costs typically measure the lost productivity potential of patients who are too ill to work or who die prematurely. While there are so far no reported cases of fatalities due to counterfeit medicinal products, indirect costs stemming from death are in principle included in this calculation.

Finally, there are a number of other quantifiable burdens to be attributed to counterfeit medicines, including:

- Costs for recalls by the manufacturer, including communications to the marketplace and distributors and reimbursement for returned counterfeit products;
- Costs for destroying seized counterfeit products which at present fall on the rightholder.

With regard to direct and indirect costs, it is noteworthy that, unlike in other fields of health economics, such as Adverse Drug Reactions,[46] counterfeit is a relatively recent phenomenon. There are to date no studies on the quantified public health effects of counterfeit medicines and resulting direct and indirect costs. Moreover, causalities are necessarily speculative. However, on the basis of existing figures and

[46] Cf., in this regard, the impact assessment report on the Commission proposal amending Directive 2001/83/EC on strengthening and rationalising EU pharmacovigilance, SEC(2008)[…].

extrapolations, and based on a value of Quality-Adjusted Life Years of 60 000 EUR[47], it can be assumed that, today, annual costs resulting from counterfeit medicinal products in the legal supply chain have direct and indirect societal costs of approx. 950m EUR.[48]

In addition, there are numerous consequences of non-action which can only be qualified. This includes in particular:

- Restoring a damaged reputation of a brand/company: Companies and their brands can suffer considerably if counterfeit products enter the legal supply chain. The public consultation has confirmed that this is a major driver for action of companies.

- Restoring trust amongst distributors: This point also holds for distributors, who have to trust on the upstream distribution chain.

- Restoring trust of patients into the legitimate supply chain: the same reasoning applies for patients – damaged trust in the legal supply can have grave consequences for revenues of retailers/pharmacies.

2.3.2. Expected development

It has to be stressed that the problem set out above (cf. 2.2.) is expected to aggravate further. Indeed, the number of incidences has been on a steady increase since 2004. For example,

- while in the UK, there were practically no "counterfeit incidences" in the lawful supply chain prior to 2004, the number of detected incidences has increased from 2 (in 2004) to 5 (in 2007);[49]

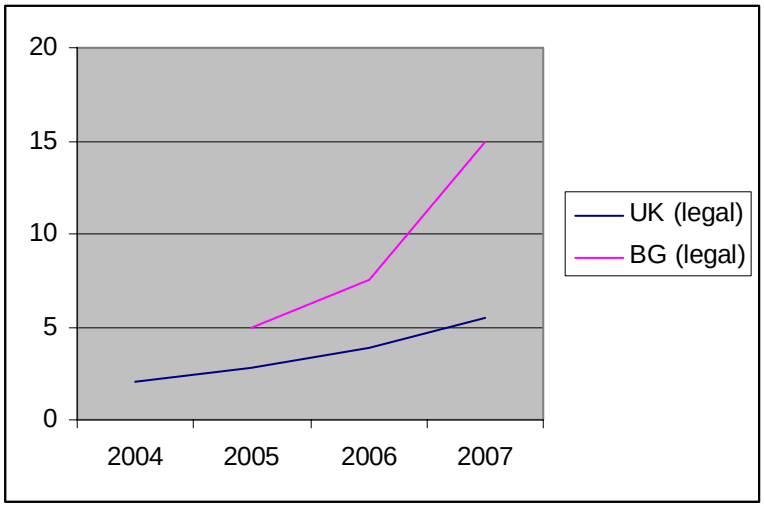
- In Bulgaria, those investigations followed up by ordinances have increased from just five (in 2005) to over 15 (in 2007).

47 For the purpose of this impact assessment, account shall be taken of a recent study assuming a medium value of QALY of 60 000 EUR (Mason et. al., Estimating a monetary value of a QALY from existing UK values of prevented fatalities and serious injuries (2006)).

48 Cf. Annex 7.

49 One „incidence" may entail many thousands packs, as was the case in the UK.

Increase of incidences in legal supply chains in some Member States since 2004

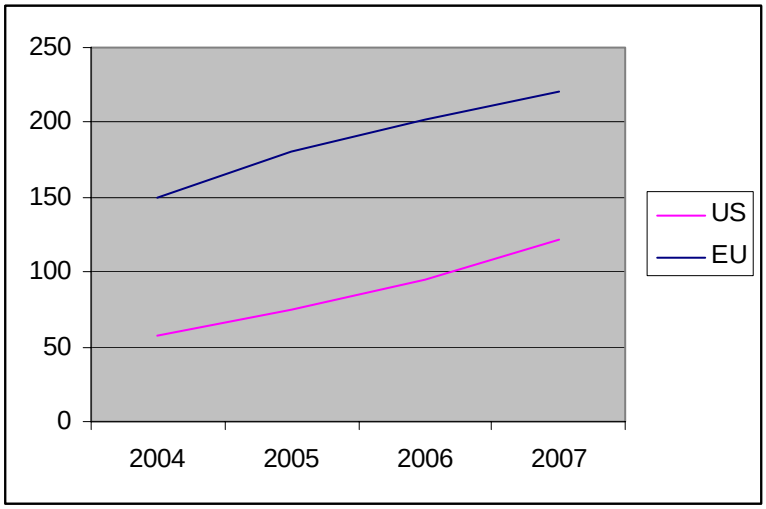


This trend is not surprising, as it confirms the general trend of counterfeit medicines, for example:

- The number of "incidences" of counterfeits has risen in Europe from at rates of approx. 10 % and reached 220 in 2007 (2002 in 2006);[50]
- A trend can also be confirmed when looking at the U.S., who has a broadly similar regulatory and economic environment. Here, the trend has been an increase from 58 incidences in 2004[51] to 120 incidences in 2007[52];
- Industry estimates that the volume of counterfeiting medicines increases by 20%-100% per year.[53]

50 Industry figures (2008).
51 Cf. http://www.fda.gov/oc/initiatives/counterfeit/update2005.html
52 Industry figures (2008).
53 Mike Muller, Director of global anti-counterfeiting operations, Eli Lilly, www.scriptnews.com, 27 June 2008.

Increase of incidences in counterfeits since 2004(EU and U.S.)[54]



Nothing indicates that the trend will reverse. On the contrary, independently of the concrete figure, it is almost certain that there will be an increase of the problem due to several reasons:

- The increase of global trade of API and medicinal products;
- The number of actors in the supply chain are going to increase as distribution chains are increasingly diverse and sophisticated; and
- The fact that counterfeit producers are increasingly parts of highly-efficient network linked to organised crime, trade in weapons and illegal drugs and smuggling.

While it is not possible to quantify precisely a future development, for the purpose of this impact assessment, an attempt shall be made to calculate the costs for a baseline of up to 2020. To this end, it is also assumed that the chosen policy options are fully applied as of 2011, i.e. excluding the time span of the legislative process and transposition/implementation of legislative amendments. Three models ("scenarios") are looked at which are based on an "optimistic", a "realistic" and a "pessimistic" scenario (cf. Annexes 6, 7).

Based on these scenarios and a baseline until 2020 it is estimated for the purpose of this impact assessment that the direct and indirect costs by 2020 are between 9.5bn EUR and 116bn EUR (cf. Annex 7).[55]

54 Extrapolations from industry sources and U.S. FDA publications.
55 Monetised benefits are expected to mount in line with inflation.

2.4. Community competence to legislate and subsidiarity

Community legislation on medicinal products placed on the EU market is based on Art. 95 EC Treaty. Its aim is to establish an internal market for medicinal products while ensuring a high level of protection of public health in the EU.

Prior to the adoption of the Medicinal Products Directive the provisions laid down by law, regulation or administrative action in force in the Member States differed from one Member State to another. These differences between national laws obliged the pharmaceutical industry to vary their production and application for marketing authorisation according to the Member State for which the products were intended. Consequently, the different national rules hindered trade in these products and, as a result, had a direct effect on the establishment and functioning of the internal market.

To address this, it was necessary to have harmonised regulation in place in the internal market. It would not have been possible to establish identical rules by each Member State individually. The EU legislation on pharmaceuticals, which was introduced in 1965, meets this need. It determines at Community level the rules to be complied with as regards *inter alia* the authorisation, manufacturing, distribution, labelling and packaging of medicinal products.

These rules are, with few exceptions,[56] exhaustive, i.e. they are not "minimum standards". Member States are not allowed to "add to" these rules. Changes made by Member States to these rules - which are transnational in nature - would conflict with the requirements of the Treaty, as only the Community can amend the rules. Hence, the criteria for examination of subsidiarity as set out in the "Protocol on the application of the principles of subsidiarity and proportionality"[57] are fulfilled.

While this reasoning applies to pharmaceutical *legislation*, its *enforcement* is a different matter. Here, Member States are responsible. The Community has merely a coordinating function which it exercises through implementing guidelines and legislation as well as technical tools, such as databases.[58]

3. OBJECTIVES

3.1. General objective

The general objective of EU pharmaceutical legislation is to give concrete form to the Treaty's objective of free movement of goods for medicinal products while ensuring a high level of protection of human health. Against this background, the general objective is defined as maximising the protection of the **legal supply chain in the EU against infiltration of counterfeit medicinal products**, i.e. that for all practical purposes the possibility **that medicinal products purchased in the legal supply chain in the EU are counterfeit** can be practically ruled out.

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56 Most relevant in this file is the authenticity labelling, cf. chapters 2.2.2.1. and 4.3.2.

57 OJ C340, 10.11.1997.

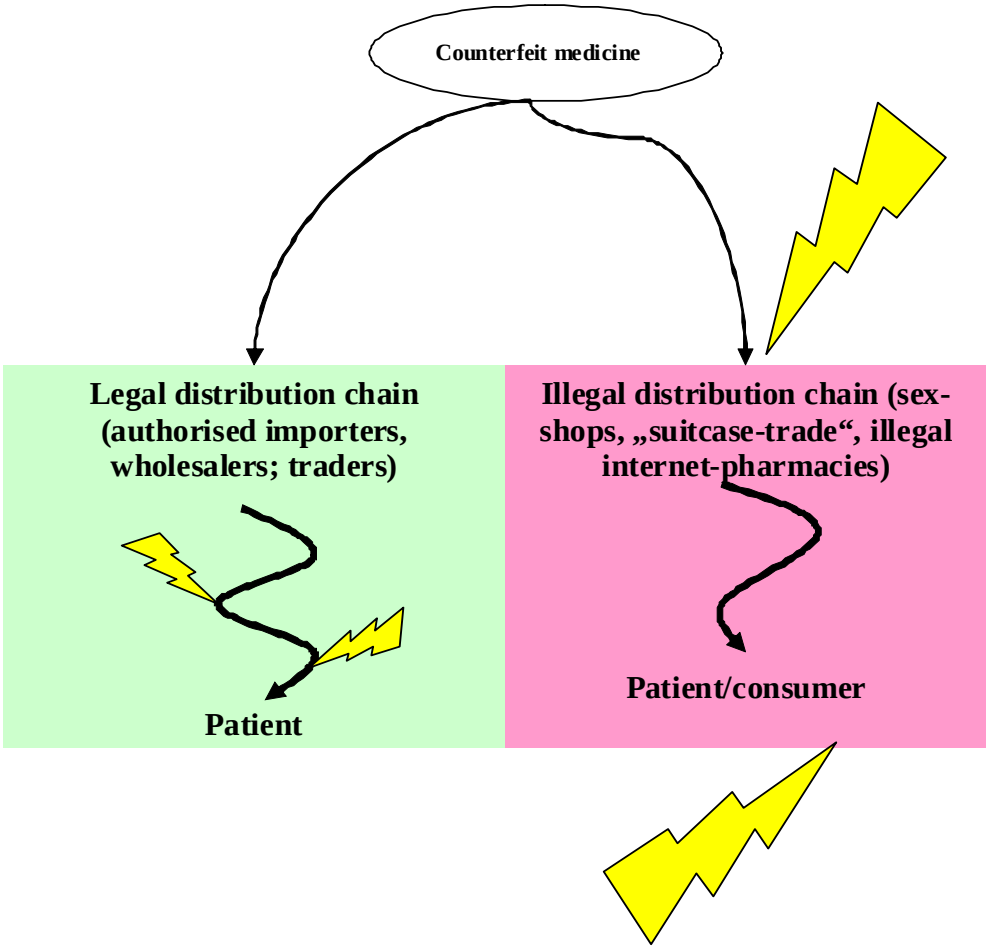
58 Concerning enforcement, cf. chapter 2.2.2.5.

At the outset, it must be stressed that this objective does not include distribution through illegal supply chains, such as retail by beauty salons, fitness centres, sex-shops or illegal internet sales. Neither does this objective address the "importation" of counterfeit drugs by individuals for their own private use ("suitcase trade").

While it is acknowledged that this aspect of public health protection merits attention by industry, regulators and policy makers, the exclusion of these aspects from the general objective as defined for the purpose of this impact assessment is justified as the supply of medicines through illegal distribution channels has very different characteristics: **In particular, these distribution channels are anyhow (no matter whether the medicine is authentic) illegal**. This means that:

- The actors are acting at the outset in bad faith concerning the legality of their activities; and
- Even the "patient" often knows that the purchase (or importation) of the medicine is illegal.

These aspects fundamentally differentiate this problem from the one addressed and discussed in this impact assessment. The situation can be exemplified as follows:



Addressing illegal supply chains requires a separate problem definition, with separate underlying causes, separate objectives and separate policy options. In particular with regard to the policy options, these may relate to awareness rising, for example in

media and schools, enforcement and cooperation of different enforcement authorities at national level.

This is not to say that the Commission is turning a blind eye on these matters. Indeed, many of the initiatives set out above 2.2.2.) were originally launched in view of (and still focus mainly on) the combat of *illegal* supply chains. However, the present impact assessment shall focus on the risks of counterfeit through legal supply chains, i.e. through supply which is still perceived by the patient and the public as a whole as "counterfeit-free".

3.2. Specific objectives

In order to be made operational, the general objective needs to be further broken down into specific objectives. These more operational objectives are closely related and follow the underlying causes for the problem.[59] Thus, this impact assessment evaluates the policy options to achieve four specific objectives:

- Ensuring that the medicinal product itself, as made available, is sufficiently protected against counterfeiting ("Specific objective n°1 – Strengthening product protection measures"): EU legislation regulates the characteristics of a medicinal product placed on the EU market. Specific objective n°1 aims to ensure that these products are sufficiently distinguishable from fake copies.

- Ensuring that the legal distribution channels of the medicinal product in the EU cannot be infiltrated by counterfeit products ("Specific objective n°2 – Ensuring reliability in the wholesale distribution"): As stated above (2.2.2.2.), it is crucial to ensure that the distribution chain is not "infiltrated" by counterfeit products. These aspects of wholesale distribution are regulated at EU level.

- Adopting efficient and proportionate rules for transit of counterfeit medicinal products through the EU ("Specific objective n°3 – Defining clear obligations for import for export"): Clarification of the legal requirements for products imported for export is needed. Depending on the content of the clarification the substantial impact can differ.

- Ensuring that the active ingredient contained in the product is not counterfeit ("Specific objective n°4 – Stepping up scrutiny of API actors").

These specific objectives are not mutually exclusive. Indeed, it is not possible to address only one of the four specific objectives in order to pursue the general objective. If only one of the four specific objectives was addressed, the influx would occur via the other three. For example:

- If only requirements/inspections for wholesalers are strengthened, this would not avoid an influx of counterfeit at the level of API.

- If only the rules (including enforcement) of API were strengthened, this would not avoid the influx of counterfeit finished products into the legal supply chain.

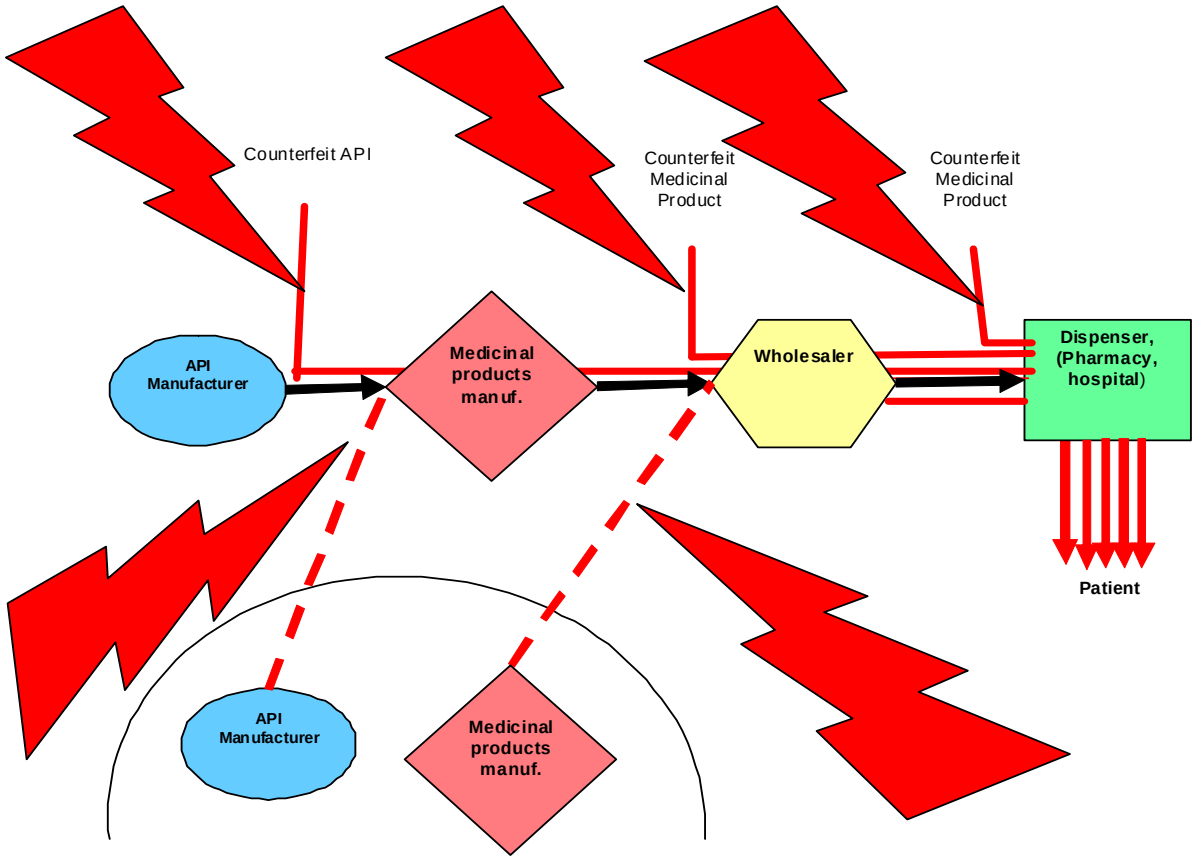
[59] Cf. chapter 2.2.2.

- If only the rules (including enforcement) governing import for export were clarified, this would not address the issue of counterfeit API and the influx of counterfeit into the distribution chain.

- If only product-related objectives were pursued, the risk arising from counterfeit API would not be addressed.

Thus, only the combined pursuit of the four specific objectives can ensure that the legal supply chain is properly protected. This can be best exemplified as follows:

The different approaches of the four broad policy-options:



Moreover, with regard to the "horizontal" issue of enforcement (cf. 2.2.2.5.), this plays a role in all four specific objectives set out above.

4. POLICY OPTIONS

4.1. Policy options initially looked at and discarded - industry self-regulation

The policy option "industry self-regulation" would mean reliance on voluntary measures by industry to address the problem.

The main difficulty of this policy option is that compliance in this case is voluntary and it is impossible for competent authorities to enforce these rules. This is a crucial

aspect which has been highlighted again recently.[60] Indeed, recent events (cf. 2.2.1 above) confirm that the pharmaceutical sector is prone to "rogue traders" who willingly put patients' lives at risk for the sake of high revenues. Thus, while self-regulation may work well in markets that have an oligopolistic industry structure, it is less workable in the pharmaceutical sector, which is characterised by many tens of thousands of suppliers, importers, manufacturers and distributors (cf. description of the players in Annex 1). Indeed, responsible companies are already doing their utmost to combat counterfeiting of the products they produce/distribute (cf. below 5.4.3. concerning audits, for example). This was highlighted in the public consultation. However, as set out above (cf. 2.3.2.), in spite of this existing support, the problem is increasing.

This not only impacts on the level playing field of competitors on the Community market. It also leads to differing levels of protection amongst Member States. Therefore, in order to ensure patient safety with regard to *all* products made available to patients, and to avoid a distortion of competition between the players, it is crucial to ensure enforceability of these rules.

Finally, and from a more political perspective, there is still an element of distrust in Europe as regards self-regulation by industry. This aspect is particularly important in the field of medicinal products, where product quality/safety/efficacy is closely linked to public health. In view of the potentially disastrous consequences (cf. 2., above), it could be perceived very critically if the Community - who exhaustively regulates the placing of these products on the market! – were to rely solely on self regulation.

4.2. Specific objective n°1: Strengthening product protection

4.2.1. Discarded policy options

4.2.1.1. "No action" at Community level

As exception to the principle of exhaustive Regulation, Community legislation on medicinal products allows Member States to lay down rules for labelling for the purpose of identification and authenticity. A policy option would be to rely on Member State action in this respect.

This policy option was discarded at an early stage: Already today, in Europe there are various differing requirements for product coding. The result is 10 different coding systems in the internal market. Moreover, France, Belgium and Greece have recently established three differing systems for authenticity checks on the basis of varying product codes. Several Member States (e.g. Spain) are currently considering (unilaterally) reforming their present coding system. These trends are not necessarily motivated by the increase in counterfeiting, but by the need to combat reimbursement fraud, which leads to considerable losses for social security schemes in the EU. As a result of this fragmentation, companies have to re-adapt the packaging to each national territory of the Community market. The public consultation repeatedly highlighted the difficulties created by a lack of harmonisation: the costs to EU industry as a result of a lack of harmonisation in this respect are currently estimated

[60] Cf. *Palzer*,et.al., Self-Regulation, Co-Regulation, Public Regulation (2004).

to be as high as 1bn EUR per year. A further fragmentation of the rules and techniques for product coding is going to raise cost even more.

4.2.1.2. Self-regulation by industry

Here, the reasoning as set out above (cf. chapter 4.1.) applies: Self-regulation would be unenforceable in view of the many actors in the pharmaceutical market. It would thus create a competitive disadvantage vis-à-vis producers who invest in product-related safety measures.

4.2.2. Broad policy option n°1/1: Obligatory safety feature on the packaging

To address the underlying cause of the problem set out above (cf. 2.2.2.1.), the broad policy option is an authenticity/traceability feature (hereinafter referred to as "**safety feature**") of the product. A safety feature would make it possible to establish (either by the consumer, by a trained eye, by an expert, or with a reading device) whether the outer packaging is original. Moreover, it would reveal any subsequent opening of the pack (similar to a seal). Finally, it may facilitate back-tracing the distribution chain of medicines by way of a "pedigree" linked to the safety feature (in the same way as the mad cow scare led to a system that electronically tracks animals as they move from fields to feed lots to food stores). The safety feature could be, for example, a RFID tag, a hologram, a colour shift feature, a watermark or a chemical marker. In addition, it may be combined with product serialisation: Product serialisation is based on a feature (usually a code) on the outer packaging which "individualises" the pack. Each pack has its own individual code. The code is read with a reading device which is connected to a central database. The identification number of the pack sold by the retailer/pharmacist is shown in the database as dispensed: this ensures that each product is dispensed only once. It also brings additional spill-over benefits as regards patient safety in general and dispensing of medicines in in particular (from automated validity date checks, to ensuring each patient receives hi or her prectiptin only, to supporting pharmacovigilance). It can also support health systems (by reducing fraudulent reimbursement claims to national social insurance schemes) and industry by facilitating logistics, storage, recalls and returns.

This broad policy option would establish an obligation to affix a safety feature on the packaging. However, no final stance on a specific safety feature would be taken in secondary EU law. Rather, the policy option would provide a legal basis for implementing measures under Comitology or via standards, where precise characteristics, including technicalities, would be set out. This approach is taken for two reasons:

- First, technical standards and the range of technical options are evolving very fast. It would be a mistake if details were written "in stone" by the co-legislator. This was also highlighted during the public consultation.

- Secondly, account has to be taken of international developments, in particular in view of trans-Atlantic economic cooperation and regulatory alignment. The U.S. regulator is currently considering safety features. Discussions in the U.S.

are roughly at the same stage as in the EU.[61] Against this background, the possibility of some flexibility to update technical provisions should be maintained.

Within this broad policy-option, there are various mutually-exclusive policy options regarding its scope:

- Policy option n°1/1a: For all medicinal products: In this policy option, the safety feature would be compulsory for all medicinal products.

- Policy option n°1/1b: For prescription medicinal products (with possibility of derogation): In this policy option, a safety feature would be compulsory for prescription medicinal products only. In addition, there would be derogations for cases where:

  – re-packaging is necessary to ensure availability in small markets; and where

  – re-packaging has been expressly permitted by the original marketing authorisation holder: This relates to cases, where

    – health bodies or national authorities repackage for legitimate clinical reasons (for example assembling emergency packs containing small amounts of a medicine used by mental health crisis resolution teams); or

    – the marketing authorisation holder designs another manufacturer to re-label a product to address shortage of a specific product in a Member State.

- Policy option n°1/1c: For products determined on a risk-basis: This policy option would leave the product scope open. It would merely set some criteria to be considered and provide a legal basis to fix the scope under Comitology. The criteria would take into consideration the risk profile i.e. by looking at where

  – counterfeit is particularly likely (in particular in terms of potential margins for counterfeiters); and/or

  – the potential damage is particularly high.

4.2.3. Broad policy option n°1/2: Prohibition of manipulation of safety features by the distributor

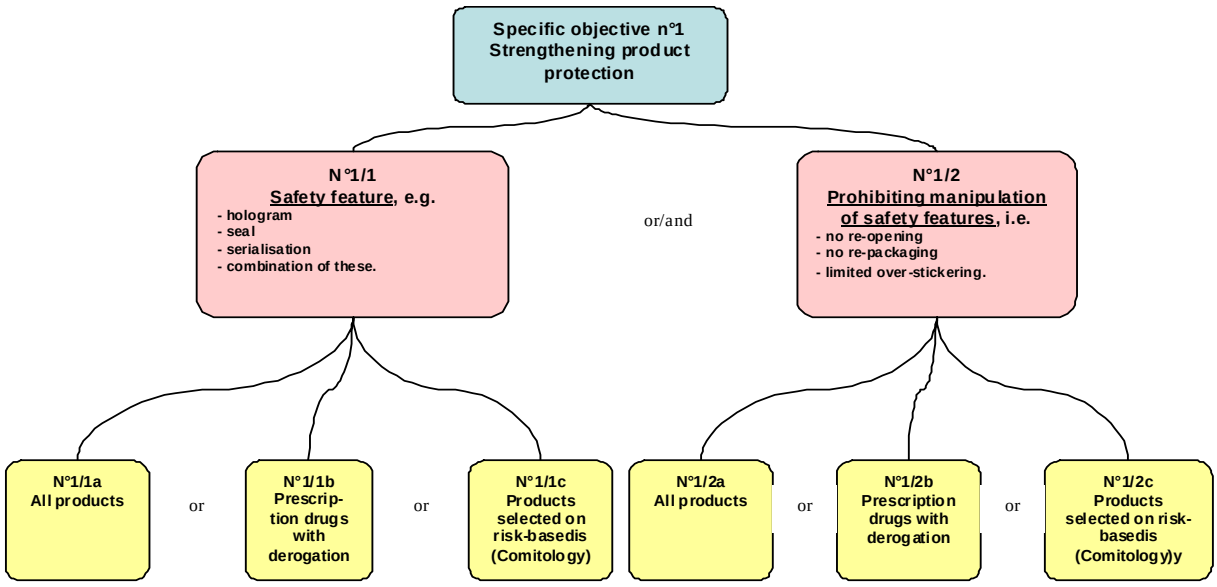
This broad policy option would complement the broad policy option n°1/1. It provides that safety features on the packaging, which may be obligatory (above 4.2.2.) or voluntary, are not manipulated in the distribution chain between the original producer and the final user. “Manipulation” would mean removing, replacing, or covering (e.g. over stickering) of these features.

[61] Cf. http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-5597.htm

In analogy to the broad policy option n°1/1, several mutually-exclusive policy options in terms of *scope* are to be considered:

- Policy option n°1/2a: For all medicinal products;
- Policy option n°1/2b: For prescription medicinal products (with possibility of derogation);
- Policy option n°1/2c: For products determined on a risk-basis, for example in view of their life-saving characteristics.

4.2.4. Overview of policy options for specific objective n°1



4.3. Specific objective n°2: Ensuring reliability of wholesale distribution

Under this specific objective, four policy options will be discussed. They are not mutually exclusive. Within one of the policy-option (audit), there are two mutually-exclusive policy options.[62]

4.3.1. Policy option n°2/1: Include "traders" into the scope of rules for safe distribution

One policy option is to address those actors who are situated "in-between" the manufacturer and the dispenser, and who clearly are not covered by the term "wholesaler" as presently defined. These actors include persons who trade medicinal products "virtually", without handling them. This policy option would mean subjecting these actors to the relevant requirements of Good Distribution Practices ("**GDP**") and a notification requirement.

4.3.2. Policy option n°2/2: Harmonised inspection provisions

One policy option would be to strengthen the Community rules for inspection of wholesalers as to their compliance with good distribution practices. At present, there

[62] Cf. overview in chapter 4.4.5.

are practically no harmonised rules on inspections of compliance with good distribution practices.

This policy option would – by analogy with inspection for good *manufacturing* practices – introduce CoCP for wholesale distribution.

4.3.3. Policy option n°2/3: Tighten control and supervision of GMP/GDP by means of audits

4.3.3.1. Policy option n°2/3a: Mandatory regular audits of supplying wholesalers

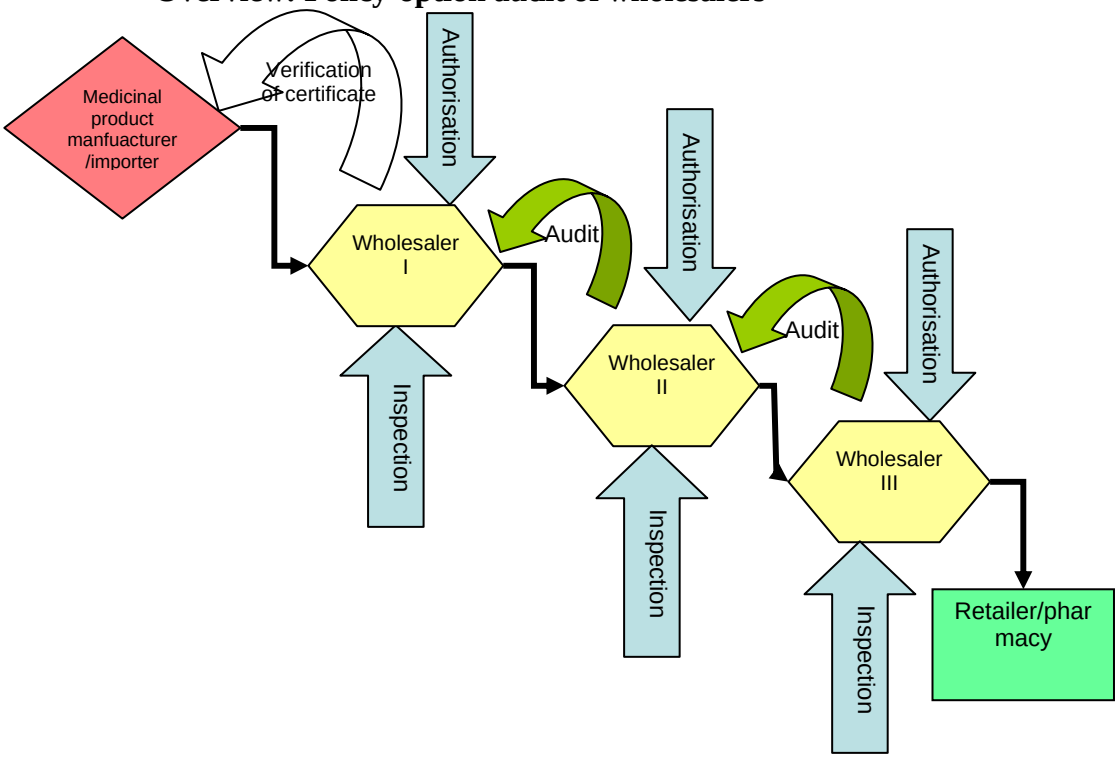
At present, there is only limited control and interaction between the various actors in the manufacturing and distribution chain. Very often, this interaction is restricted to the actual business transaction.

A stronger interaction would help to broaden the responsibility of the various actors. This interaction would be achieved through audits. Audits are assessments of a body or a person by another party to verify the effectiveness of a quality management system.

Supervision by the competent authorities of the Member State would be an "add on" to this control function.

This policy option can be best exemplified as follows:

Overview: Policy-option audit of wholesalers



It should be noted that audits in the pharmaceutical sector (manufacturing and distribution) are nothing new. However, they are voluntary and thus do not act as a real deterrent to irresponsible actors in the supply chain.

Audits are not necessarily performed by the business partners themselves. Instead, very often, audits are performed by third party auditors, who make the audit result available to a number of economic operators ("**shared third party audit**"). These third party auditors would have to be sufficiently qualified and experienced.

4.3.3.2. Policy option n°2/3b: Risk-based audits of supplying wholesalers

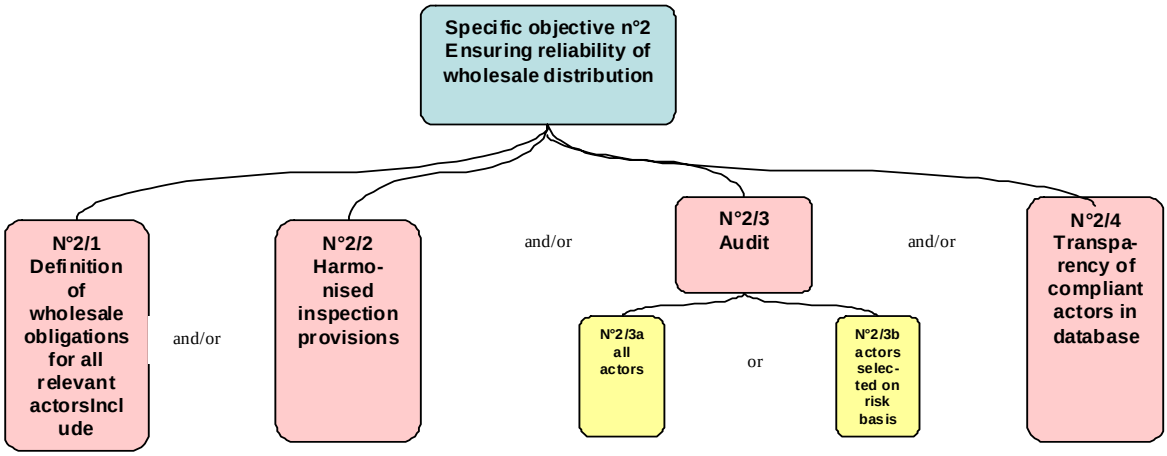
This policy option is essentially identical to the one above (4.3.3.1.). However, under this option, audits would be restricted to situations where the auditor has reason to believe that the business partner is not complying with the requirements for GMP. The number of obligatory audits would therefore be limited.

4.3.4. Policy option n°2/4: Making wholesale activities and compliance with GDP more transparent

To avoid counterfeit medicinal products being channelled into the distribution chain, it is crucial for wholesalers to work with reliable partners. To this end, a publicly-accessible database of the wholesale authorisations could be considered. It has to be stressed that a database for holders of a *manufacturing/import* licence already exists. This database would be extended to wholesalers of medicinal products.

Moreover, to "reward" GDP compliance, the certificates issued by competent authorities could be referred to in the database. Here, too, similar provisions already exist for manufacturers and would be extended to wholesale distributors.

4.3.5. Overview policy options for specific objective n°2



4.4. Specific objective n°3: Defining clear obligations for import for export

Under this specific objective, three mutually-exclusive policy options are discussed.

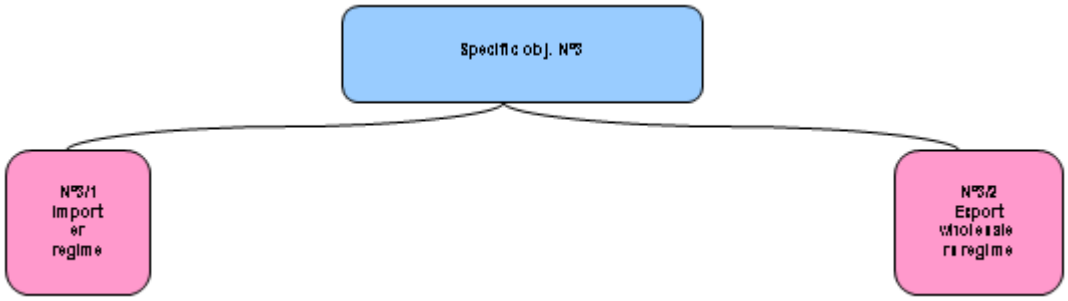
4.4.1. Policy option n°3/1: Clarification to the effect that marketing authorisation is required for all imported products

One policy option would be to make it clear that all medicinal products brought physically into the Community for storage/handling must have a marketing authorisation.

4.4.2. Policy option n°3/2: Clarification of the legal provisions – applying rules for export wholesalers

One policy option would be clarification that the obligations for wholesale distributors also apply to wholesale distributors *exporting* medicinal products. These rules would apply no matter whether the export wholesale distributor handles products placed on the market (incl. imported) or merely introduced products (i.e. brought into the Community without being released for free circulation).

4.4.3. Overview of policy options for specific objective n°3



4.5. Specific objective n°4: Stepping up scrutiny of API actors[63]

Under this specific objective, three policy options are discussed, which are not necessarily mutually exclusive. Within two of these policy-options (authorisation and notification), several mutually-exclusive policy options are discussed.[64]

4.5.1. Policy option n°4/1: Authorisation/more inspections in third countries

4.5.1.1. Policy option n°4/1a: Authorisation (incl. inspection) by EU competent authorities of all manufacturers of API, including those in third countries supplying the EU

In the EU legislation on medicinal products, the manufacturer/importer of the finished medicinal product is under an obligation to use only API from GMP-compliant plants. There is no legal obligation for the API manufacturer to obtain authorisation (following inspection) from a competent Member State authority. Instead, Member States inspections are left to the discretion of Member States and only carried out where there is suspected non-compliance.

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63 The options discussed under this broad policy option shall only concern amendments to the Medicinal Products Directive. Other aspects may concern amending the GMP which would be discussed in a separate impact assessment.

64 Cf. overview in chapter 4.6.4.

Policy option n°4/1 makes all foreign and EU API manufacturers subject to an authorisation requirement to be issued (following inspection) by a competent EU authority. It should be noted that this policy option would go beyond the current legal regime for the manufacturing of medicinal products.

4.5.1.2. Policy option n°4/1b: Authorisation of all API manufacturers/importers in the EU

An alternative policy option would be to authorise all manufacturers/importers in the EU. The system for API would then be identical to that for medicinal products.

4.5.1.3. Policy option n°4/1c: Strengthening scrutiny of plants in 3rd countries if level of protection poses risks to public health in the EU

A further policy option is to strengthen scrutiny of API manufacturer supplying the EU unless there is assurance that the third country applies standards of good manufacturing practice at least equivalent to those laid down by the Community and mechanisms for supervisions are at least equivalent to those applied in the Community. In other words, only if the standards in a given third country are not equivalent to those in the EU, inspections are required.

4.5.2. Policy option n°4/2: Notification requirements

4.5.2.1. Policy option n°4/2a: For all actors (EU and 3rd countries)

One policy option would be the requirement for EU and third country manufacturers and distributors of API to notify their activities before starting their operations of supplying the EU market.

4.5.2.2. Policy option n°4/2b: For EU actors

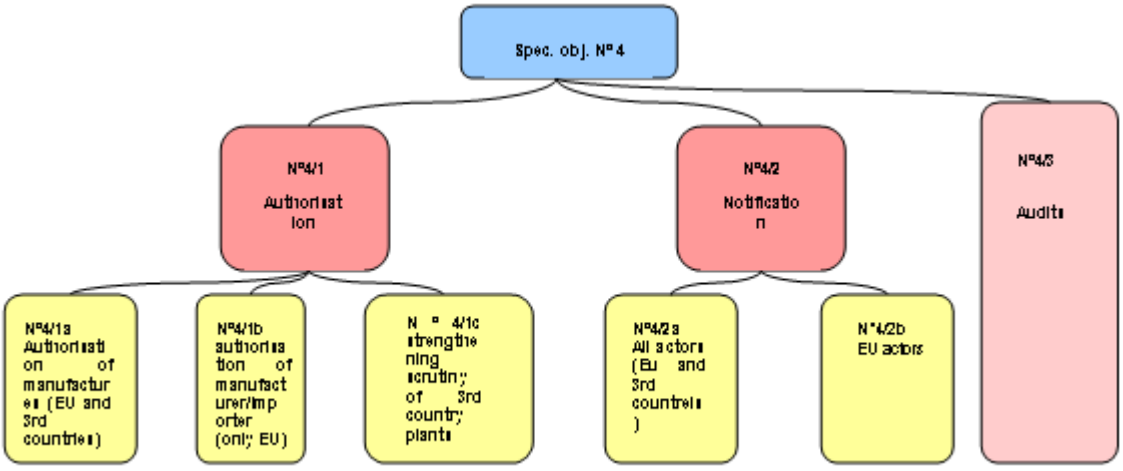
One policy option would be the requirement only for EU manufacturers and importers of API to notify their activities before starting their operations.

4.5.3. Policy option n°4/3: Mandatory audits of active substance manufacturers by medicinal products' manufacturers

Manufacturers of medicinal products are currently expected, in practice, to audit the manufacturer from whom they purchase the API. Importers verify whether the third-country manufacturer has been involved in an audit.

To strengthen this requirement, the requirements of audit – including shared audit by an accredited third person - could be spelled out clearly in the legislation. This would also mean that importers of finished pharmaceutical products have to ensure that a non-EU manufacturer who supplies the EU has audited the API manufacturing facilities.

4.5.4. Overview of policy options for specific objective n°4



5. IMPACT ANALYSIS AND COMPARISON

The analysis of impacts of the different policy options within each specific objective and their comparison is done against the **baseline** set out above (cf. 2.3.).

It has to be stressed that environmental impacts are negligible. Where they play a role, they are explicitly highlighted (for example, chapter 5.1.1.1. and 5.3.1.).

5.1. Specific objective n°1: Strengthening product protection measures

5.1.1. Broad policy option n°1/1: Obligatory safety feature

As set out above (cf. 4.2.2.), details for a safety feature would be set out under Comitology or in standards.[65] Generally speaking, safety features can be efficient measures to contribute to the general objective. In the public consultation, it was repeatedly highlighted that no single safety feature is a "magic bullet". However, it was also widely acknowledged that a combination of several techniques (concealed, open, forensic) can be an effective contribution to strengthen product protection measures. Some of these safety features might not be readable or detectable to the untrained eye of the patient/medical practitioner or may require specific reading devices. However, in these cases, verification at retail level allows for detection of fake products. This holds in particular for product serialisation features: Authenticity of a product would be verified on an ad-hoc basis at the point of wholesale or retail/pharmacy.

5.1.1.1. Policy option n°1/1a: All products

On the positive side, this option, if implemented efficiently under Comitology, would allow for a far-reaching product-related protection covering all products.

[65] An additional impact assessment may then be discuss technical details in more detail.

On the negative side, this policy option would cover products which have a low risk-profile as they are less costly than innovative drugs and thus typically not targeted by counterfeiters. This includes in particular OTC medicines and generic products.

The costs of this option for the pharmaceutical industry would be considerable[66]: Depending on the technique chosen[67], one-off costs are between 1.35bn EUR (tamper proof feature) and 11.55bn EUR (product serialisation). These costs relate in particular to necessary adaptations to packaging lines, and (in the case of serialisation) setting up an IT-structure.

To this add annual costs in the range between 370m EUR (costs for manufacturers to run serialisation) and 1 070m EUR (tamper-proof feature, in particular design and devising it) for EU manufacturers.

This policy option would hit in particular the generic and over-the-counter ("**OTC**") industry for two reasons:

- Unlike branded/prescription industry, the OTC/generics sectors makes limited use of safety features today and would thus be hit stronger with new regulatory measures.

- Products in these sectors are often (relative) low-price products with lower margins.

This aspect is particularly critical as the approx. 40% SMEs in the manufacturing sectors are mainly in the generic and OTC sector.

Retail/pharmacy (one-off costs)

To these costs would add (in the case of serialisation) costs for dispensers (i.e. shops selling OTC medicines and pharmacies) which would have to be equipped with verification installations. Costs for reading devices and IT systems in shops and pharmacies can be – depending on the technique used - up to 2 250m EUR.[68] This is particularly critical for normal retailers (i.e. shops, not pharmacies), who may have only a small share of their portfolio dedicated to medicinal products.

Moreover, on the negative side, it has to be recalled that, regarding serialisation, the data generated may be prone to abuse. This involves issues of competition law and business confidentiality.

However, a harmonised safety feature can bring about important savings for industry. These savings relate to the following:

- Replacing national product codings: As shown above (chapter 2.2.2.1.), a harmonised system of safety features would allow for important savings. Industry estimates these savings to be as high as 1bn EUR per year. The public

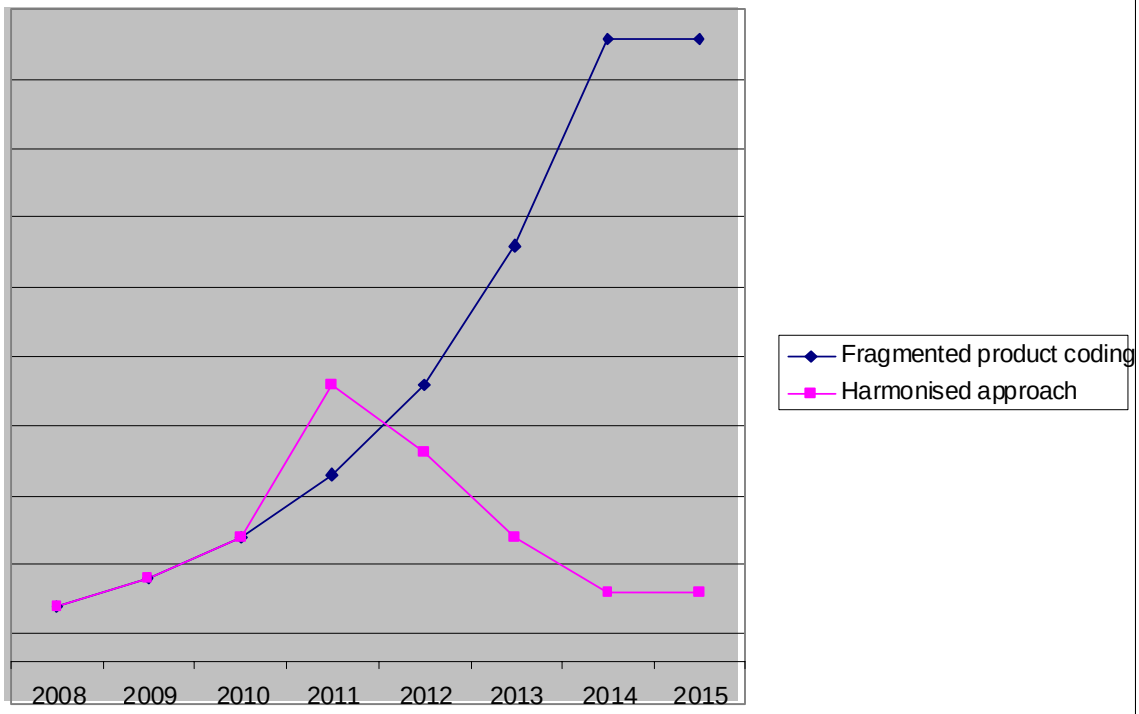
66 Cf. Annex 2, point 1.

67 In the framework of the implementation measures, an additional impact assessment may discuss technical details in more detail.

68 Cf. Annex 2, point 1.

consultation has confirmed that a further fragmentation of the rules and techniques for product coding has to be expected, leading to further increases in costs, but without any added value. Thus, while this policy option is certainly costly, further fragmentation in the EU is likely to bring about even higher costs in the long term. The situation can thus be described as follows:

Development of costs (schematic) for fragmented product-related measures



- Facilitated recalls: Certain safety features facilitate recalls which can be rendered more targeted and thus more efficient.

- Facilitated handling of product returns: Apart from recalls, distributors and retailers/pharmacists return products for various reasons, such as expiration of the expiry date of the product and damage to the packaging. Approx. 1% of products are returned every year. Handling of returns is currently very burdensome and costly for industry. Certain safety features could facilitate handling of product returns thus leading to major savings.

- Better access to data: As in any market, it is crucial to have reliable market data. While access to certain information – depending on the technique chosen - would be restricted, even this limited information should help industry to make savings in its expenditure on market research and consumer behaviour.

In applying these considerations, the annual savings for the pharmaceutical industry of a harmonised safety feature can total approx. 2.53bn EUR.[69]

[69] Cf. Annex 2, point 1.

These figures show that the high investments for industry, in particular the one-off costs of up to 11bn EUR, would be quickly offset by the savings achieved with this policy option.

Apart from these savings, there are other potential gains. For example, certain safety features

- help tackling fraudulent reimbursement claims to national social insurance schemes;
- allow better targeting of pharmacovigilance; and
- facilitate logistics and storage by wholesalers and retailers/pharmacies.

5.1.1.2. Policy option n°1/1b: Prescription medicines with possibility of derogation

Social impact/public health and related costs

As set out above (4.2.2.), this policy option would restrict safety measures to prescription drugs, including a possibility to further exclude certain products thus restricting the scope further.

In terms of efficacy of this policy option, the benefits set out above would only apply to prescription medicines. While this reduces efficacy of the measure, this could be justified in view of the fact that OTC medicines are less likely to be targeted by counterfeiters as their price is typically lower. Indeed, there is so far no evidence that OTC medicines have been targeted by counterfeiters. Moreover, the risks associated with ineffective OTC medicines are typically lower than drugs prescribed by a doctor. On the other hand, apart from efficacy, counterfeit OTC medicines may still be toxic, i.e. posing a risk to human health. In addition, there is a risk that the exclusion of OTC drugs might simply divert illegal activities into that sector.

Economic impact on businesses (compliance costs, including administrative costs)

Under this policy option, the OTC sector (i.e. approx. 1000 companies of the 3700 EU pharmaceutical companies) would not be affected by costs. Costs would only have to be borne by the non-OTC companies. Their one-off costs would range (depending on the technique chosen[70]) between 1 080m EUR and 8 850m EUR. To this would add annual cost between approx. 185m EUR and 535m EUR.[71]

It is important to note, that the OTC-sector makes up a large part of the approx. 40% SME in the manufacturing sector. Moreover, the part of the generics sector who produces OTC medicines (approx. 12%) would be outside the scope of these measures as well.

Moreover, depending on the scope of the derogation, other medicinal products manufacturers, including generic manufacturers, may be exempted thus avoiding compliance costs.

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70 An additional impact assessment may then discuss technical details in more detail.

71 Cf. Annex 2, point 1.

In terms of the costs for pharmacies/retailers, costs would only hit the former. The precise costs depend on the technique employed. For example, in the case of serialisation, one-off costs for EU-pharmacies for IT installations and reading devices would be approx. 157m EUR.[72]

5.1.1.3. Policy option n°1/1c: Risk-based scope determined in Comitology

Social impact/public health and related costs

On the positive side, this policy option would allow for a wide degree of flexibility to respond to changing patterns in counterfeit. On the other hand, it would create uncertainty as to the products addressed. Care would have to be taken that an implementation time remains sufficiently long if products are moved into the scope of obligatory safety features.

On the negative side, a risk-based (i.e. changing) scope brings about considerable inefficiencies: A reduced scope is likely to shift the activities of counterfeiters from the "covered" to the "uncovered" scope. In view of the need of a long implementation time for regulatory changes, it would not be possible for the regulator to "shift" the scope as swiftly as a counterfeiter. This was also highlighted by Member States and some industry sectors during the public consultation.

Economic impact on businesses

As set out above, different manufacturing sectors are disproportionately affected by an obligatory safety feature. The flexibility concerning the scope would allow taking this into account. For example, apart from the OTC medicines (see above, policy option n°1/1b), a larger bulk of generic medicines (approx. 12% of generics are anyhow OITC medicines) could be excluded from the scope depending on the risk profile. This would remove compliance burdens not only from OTC medicines but also from generic producers, who often act under the same circumstances as the OTC-sector: Prices are typically lower and margins reduced. This, in turn, means that

- the risk-profile of counterfeit is potentially less high; and
- increase of costs for regulatory compliance are particularly critical.

This aspect is important, as the bulk of the 40% SMEs in the manufacturing sector are active in the OTC-sector and in the generics sector.

Costs would depend largely on the question which products are covered. For the purpose of this impact assessment, it shall be assumed that the scope would be 1/3 of all prescription drugs. Thus, one-off costs for manufacturers (adapting packaging lines, necessary IT, etc.) would be in the range[73] between 360m EUR and 2 950m EUR. Annual costs would be in the range between 60m EUR and 178m EUR. The costs for EU pharmacies, which would have to be equipped anyway, would remain the same.

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72 Cf. Annex 2, point 1.

73 An additional impact assessment may then be discuss technical details in more detail.

5.1.2. Broad policy option n°1/2: Prohibition of manipulation of safety features

Any safety feature – be it obligatory (cf. 4.2.2.) or voluntary – only makes sense if it is not removed or discarded subsequently by actors in the supply chain. To address this, the second broad policy option complementing the first broad policy option is a ban of manipulation of safety features.

This broad policy option can mean in principle that practices of over-labelling of products is only possible if safety features remain detectable and intact. Moreover, re-packaging (i.e. exchanging the outer box) could become unlawful. The extent of these consequences depends on the scope of this broad policy option. Regarding the scope, there are three mutually-exclusive policy options discussed:

5.1.2.1. Policy option n°1/2a: All products

Social impact/public health and related costs

The positive aspect of this policy option lies in its contribution to the fight against counterfeiting by ensuring that the safety features remains effective. During the public consultation, in particular the research-based industry highlighted the importance of this measure, stressing that expensive safety features (holograms, micro-printing etc.) become pointless if they can be subsequently destroyed by an actor in the distribution chain. The incidence in 2007[74] illustrates this: While it is true that a re-packager noticed the counterfeit packaging, this could not prevent that several thousand packs of medicines had been passed on in the distribution chain. As these products had been re-packaged, it was not possible for subsequent distributors or the end-users to verify safety features.

Moreover, apart from the issue of counterfeit, this policy option has several positive health-related effects.[75] It would also address:

- Errors in repackaging and relabeling and outdated patient information leaflets: According to information from the originator industry, between 2002 and 2005, 700 packs of product faults due to re-packaging and re-labelling were found in the supply chain.[76] With regard to faults stemming from re-packaging, they would be addressed in this policy option.

- Patients being confused by changes to the packaging: Changes of the packaging cause in some cases irritation amongst patients which may lead to wrong application of a medicinal product.

- The possible inefficiencies of pharmacovigilance and recalls: The re-packaging practices can render recalls by manufacturers more difficult, as certain identification features have been over-labelled or disposed of.

Although risks vary in degree, they are inherent in the practices of re-packaging and re-labelling.

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74 Cf. the example under 5.1.2.

75 Cf. study "Safe medicines through parallel trade", Europe Economics (2008), p. 32 ff.; (referred to in chapter 1.4. in this report).

76 Cf. *idem*, p. 51.

On the negative side, it has to be recalled that restrictions of re-packaging would cause difficulties for those Member States with smaller national markets (e.g. Malta or, for the EEA Iceland) who depend on re-packaging in order to ensure a supply of medicinal products complying with national language requirements. During the public consultation and consultation with Member States, these Member States/EEA-States stressed repeatedly that they strongly depended on practices of re-labelling and re-packaging in order to ensure supply of pharmaceuticals to their markets. For these Member States/EEA-States, this policy option would amount to a major health problem.

Direct impact on businesses

Parallel traders have to re-label or re-package practically all the medicinal product packs in order to comply with national and Community requirements for language of the labelling and packaging sizes. According to this policy option, parallel trade would thus in practice become impossible. This was also highlighted by parallel traders in the public consultation.

Parallel trade has a turnover of approx. 3.5-5bn EUR per year. It is estimated that the approx. 100 companies[77] engaged in parallel trade have annual profits of the order of 400-500 m EUR. Market share of parallel traders is approx. 5% in the EU, with 15% each in the UK and in Denmark, approx. 13% in Sweden, approx. 10% in the Netherlands, approx. 7-8% in Germany, and approx. 2% in Finland.[78]

This turnover of parallel trade would, in a first-round-effect, be lost, which raises the question of second-round/distributional effects. Here, it can be assumed that the revenue and employment generated so far by parallel traders would be re-distributed mainly to two players:

- to wholesale distributor in the importation country: To the extent that parallel traders are de facto exercising wholesale distribution, revenues would shift to wholesale distributors of pharmaceutical products; and

- to the research-based industry: It can be assumed that part of the turnover (and profit) generated by the arbitrage of parallel traders would be re-covered by the originator, thus profiting from the absence of intra-brand competition of the patented medicine. The research-based industry, in turn, may increase investment in R&D and production.

In view of the proportion of share in the value-added chain, it can be expected that patent holding manufacturers would profit most from distributional second-round effects.

Direct impact on employment

[77] DE: approx. 25; UK: approx. 55; Scandinavia: approx. 10 – 15 ; Concerning UK, 14 companies account for approx. 50 – 60% turnover (80 – 85% volume) of parallel trade.

[78] Source: EFPIA, The pharmaceutical industry in figures (2008), p. 5. In the public consultation, these figures were largely confirmed.

It is estimated that the parallel trade sector employs approx. 10 000 persons[79] in the EU. The bulk of these jobs relates to the re-packaging and re-labelling which is largely manual work. With a prohibition of these practices, these jobs would, in a first-round effect, disappear. Here too, distributional and second-round effects have to be considered:

Concerning distribution effects to the benefit of wholesale distributors, these may increase employment in order to respond to possible increase of demand. However, wholesale distribution is less labour-intensive than parallel trade, as it does not involve re-labelling and re-packaging, which is usually done manually. Apart from wholesalers, the shift of revenues to patent-holding pharmaceutical industry might lead to positive effects in employment in this sector. However, here too, one has to caution that the employees of parallel traders might not necessarily have the mobility and education required by the research-based pharmaceutical sector.

Impact in terms of innovation, pricing and availability of medicinal products

Reduced parallel trade would have arguably impacts on innovation, pricing and availability. These effects depend on an appraisal of the role of parallel trade in these respects. This role is highly controversial. It has been discussed by economists, lawyers and politicians for decades. Viewpoints differ largely. They are even publicly voiced from within the ECJ.[80] Moreover, factual evidence by "independent" economic studies is unreliable as it delivers views depending on who financed them.

It is often argued that the main benefit of parallel is savings for taxpayers and social security schemes in high-price countries. This was also stressed by parallel traders and health insurers in the public consultation. The difficulty lies in the quantifying the savings: Here, figures are controversial and vary. For example:

- A study by the London School of Economics contracted by Johnson&Johnson concluded, in 2005, that savings by parallel trade for health insurers are approx. 100m EUR in the six main importing countries;[81]

- On the other hand, in a study conducted by the Centre for Applied Health Services Research and Technology Assessment in 2006 for the European Association of Euro-Pharmaceutical Companies ("**EAEPC**") concluded that direct savings in the main destination Member States (DK, SV, DE, UK) were 441.5m EUR in 2004;[82]

79 DE: 2 000 – 3 000; UK: 3 000 – 5 000; Scandinavia: 1 000 - 1 500.

80 Cf. Conclusions of AG D. Ruiz-Jarabo Colomer of 1 April 2008 in case C-468/06 Sot. Lélos Kai Sia EE (and others) vs. GlaxoSmithKline AEVE and Conclusions of AG F. G. Jacobs of 28 October 2004 in case C-53/03 Synetairismos Farmakopoion Aitolias & Akarnanias (Syfait) vs. GlaxoSmithKline AEVE.

81 *Kanavos*, *Costa-Font*, Pharmaceutical parallel trade in Europe: stakeholder and competition effects, London (2004).

82 *Enemark*, *Møller Pedersen*, *Sørensen*, The economic impact of parallel import of pharmaceuticals, University of Southern Denmark (2006).

- Similarly, a study by the York Health Economics Consortium and financed by EAEPC published in 2003 concludes that savings from parallel trade in 2002 in UK, Germany, Sweden, Netherlands and Denmark were 631m EUR[83]

- In the public consultation, Germany has stressed that savings for the statutory health insurance schemes in Germany were approx. 200m EUR in 2002 and assumed that they reach up to 380m EUR today.

Moreover, apart from direct savings, it is argued that price decreases of patented medicines are largely due to lower prices of parallel imports.[84]

While it is generally acknowledged that parallel trade allows for intra-brand competition in patented medicines with savings for public health insurers, there are, however, also important counter-arguments.

In particular, it has to be recalled that all high-price countries have regulatory mechanisms in place which allow controlling the expenditure for medicines. In order to achieve lower prices, parallel trade is not necessary, as these prices could normally have been achieved through lower re-imbursement prices anyhow.[85]

In addition,

- savings through parallel trade are not directly passed on to the patient, as patients make only a mall flat-rate contribution towards the price of the prescribed medicinal product;[86]

- parallel trade may lead to dry-outs of supply and price increases of medicinal countries in low-price countries:[87] For example, there were several product shortages in France in 2005 and in Greece in 2000 and 2001.[88]

- parallel trade delays product launches in low-price countries;[89] and

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83 *West, Mahon*, Benefits to payers and patients from parallel trade, York Health Economics Consortium (2003).

84 *Ganslandt, Maskus*, Parallel imports of pharmaceutical products in the European Union (2002), The research instittue of industrial economics, Working paper No. 546, 2001.

85 Cf. conclusions of AG F. G. Jacobs of 28 October 2004 in case C-53/03 Synetairismos Farmakopoion Aitolias & Akarnanias (Syfait) vs Glaxosmithkline AEVE, paras. 99. However, in its recent ruling C-468/06 Sot. Lekos kai Sia EE v Glaxosmithkline of 16 September 2008, the Court stressed that, in its view, "it should be noted […] that the control exercised by Member States of over selling prices or the reimbursement of medicinal products does not entirely remove the prices of those products from the law of supply and demand" (para. 61).

86 Cf. conclusions of AG F. G. Jacobs of 28 October 2004 in case C-53/03 Synetairismos Farmakopoion Aitolias & Akarnanias (Syfait) vs Glaxosmithkline AEVE, paras. 97, 99. However, in its recent ruling C-468/06 Sot. Lekos kai Sia EE v Glaxosmithkline of 16 September 2008, the Court stressed that, in its view, "[…] even in the Member States where the prices of medicines are subject to State regulation, parallel trade is liable to exert pressure on prices and, consequently, to create financial benefits not only for the social health insurance funds, but equally for the patients concerned, for whom the proportion of the price of medicines for which they are responsible will be lower" (para. 56).

87 Cf. conclusions of AG F. G. Jacobs of 28 October 2004 in case C-53/03 Synetairismos Farmakopoion Aitolias & Akarnanias (Syfait) v Glaxosmithkline AEVE, paras. 91-92.

88 Cf. study "Safe medicines through parallel trade", Europe Economics (2008), p. 51; (referred to in chapter 1.4. in this report).

- parallel trade, albeit welcome for the exchequer and health insurance schemes, leads to losses of the pharmaceutical industry thus reducing its resources to innovate and research: it is argued that total industry losses in the six main destination countries of parallel import amount to 755.5m EUR per year.[90]

The environmental effects of a major reduction in parallel trade would include less waste from re-packaging by parallel traders of approx. 56m packs a year, and lower transport-related costs due to additional movement of products from lower-income Member States to higher-income Member States.

5.1.2.2. Policy option n°1/2b: Prescription products with possibility of derogation

On the negative side, this policy option would not address OTC medicines, which may not be secured with a safety feature. However, this aspect may be negligible as OTC medicines are not the main target for counterfeiters.

On the positive side, this policy option would – in analogy to above (cf. 5.1.2.1.) - contribute to tackling counterfeit by rendering safety features more efficient. Moreover, it would allow addressing the concerns of smaller Member States concerning availability. In addition, this policy option would provide some flexibility for the marketing authorisation holder to authorise third parties to manipulate the safety feature. This flexibility might be needed in instances where re-labelling is necessary for the marketing authorisation holder to redirect a product to another market.

With regard to the repackaging business, this business would be reduced by the extent it trades prescription medicines and does not fall within the derogations set out above (4.2.2.). It is realistic to assume that the remaining parallel trade would be approx. 12.5% of value as compared to today. This is based on the following reasoning:

- It is crucial to remember that parallel trade is based on arbitrage of price differences. These difference are typically greatest if prices are regulated which is usually not the case for OTC-medicines. In practice, parallel traders handle OTC-medicines only to respond to clients' wishes for a larger product portfolio. Thus, it can be estimated that the turnover value of prescription medicines is approx. 90% of products traded in parallel distribution.

- To this add situations where re-packaging/re-labelling would be permitted to ensure availability in small markets. The ten smallest markets in the EEA have approx. 4.7% market share.[91] It shall be assumed that approx 25% of this market share is supplied through re-packagers, i.e. approx. 1.2%.

- Finally, under this policy option the marketing authorisation holder may authorise a re-packager to manipulate the safety feature to address public

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89 Cf. *Danzon, Wang, Wang*, The impact of price regulation on launch delay of new drugs – evidence from twenty-five major markets in the 1990s, Health Economics 14.269 (2005).

90 *Kanavos, Costa-Font*, Pharmaceutical parallel trade in Europe: stakeholder and competition effects, London (2004).

91 The ten smallest Member States in the EEA have a market value of approx. 5 600m EUR (at ex-factory prices), i.e. approx. 4.7% of the EEA market.

health issues (for example, production of emergency kits or diverting products already packaged into other regions). It is difficult to estimate the proportion to which these authorisations happen today. A value of 1.3% seems not unrealistic.

Thus, taken together, in this policy option, the trade value of parallel trade would reduce to approx. 12.5%.

In terms of employment, the immediate effect would be a decrease of employment by parallel traders. It shall be assumed that the volume is proportionate to value. In addition, it is certain that the reduction of labour is proportionate to the reduction in volume traded, employment in this sector is largely based on the manual work of re-packaging or over-labelling of medicinal products. Thus, reduction of employment in first-round effect would be approx. 87.5%.

With regard to distribution effects/second-round effect, the reasoning set out above (5.1.2.1.) applies. This means that in second-round effects wholesale distributors and patent-holding manufacturers would gain market shares and increase value and volume. In this respect, the explanations set out above (5.1.2.1.) apply in analogy.

5.1.2.3. Policy option n°1/2c: Scope determined under Comitology on a risk-basis

This policy option gives the Commission the possibility - on a risk-basis - to protect safety features by prohibiting their manipulation. This policy gives thus the possibility for a targeted approach. It would allow for a flexible response to trends observed by market actors and competent authorities in the Member States. This is a particular advantage in an innovative sector where risk patterns can change quickly. Also the issue of availability in smaller markets could be addressed. On the negative side, this policy option would only have a restricted impact on the problem related to the manipulation of safety features insofar as it would not necessarily cover all products.

Concerning parallel trade, the impact of this policy option depends on the product (groups) identified as high risk groups. In order to take an informed policy-decision, for the purpose of this impact assessment it shall be assumed that all (prescription) medicines whose efficacy has lifesaving characteristics would be subsequently included in the scope of this restriction.

In terms of direct business impact, it can be assumed that the value of trade medicines would reduce by 50%. This rather high number can be explained by the fact that products with life-saving characteristics are high-price products where arbitrage brings about relative higher margins for parallel traders. Regarding distribution/second-round effect, the reasoning above (5.1.2.1.) applies.

Employment in this sector is proportionate to the volume of parallel trade (cf. 5.1.2.1.). As life-saving products are typically high-price products, it can be assumed that a reduction of parallel trade by 50% would mean a less than proportionate reduction of volume, i.e. approx. 30%. In terms of second-round effects, the reasoning set out above (5.1.2.1.) applies.

5.1.3. Comparison of policy options for specific objective n°1[92], synergies

In comparing the policy options relating to safety features, it becomes apparent that the scope of safety measures should encompass all prescription medicines (i.e. policy option n°1/1b). While it is true that a risk-based approach may reduce costs for compliance, it is unlikely to achieve the objective: counterfeiters can too easily adapt their activities to changes of the scope of this measure. On the other hand, it is not possible for the regulator to amend a list of risk-product (groups) swiftly, since long implementation times are needed to adapt production and packaging lines.

It is noteworthy that the preferred policy option takes account of the fact that OTC producers (of which many are SME's) are not affected by this policy option.

As regards the second broad policy option, a *de-facto* ban of repackaging/re-labelling for all products without exception would be counter-productive, as it would lead to severe problems of availability in smaller markets. Therefore, the decision has to be made between the policy option n°1/2b and n°1/2c. Both policy options allow for a more flexible approach: Policy option n°1/2b has more far-reaching impacts on parallel trade. However, this policy option contributes better than option n°1/2c to the specific objective to strengthen product safety thereby protection public health.

For the purpose of this impact assessment, it is not necessary to conclude on a recommendation regarding the final choice in this regard. That final choice is always left to the College of Commissioners. Rather, in accordance with the Commission guidelines for impact assessments, the impacts have been presented with view to first-round effect and distributional effects, thus allowing for an informed political decision-making.[93]

Both broad policy options have synergetic effect, as safety features are of limited use if their manipulation is legally possible.

[92] Cf. overview under 4.3.4.

[93] European commission impact assessment guidelines, (SEC(2005)791), with March 2006 update, section 5.3.

Overview regarding the policy choices for the first specific objective:

Policy option n°	Final choice	Contribution to achieving specific objective	Other positive impacts	Negative impact in terms of increase of compliance costs	Increase of compliance costs (in m EUR), other negative impacts		
					Manufacturers	Distributors	Other
1/1 Safety feature							
1/1a (All products)	×	very high	Ensures patient confidence Contribution to fight reimbursement fraud Potential gains from future international alignment Important annual savings of approx. 2500m EUR p.a. through End of fragmentation of product coding; Facilitated recall; Facilitated product returns.	- - - -	Seal: One-off:1 350 Annually:[93]1 070 Serialisation: One-off: 11 550 Annually:[94] 370		Max. one-off: Retail-shops: 2 250 Pharmacies: 157.5
1/1b (Prescription medicines with derogation)	✓	very high	*Idem*, but only for prescription medicines	- - -	Seal: One-off: 1 080 Annually: 535 Serialisation: One-off: 8 850 Annually: 185		Pharmacies: 157.5 (one-off)
1/1c (Risk-based, determined under Comitology)	×	high		- -	Seal: One-off: 360 Annually: 178 Serialisation. One-off: 2 950 Annually: 60		Pharmacies: 157.5 (one-off)
1/2 Prohibiting manipulation of safety features							
1/2a (All products)	×	**high**	Renders safety features efficient				Parallel trade value minus 100%

1/2b (Prescription medicines with derogation)		**high**	*Idem*, but only for prescription medicines Allows addressing issues of availability in small markets				Parallel trade value minus 87.5%
1/2c (Risk-based, determined under Comitology)		**moderate**	Risk-based, more targeted approach; Allows addressing issues of availability in small markets				Parallel trade value minus 50% (volume: minus 30%)

93 Over 10 years, without considering savings.

94 Over 10 years, without considering savings.

5.2. Specific objective n°2: Ensuring reliability of wholesale distribution

5.2.1. Policy option n°2/1: Include "traders" into the scope of rules for safe distribution

Social impact/public health and related costs

This policy option would make actors in the distribution chain accountable, who have up until now not borne any responsibility as they were not legally considered as "wholesale distributors".

Example: In the past, these actors - who often have very limited expertise in the sector – have been involved – in good or bad faith – in trading counterfeit medicinal products.

This should contribute to reducing the influx of counterfeit medicinal products into the distribution chain. This chain is "as weak the weakest link": If one actor is irresponsible and/or careless, counterfeit products can penetrate the distribution chain and often remain undetected afterwards.

The importance and effectiveness of this policy option has also been highlighted by the WHO in its "Principles and Elements for National Legislation against counterfeit medical products", as endorsed on 12 December 2007.[94]

Economic impact on businesses (compliance costs, including administrative costs)

Compliance costs, including administrative costs, are two-fold: costs for obtaining the wholesale authorisation (fees and administrative costs) and costs for inspections (fees and administrative costs to submit information, accompany inspectors, etc.). These costs amount to 1.14m EUR one-off costs (incl. 0.14m EUR administrative costs) plus 0.8m EUR per annum (incl. 0.138m EUR administrative costs).[95]

5.2.2. Policy option n°2/2: Strengthen inspection of compliance with GDP

a) Social impact/public health and related costs

As set out above (cf. 2.2.2.5.), enforcement and inspection are crucial. This applies in particular to wholesalers, as they are often the "point of entry" for counterfeit products into the distribution chain.

b) Economic impact on businesses (compliance costs, including administrative costs)

Costs would rise in terms of fees (which would be higher for CoCP compliant inspections) and administrative costs (related to paper work, accompanying inspectors and follow-up information). This rise would be approx. 8.27m EUR per year.[96]

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94 http://www.who.int/impact/en/.

95 Cf. Annex 3, point 1.

96 Cf. Annex 3, point 2.

5.2.3. Policy option n°2/3: Tighten control and supervision of GMP/GDP through audits

5.2.3.1. Policy option n°2/3a: Mandatory regular audits of supplying wholesalers

Social impact/public health and related costs

Audits as such do not detect counterfeiting. However, audits do help to single out companies that are untrustworthy and they act as a deterrent to rogue traders wanting to enter the business. They represent a kind of self control amongst business partners. The usefulness of obligatory audits to avoid "back-to-back" business was also stressed during the public consultation.

Economic impact on businesses (compliance costs, including administrative costs)

Any estimate of compliance costs has to differentiate between the business that is audited and the auditor. Moreover, it has to be borne in mind that, nowadays, responsible traders already perform audits at certain intervals. Finally, this policy option is based on a concept of shared third party audits as already practised today (above 4.3.3.1.). If shared third-party audit were not accepted, costs would increase accordingly. However, this also means devising ways of ensuring that third-party auditors are qualified and credible.

On the basis of this assumption, the increase in annual costs for compliance would be 17.28m EUR (for the auditing distributor) and 2.3m EUR (for the audited party).[97]

5.2.3.2. Policy-option n°2/3b: Risk-based audits of supplying wholesalers

Social impact/public health and costs related thereto

The difficulty of this policy option would lie in the legal uncertainties created. In particular, it is difficult for the auditing party to assess when there is a risk of non-compliant by the audited. As audit would be mandatory in these cases, this creates considerable legal uncertainty.

Economic impact on businesses (compliance costs, including administrative costs)

In terms of compliance costs, these depend on the degree to which auditing companies have reason to suspect non-compliance.

In view of the interest of the auditing company to cover-up itself, one can assume that the increase in audit activity compared to policy option n°2/3a would be largely the same (90%).

The increase in annual costs of compliance would fall by 10% as compared to policy option n°2/3a (i.e. increase of annual costs by 15.6m EUR for auditing party and 2.0m EUR for audited party).

[97] Cf. Annex 3, point 3.

5.2.4. Policy option n°2/4: Make wholesale activities and compliance with GDP more transparent

Social impact/public health and related costs

A database of GDP authorisation and inspection certificates would provide an assurance about whether and when a wholesaler has been authorised and inspected, and considered GDP-compliant by the competent authority. Such a data base therefore helps to create trust in the distribution chain and ensures the trustworthiness of the supplier. To avoid risks of "false assurance", it has to be clear that the information in the database does not give relief from the responsibilities set out in the relevant legislation.

Economic impact on businesses (compliance costs, including administrative costs)

The GDP database would be managed by the EMEA. Entries would be made by the national competent authorities. Their costs would be passed on to the wholesalers in the form of fees. It is important to note that there is already a database that gives an overview of GMP-compliant *manufacturers*. This approach would simply be extended - as regards legal provisions and technical arrangements - to the *wholesalers*.

It can be expected that costs for administrations will be passed on to the wholesalers. One-off costs would be passed on over a period of 10 years. Annual costs for industry would thus be 0.3m EUR.[98]

Impact on Community/EMEA budget

In view of the experiences with the existing EudraGMP database at Community level for *manufacturers/importers*, the costs for extending these IT-arrangement would be approx. 500 000 EUR over a time-frame of 2 years.

5.2.5. Comparison of policy options for specific objective n°2[99], synergies

Policy options n°2/1, n°2/2 and n°2/4 are three very useful and cost-efficient tools to enhance enforcement, i.e. to improve and target inspections and controls. In this respect, these policy options take account of the fact that, rather than introducing new (expensive) rules, comparatively small changes by the legislator can enhance observance of *existing* provisions, thereby ensuring a level playing field of regulatory provision for all competitors.

On top of this comes audit. Audit is crucial and has to be the "main pillar" of scrutiny. Official inspections by competent authorities are merely a "supplement" to this. In view of the slight difference in costs, relative to the significant difference in the efficacy of the measure, policy option n°2/3a should be preferred over option n°2/3b.

98 Cf. Annex 3, point 4.

99 Cf. overview under 4.4.5.

There are synergies between the chosen policy options to the extent that the various options mutually support each other. For example, transparency of compliant wholesalers do contribute to the efficient use of resources for inspections by administrations.

Overview regarding the policy choices for the second specific objective:

Policy option n°	Final choice	Contribution to achieving specific objective	Other positive impacts	Negative impact in terms of increase of compliance costs	Increase of compliance costs (in m EUR), other negative impacts		
					Manufacturers	Distributors	Other
2/1 (Include "traders" into the scope of rules for safe distribution)	✓	**high**	Facilitates greatly enforcement	-		5.14 (one-off)	
2/2 (Strengthened inspections)	✓	**high**	Indirect increase of self-responsibility	- -		8.27 (p.a.)	
2/3 Audit							
2/3a (All suppliers)	✓	**high**	Indirect increase of self-responsibility Short term applicability	- - -		19.55 (p.a.)	
2/3b (Risk-based)	×	**low**		- -		17.6 (p.a.)	
2/4 (GDP-database)	✓	**high**	Transparency, increase of self-responsibility Short term applicability	-		0.3 (p.a.)	EMEA: 0.25 (over 2 years)

5.3. Specific objective n°3: Defining clear obligations for import for export

5.3.1. Policy option n°3/1: Clarification that marketing authorisation is required for all imported products

Social impact/public health and related costs

On the positive side, this policy option is clear and easily enforceable: Any product entering the EU-territory for storage/handling would be illegal if it were not covered by a marketing authorisation.

On the negative side, it has to be remembered that the large majority of products imported for export do not comply with EU-legislation for marketing medicinal products because of marketing authorisation requirements relating to the product and language requirements relating to the packaging. This policy option would thus lead to a *de facto* ban on the import-for-export trade in pharmaceuticals. This, in turn, would impact on third countries, in particular developing African countries, which are supplied with medicinal products that transit through the EU.

Economic impact on businesses (compliance costs, including administrative costs)

A *de facto* ban on transit and import-for-export would lead to a loss of revenue for mainly two actors:

- EU-forwarding agents and, cargo companies, incl. airlines, and airports: It is critical that, in practice, transit shipments via the EU are done by EU companies. If transit movements are diverted into other regions, typically this business gets lost for EU-companies;
- Other operators engaged in import for export, incl. storing and handling medicinal products.

The nature of transited goods makes it very difficult to estimate what proportion of pharmaceuticals entering the EU is imported for export: These activities are subject to only minimal customs control. They are not recorded in official trade statistics, let alone in official product-related statistics. For these reasons, estimates and extrapolations which are based on:

- statistical information from these air- and seaports concerning transit volume;
- industry opinion and case studies on the revenue generated by this trade; and
- data on unlicensed wholesalers, and EU import volumes.[100]

In conclusion[101], it can be estimated that this policy option would lead to a loss of annual revenue for EU-businesses of 4.651bn EUR.

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100 See Annex 4, point 1 for details of all estimations and extrapolations.

101 See Annex 4, point 1 for calculations.

Environmental impacts

One may argue that there will be a reduction in transport, which is beneficial to the environment. However, a de-facto ban on EU transit trade would not necessarily mean a reduction in global shipping. It is more likely that trade would be diverted instead to other emerging hubs, particularly in the Middle East.

5.3.2. Policy option n°3/2: Clarification of the legal provisions – applying rules for export wholesalers

Social impact/public health and costs related thereto

A positive impact is a control of the economic actor handling products independently of whether the products are intended to be placed on the market or exported.

Another positive "side-effect" of this policy option concerns the protection of third country residents from counterfeit (und incorrectly stored) products: Even if counterfeit products are not channelled into the legal supply chain of the EU, they are usually exported to third countries. Protection in these third countries may be lower because:

- enforcement structures are weaker (in certain developing countries, for example);
- authorities refrain from enforcement, as they (erroneously) regard incoming goods as Community goods; or
- customs focus on bulk, imports, while goods may be "transited-on" by direct mail to the patient.

While this aspect is not the main purpose of this initiative, it is nevertheless a positive side-effect. This is even truer in the light of the global challenge presented by counterfeit medicinal products.

Economic impact on businesses (compliance costs, including administrative costs)

The direct business costs of meeting the requirements of this policy would fall upon the 1 100 or so unlicensed actors handling medicinal products destined for exportation who would face one-off costs of 2.35m EUR (caused by fees for authorisation and administrative costs related thereto) and annual costs (relating to costs for additional qualified personnel and administrative costs) of approx. 40.1m EUR.[102]

[102] Annex 4, point 2.

5.3.3. Comparison of policy options for specific objective n°3[103]

The two policy options discussed for this specific objective have very different economic consequences, which are indirectly proportional to their usefulness in achieving their objective.

Policy option n°3/1, however, also has negative effects for third countries, whose supply of medicinal products may depend on transit through/via the EU.

[103] Cf. overview under 4.5.4.

Overview regarding the policy choices for the third specific objective:

Specific objective	Policy option n°	Final choice	Usefulness to achieve specific objective	Other positive impacts	Negative impact in terms of increase of compliance costs	Increase of compliance costs (in m EUR), other negative impacts		
						Manufacturers	Importers	Others
Defining obligations for import for export	**3/1 (Marketing authorisation)**	×	++++	Easy to enforce/control				Revenue losses p.a. : Air-/seaport 886 Importers: 3700
	3/2 (wholesale exporter)	✓	+++	Patients in destination market profit	- - -		2.35 (one-off) 40.1 (p.a.)	
Total costs (of chosen policy options)								

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5.4. Specific objective n°4: Stepping up scrutiny of API actors

5.4.1. Policy option n°4/1: Authorisation

5.4.1.1. Policy option n°4/1a: Authorisation (incl. inspection) by EU competent authorities of all manufacturers of API, incl. those in third countries supplying the EU

Social impact/public health and costs related thereto

In view of the difficulties with compliance experienced by third country manufacturers, this policy option would be a useful tool to achieve compliance with GMP, and to enhance the safety and efficacy of API not only when manufactured in the EU but also abroad. However, inspections by EU competent authorities raise practical difficulties, as these inspections are resource-intensive and usually require knowledge of a foreign language, and partly expertise in foreign laws and regulations, as well as some intercultural communication skills. This is particularly critical in view of the large number of third-country API plants supplying the EU (approx. 20 000).

This assessment is confirmed by looking at the U.S., where this policy option has been discussed recently in U.S. Congress: the U.S.-FDA opposed this approach, pointing out that U.S.-FDA inspections of China's API facilities alone would take over 30 years.[104]

Moreover, local authorities – provided that the standards are sufficiently high and applied correctly – have easier access to plants and more efficient possibilities for sanctions.

Economic impact on businesses (compliance costs, including administrative costs)

Economic impact on businesses relates to authorisation and the subsequent inspections, which usually take place every three years. While there is no authorisation requirement in the EU at present, many EU-based API manufacturers are inspected regularly. Increases in costs would hit third-country manufacturers in particular, as they would face an increase in one-off costs (fees and administrative costs relating to authorisation) of approx. 302.4m EUR (EU-manufacturers 4.84m EUR) and increase in annual costs (fees and administrative costs) of approx. 100m EUR (EU-manufacturers 0.3m EUR).[105]

5.4.1.2. Policy option n°4/1b: Authorisation of all API manufacturers/importers in the EU

Social impact/public health and related costs

The arguments set out for policy option n°4/1a apply. However, the usefulness of this policy option would be more limited, as it would only address EU actors, while the bulk of API are currently being produced in third countries. As far as third-country

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104 Report from hearing of FDA Commissioner in Congress subcommittee on 21 April 2008.

105 Cf. Annex 5, point 1.

manufacturing is concerned, compliance with GDP would be monitored "via" the importer, i.e. the importer is only authorised if he verifies the CMP compliance of the manufacturer abroad.

Economic impact on businesses (compliance costs, including administrative costs)

Costs to be borne by EU-businesses would consist essentially of one-off administrative costs and fees of 59.5m EUR (one-off costs) and an increase of annual administrative costs (mainly for inspections and preparatory work) by 18.5m EUR.[106]

5.4.1.3. Policy option n°4/1c: Strengthened scrutiny of plants in 3rd countries if level of protection poses risks to public health in the EU

Social impact/public health and related costs

In view of the weak controls of API-production (above 2.2.2.4), this policy option would be an important factor in strengthening safeguards against counterfeit, sub-standard API. It would create an incentive for third country authorities to step up regulation and enforcement of GMP for exported API and to bring it up to a level that is acceptable in the Community.

Economic impact on businesses (compliance costs, including administrative costs)

The public consultation and consultations with Member States experts have confirmed that approx. 80% of the plants in third countries are not subject to proper rules and enforcement.

Making these plants subject to rules equivalent to those in the EU would involve administrative costs of approx. 31.8m EUR (details in Annex 5, point 3).

It may also be argued that another positive impact of this policy option is that it improves the competitive position of the EU API-manufacturer in relation to third country manufacturers. While it is true that EU-based API manufacturers have found it hard to compete with non-EU-based API manufacturers, the issue of GMP-compliance is a relatively minor aspect. In particular in the API-sector, other factors - such as IP-rights issues, wages, and qualification of staff - are far more important. Nevertheless, this policy option may have a (minor) part to play in creating a level playing field with EU API manufacturers.

5.4.2. Policy option n°4/2: Notification

5.4.2.1. Policy option n°4/2a: Notification of EU and third country actors handling API

Social impact/public health and costs related thereto

A notification does not in itself address the underlying causes of the problem set out above (2.2.2.4.). However, a notification is a helpful tool to render the existing mechanisms of risk-based inspections (cf. above 2.2.2.4.) more efficient: A notification allows the competent authority to screen potential non-compliant firms,

[106] Cf. Annex 5, point 2.

for example by focussing on new participants in the sector or by focussing on participants with a certain risk-profile.

A notification requirement for all actors handling API worldwide for the purpose of placing them on the EU market might thus well contribute to a facilitated and more targeted risk-based surveillance.

However, it may not be realistic to assume that competent authorities have the resources to even screen (let alone assess) the many notifications that have to be expected: Today, there are approx. 4 800 API manufacturers in third countries. To this add the distributors in third countries involved in the supply of the EU market, which may be in the range of 30 000.[107]

Social impact/public health and costs related thereto

One-off costs would be 1.7m EUR for third country actors, and 4.2m EUR for EU actors.[108]

5.4.2.2. Policy option n°4/2b: Notification only of EU actors handling API

Social impact/public health and costs related thereto

A notification procedure would contribute to achieving the objective, as it would facilitate targeted inspections. It would address the present situation where the actors within the EU are not known and thus inspections are less efficient. On the negative side, this policy option is less useful, as it is aimed only at EU-based actors (cf. above 5.4.1.2.)

Economic impact on businesses (compliance costs, including administrative costs)

One-off costs for EU API manufacturers and –importers would be 4.2m EUR.[109]

5.4.3. Policy option n°4/3: Mandatory audits of API manufacturers by medicinal products manufacturers

Social impact/public health and related costs

As shown above (cf. 5.2.3.1.), audit is a crucial *technique* to ensure trust and co-responsibility in the supply chain of medicinal products - a view which was also widely confirmed in the public consultation. This holds even more true in the field of API where, as shown above (cf. 2.2.2.4.), the manufacturer ensures the safety of the finished medicinal product.

Economic impact on businesses (compliance costs, including administrative costs)

Audits would be conducted as a shared third party audit (cf. above 4.5.3., 4.3.3.1.). The submissions in the public consultation stressed that:

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107 To compare, the number of API distributors in the EU is approx. 5 500.

108 Cf. Annex 5, point 4.

109 Cf. Annex 5, point 4.

- The around 11 300 importers would have to ensure that an audit had been carried out on their behalf. Even if the audits are in fact done by the supplier, it has to be assumed that their suppliers "pass on" the costs of the audits; and

- Today, 60% of all manufacturers supplying the EU already audit their API-suppliers in a reliable manner.

In view of these facts, annual costs for industry (manufacturers and importers) would increase by 33.6m EUR.

It has to be stressed that this sum is going to spread unevenly amongst the medicinal products manufacturer, depending on:

- How many API are purchased by one medicinal products manufacturer;

- How many medicinal products manufacturers purchase the same API; and

- To what extent reliable audits are already performed.

In view of this, producers of generic medicines and of OTC medicines may be particularly affected: While several manufacturers may purchase the same API, the usually purchase many different API for the product portfolio and produce very few (if any) API in-house. Therefore, these producers may be particularly affected by this policy option. This is an important aspect, as most of the generic/OTC producers are SMEs.

5.4.4. Comparison of policy options within specific objective n°4[110], synergies

As with the discussion of specific objective n°2, the aim of most policy options discussed under specific objective n°4 is to make surveillance, enforcement and inspections more efficient. However, policy options n°4/1a and n°4/1b are disproportionate and too difficult to implement in practice. Particularly with regard to policy option n°4/1a, the aim can be achieved more quickly, more cheaply, and in a more pragmatic way, by means of policy option n°4/1c. Within policy option n°4/2, two mutually-exclusive policy options were presented. The discussion shows that a notification of *all* actors – including those in third countries – would be counter-effective, as the scope would be too large. Therefore, policy option n°4/2b is preferable. Policy option n°4/3 (audit) is an efficient tool to ensure compliance with good manufacturing practice of API with reasonable increase in costs in the API sector. There are synergies between the chosen policy option to the extent that audit and enforcement are two parallel activities which may in practice support each other.

[110] Cf. overview under 4.6.4.

Overview regarding the policy choices for the fourth specific objective:

Policy option n°	Final choice	Contribution to achieve specific objective	Other positive impacts	Negative impact in terms of increase of compliance costs for EU	Increase of compliance costs (in m EUR), other negative impacts		
					API manufacturers in EU	API manufacturers in 3rd countries	Other
4/1 (Authorisation/Inspection)							
4/1a (Authorisation of manuf. in EU and 3rd country)	×	very high		-	4.84 (one-off) 0.3 (p.a.)	302.4 (one-off) 100 (p.a.)	
4/1b (Authorisation of EU-manuf./importers only)	×	very high	Coherence with rules for med. products	- - - -	59.5 (one-off) 18.5 (p.a.) (incl. importers)		
4/1c (3rd country equivalenz)	✓	high	Level playing field with EU companies			31.8 (p.a.)	
4/2 (Notification)							
4/2a All actors (EU and 3rd countries)	×	moderate		- - (in addition, possible negative effects))	4.2 (one-off)	1.7 (one-off)	EMEA: 0.25 (over two years)
4/2b (EU actors)	✓	moderate	Indirect stimulation of self-responsibility	- -	4.2 (one-off)		EMEA: 0.25 (over two years)
4/3 (Audit)	✓	high	Swift implementation	- -			Med. prod. manuf./importers: 33.6 (p.a.)

6. CONCLUSION - FINAL CHOICES OF POLICY OPTIONS[111]; IMPACTS ON SME ("SME TEST")

6.1. Final choices of policy options

Assessing and comparing the policy options for the four specific objectives reveal the following:

Concerning the ***specific objective to strengthen product protection***, the **first broad policy option** of an **obligatory safety feature** means establishing a legal basis for the Commission to determine under Comitology (or with standards) criteria and technicalities for an efficient safety feature (or a combination of them) such as a seal, a serialisation code, or a tamper-proof device. It is necessary to refer these implementing powers to the Commission: If concrete and detailed criteria for such a feature were established in secondary legislation, the necessary flexibility in a sector which evolves extremely quickly would get lost. Moreover, this approach gives the Commission the possibility to ensure global convergence and synergies. Finally, a flexibility is needed to assess more in depth which safety feature (or which combination of them) is most effective and cost-efficient and allows considering an appropriate differentiation for specific risks.

With regard to the *scope* of this broad policy measure there are various mutually-exclusive options to be considered. Of these, the policy option to include all products - without having regard to their risk-profile - into the scope should not be followed. This approach would include products into the scope which have a low risk-profile as they are typically not targeted by counterfeiters. This aspect is critical, as costs for regulatory compliance can be high.

Still on the scope, it would be equally wrong to have a merely risk-based approach based on implementing measures by the Commission. This measure would merely "shift" counterfeit activities into product groups which are not covered by specific product-related safety features. It would not be possible for the regulator to follow-up these changes of the risk-profile swiftly enough.

Therefore, the preferred policy option is to include in the scope all prescription medicines. This addresses the risk of counterfeiters "shifting" their activities to other profitable product groups within prescription products. It would leave OTC-medicines out of the scope, as these are typically no high-risk products. Moreover, it would reduce regulatory burden from the OTC sector, which consists of many SME.

Concerning the **second broad policy option**, it is evident that **safety features**, in order to be efficient, **must not be manipulated** by actors situated "in-between" the originator and the last actor in the distribution chain/the patient. Otherwise, any safety feature - be it a regulatory obligation or voluntary – would not make sense.[112]

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111 For an overview over the policy options see above (Chapter 4) and the table below.

112 It is in particular not realistic to oblige manufacturers to render the *technique* of a safety feature accessible to other actors in the distribution chain, who re-package medicines as part of their business model.

Within this broad policy option, the question is again the scope: Three possible scopes have been identified in the impact assessment.

Within this broad policy option, as a first policy option, a general ban of manipulation of the safety feature for all products is considered. This would affect those distributors who re-label and, in some cases, re-pack medicinal products. This is done by traders in order to ensure availability in small markets or in order to exploit the price differential due to differences in national pricing regulations. To the extent that re-packaging and re-labelling implies a manipulation of the safety feature, these practices would be strongly impaired. Thus, availability of medicinal products in small markets would be reduced which raises public health concerns.

This would be addressed in the second policy option: this policy option includes in the scope all prescription drugs but allows for a derogation which permits, for in particular, addressing issues of availability.

The third policy option would approach the issue of flexibility by providing merely a legal basis for the Commission to decide under Comitology on a risk-basis which products are within the scope of the broad policy option.

Both the second and the third policy option allow for flexibility. The difference is the impact in parallel trade. For the purpose of the impact assessment it is not necessary to take a definite decision between these two options. Rather, it is up to the Commission as political actor to propose, in view of the arguments brought forward, an approach to the co-legislator.

Concerning the ***specific objective to ensure reliability of wholesale distribution***, some of the policy options may apply cumulatively. Three of the policy options (wider scope to include all actors in the distribution chain, harmonised inspection provisions, database of compliant firms) are essentially improvements of Community law in order to facilitate control and inspections. All three options have been identified in the impact assessment report as efficient and effective measures to pursue the specific objective. The remaining policy option, audits, is in principle a useful means to ensure auto-surveillance by economic actors. The question is whether audits should be obligatory for all actors or only for actors selected on a risk basis. The impact assessment shows that the latter approach brings about considerable legal uncertainty while only marginally reducing costs for regulatory compliance. Therefore, this impact assessment report supports obligatory audits for all actors in the supplying chain.

As to the ***specific objective to define the obligations for import for export***, two mutually exclusive policy options have been discussed. Both policy options aim at clarifying the conditions under which medicinal products allegedly not destined for the EU market are brought into the EU customs territory for storage or minor handling. The business impact in terms of compliance costs varies considerably. The first policy option (requirement of marketing authorisation) leads to important revenue-losses for EU-based freight companies, storage-companies and companies engaged in the "forwarding" of goods under certain customs procedures. Moreover, this policy option may have far-reaching impacts on the supply of medicines to third countries, which often use the Community customs territory as transit hub. The

second (wholesale exporter) policy option costs less, while being only slightly less effective.

Finally, regarding the ***specific objective to step up scrutiny of actors handling active pharmaceutical ingredients ("API")***, within the broad policy option "authorisation", various mutually-exclusive policy options have been discussed. The assessment had to take in particular into account that most API producers are established in third countries. Therefore, it is in practice difficult to subject these producers to an authorisation regime (i.e. the first policy option), as this would imply an inspection of the plant (or, at least, of certain documentation). On the other hand, submitting only the EU manufacturers/importers to authorisation (i.e. second policy option) brings about high administrative costs for these actors, while the indirect scrutiny of authenticity/quality of imported API may have inherent limitations. Therefore, the third policy option is favoured: the authorisation requirement in third countries is only triggered if it is established that the regulatory framework in the respective third country does not ensure a comparable level of protection for human health for products exported to the EU. It is expected that this policy option would in practice raise standards in third countries without introducing an expensive and resource-intensive worldwide mechanism of EU-authorisation. Moreover, this policy option would not necessarily place additional administrative costs on Community manufacturers.

The broad policy option "authorisation" may be complemented by notifications of actors not covered by an authorisation obligation. Notifications are in principle a useful tool to render existing inspection schemes more targeted, risk-based and efficient. Against this benefit the additional administrative costs generated by this policy option for EU businesses are acceptable. Within the broad policy option, the possibility of including every actor involved in the manufacturing/distribution chain of products destined for the EU market has been discussed as one policy option. The administrative costs for third country actors would remain modest. However, this large scope would not effectively support targeted inspections: the number of notifying parties would be too large and thus render the entire exercise counter-productive. The alternative scope would be restricted to companies established in the EU. This would still raise administrative costs for EU businesses, but would be an equally effective measure to facilitate risk-based inspections and official controls.

Finally, audits of API producers are, just as for distributors of medicinal products, an important element of control amongst business partners, which can only be supplemented by risk-based controls of competent authorities.

6.2. "SME test"

In its Communication of July 2008 "'Think small first' – A 'Small Business Act' for Europe"[113], the Commission commits to strengthen its assessment of the impact of forthcoming legislative and administrative initiatives on SMEs (so-called "SME-test"). Commission guidelines for the SME-test are still under development. Nevertheless, to reflect this Commission commitment already now, this chapter

[113] COM(2008) 394 final.

addresses specifically the impact on SME and discusses how the chosen policy options take into account the peculiarities of SME.

The impact assessment shows that the main compliance costs are with the manufacturers of medicinal products who have to comply with safety features. Therefore, this aspect shall be looked at specifically (below, 6.2.1.). The other chosen policy options are going to ne discussed under 6.2.2.

6.2.1. Safety features

The policy option n°1/1b concerns in particular manufacturers of prescription medicines. In the EU, approx. 30% of these companies fall within the definition of SME.

Within this "SME share", the majority of companies are manufacturers of generic medicines. These SME are going to profit from the possibility to pursue a risk-adapted approach. This risk-adapted approach relates to a variety of safety features, and in particular to the need to "individualise" packages.

Therefore, it can be expected that both OTC manufacturers and generic manufacturers, who form the large share of SME-manufacturers in the pharmaceutical sector, are less affected by compliance costs.

Moreover, in order to reduce the impact of any measure related to the safety feature, it is crucial to ensure that the implementation time of such a safety feature is sufficiently long. The longer the implementation time of an obligatory safety feature, the cheaper it is – in particular for SME – to comply with these requirements. This logic also holds for distributors/pharmacies who would verify a safety feature.

6.2.2. Other chosen policy options

The impact on SME can be summarised as follows:

- Policy option n°1/2b/c: Both policy options (the final choice is left open) affect exclusively parallel traders. With very few exceptions, practically all of the approx. 100 parallel traders in the EU are SME.

- Policy option n°2/1: The actors referred to in this policy options are practically all SME. They would be hit by additional costs in order to comply with the requirements foreseen in this policy option.

- Policy options n°2/2 and n°2/3a: Out of the approx. 20 000 wholesalers in the EU, the large majority are SME. In order to mitigate costs, the possibility of third-party audits is foreseen under this policy option. This means that costs for audits are shared amongst purchasing wholesale distributors.

- Policy option n°3/3: Exporter/transhipment companies usually fall within the SME definition as they are of limited size. In order to keep costs reasonably low, the policy option with the least business impact was chosen.

- Policy options n°4/1c and n°4/3: As set out in the impact assessment, these costs would mainly concern third country plants. However, in a second round

effect, additional costs are likely to be passed on to the EU manufacturers of medicinal products. This would affect in particular producer of generic medicines, who purchase most active ingredients from third countries. In the generic medicines sector, approx. 75% of manufacturers fall within the definition of SME.

- Policy option n°4/2b: Approx. 70-80% of all API manufacturers and importers are SME. While SME are thus mainly hit by the costs of this policy measure, it has to be stressed that costs remain modest.

In order to reduce the impact of any measure related to the safety feature, it is crucial to ensure that the implementation time of these measures is sufficiently long. The longer the implementation time of additional regulatory measures, the easier it is for companies – in particular for SME – to render the costs for compliance low.

Overview over impact of final policy choices (applying the baseline of a forecast 2011 to 2020):[114]

Chosen policy options n°	Compliance costs (over period 2011-2020) in m EUR (first-round effect)							Impacts on parallel trade (first-round effect)	Benefit (objective) in m EUR	Other remarks
	Med. product manuf./ importers	Med. product wholesale distributors	"Traders"	wholesalers engages in export	API manufacturers		Pharmacies			
					EU	3rd country				
1/1b (*no decision on technical feature now but in Comitology*)									**Between 9 500 and 116 000 (depending on scenario)**	*No decision on technical feature now but in Comitology*
Seal	6 430									
Serialisation	10 700						157			
1/2b/c (*no final choice – political appreciation*)										*No final choice in impact assessment report – political appreciation*
1/2b (prescription drugs)								Parallel trade value/volume minus 87.5%		
1/2c (risk basis)								Parallel trade value minus 50% (volume: minus 30%)		
2/1 (include "traders")			5.14							
2/2 (Inspections)		83								
2/3a (Audits)		195								
2/4 (GDP Database)		3								*Add. costs for database in EC budget: 0.25m EUR*
3/2 (export wholesalers)				403						*Add. costs for database in EC budget: 0.25m EUR*
4/1c (3rd country equivalenz)						318				
4/2b (Notification)					4.2					
4/3 (Audits)	336									
TOTAL COSTS	**6 766< 11 036**	**281**	**5**	**403**	**4**	**318**	**157**			

[114] It is assumed that costs mount in line with inflation.

7. MONITORING AND EVALUATION

The proposal, once adopted, will be implemented in close cooperation with all stakeholders concerned. To this end, the Commission - and the EMEA - have already established valuable *fora* and are planning to use them in the future.

The policy will also be monitored under the auspices of the Pharmaceutical Committee, in which the competent authorities meet on a regular basis.

In order to measure progress, in particular with regard to improvements in product safety, the Commission intends to continuously assess:

- The development on the market with regard to counterfeit medicinal products; and
- Any occurrence of undesirable events due to counterfeit medicinal products.

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Annex 1 – The actors involved in the production and distribution of medicinal products

The pharmaceutical sector at large involves many different players, including manufacturers, importers, (upstream) suppliers, (downstream) distributors and retailers/pharmacies. As the policy options discussed may impact on these players, the key characteristics shall be described here.

1. Medicinal products manufacturers

The pharmaceutical industry is one of the best performing high technology industries in Europe. This sector accounts for more than 17% of the EU Research and Development (R&D) expenditure. Pharmaceutical R&D spending typically represents around 15% of sales in any year.

There are around 3 700 pharmaceutical companies in the EU with a combined turnover of 170bn EUR; they employ more than 634 000 people.[115] Of these companies,

- approx. 1000 are producing generic, i.e. non-patented, medicinal products[116]; and (not necessarily mutually exclusive)
- approx. 1 000 are active in the non-prescription sector.

While only estimations exist, it can be assumed that approx. 40%[117], i.e. approx. 1500 pharmaceutical companies fall within the SME definition of the EU. The large majority of these companies produce generic and/or OTC medicines.

While the EU has an export surplus of approx 35bn EUR, it is also a major import market with an import value of approx. 150bn EUR. 82% of imports of medicinal products come from the U.S. and Switzerland.[118]

It is worth highlighting the large volume of traded medicinal products: Approx. 29.7bn packs are traded in the EU per year. 50% of these packs are non-prescription (OTC) medicines, representing 15% of market share in value (retail price). 40-50% of these are generic medicines, which account for approx. 20% of the market share in value terms.[119]

The OTC-market accounts for approx. 10% in value of the total generic pharmaceutical market.

In terms of packaging lines (relevant for questions of new safety features), there are 15 000 packaging lines operating for the EU market. Approx. 10 000 lines operate in the generics sector; 3000 of them in the non-prescription sector.

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115 Eurostat (2005).

116 In terms of SME, approx. 5% of these companies have a turnover of >50m EUR per year.

117 Based on more aggregated figures of numbers of personnel employed ("pharmaceuticals, medicinal chmicals, botanical products") of Eurostat (2004)

118 Eurostat (2006).

119 European Generic Medicines Association (2006).

A production line life cycle is approx. 20-25 years; a packaging line life cycle is approx. 10-15 years.

While there are no precise figures, it is assumed that there are approx. 7 000 plant sites located within the EU. There are around 8 000 plants outside the EU which supply the Community market.

The branded pharmaceutical industry is rather concentrated. The top ten manufacturers of medicinal products account for approximately 80% of brand medicines sold in Europe.

2. Importers of medicinal products

There are approx. 11 300 importers of medicinal products in the EU.

3. Manufacturers of active ingredients ("suppliers")

The core of medicinal products is the active pharmaceutical ingredient ("**API**"). API are produced by the medicinal products manufacturer or by the special chemicals industry. Depending on the complexity of the substances, considerable know-how is needed in order to produce active substances.

Today, there are approx. 700 companies in the EU, with 1 000 plants supplying the pharmaceutical sector with API. These companies employ approx. 80 000 people across Europe.

In particular with regard to generic medicinal products, a large part of API is produced by approx. 4500 API manufacturers based in third countries. These third country manufacturers have approx. 20 000 production lines for API. Some 90% of these manufacturers (and the respective production lines) are in India[120] and China[121] alone.[122,123]

Large generic companies have, on average, around 500-1000 suppliers of active substances. Smaller generic companies have on average around 200-500 suppliers of active substances. Non-generic companies have fewer such suppliers.

4. Distributors

The distribution business for pharmaceuticals is highly sophisticated. This is due, in particular, to the need to ensure a constant supply to retailers and special needs, such as cooling. The features of the distribution business have evolved over time. There are many different players involved in the distribution chain. Moreover, the number of intermediaries that trade medicinal products without actually handling them has been growing continuously: For example, today, in the UK alone, there are many hundreds of these intermediaries trading and supplying medicinal products. There are around 20 000[124] licensed wholesalers and approx. 1 000 unlicensed brokers/traders

120 Approx. 1000 manufacturers.
121 Approx. 3000 manufacturers.
122 *Pollak*, Fine chemicals – the industry and the business (2007), p. 164.
123 *Weinmann, Cerrutti*, L'industrie pharmaceutique, Les notes bleues de Bercy 2006, n. 303, p.3.
124 EMEA

of medicinal products in the EU, accounting for a turnover of 282 billion EUR and employing approx. 46 000 European workers.[125]

Distributors have an important role to play: they ensure a constant supply of medicinal products. On small markets, this can sometimes include re-labelling and changing of leaflets to comply with language requirements.

One particular form of distribution[126] is "parallel trade". Parallel traders exploit the differences in prices in different Member States by purchasing medicinal products in low-price countries and selling them in high-price countries. These price differences are often a result of the various regulatory measures taken by Member States or social security schemes to contain expenditure on pharmaceuticals. As far as Member States are concerned, these measures do not infringe the fundamental freedom of free movement of goods as such.[127] As far as social security schemes are concerned, these have significant bargaining power on the demand side, and the relevant competition rules do in principle not apply to them.[128]

In order to comply with the regulatory requirements (in particular regarding the language of the labelling and package insert), medicinal products are usually re-labelled (approx. 60% of all parallel-traded products) or re-packaged (approx. 40% of all parallel-traded products).[129] In practically all cases the leaflet is exchanged. Parallel traders handle approx. 140 million packs per year.[130] They have a turnover of approx. 3.5 – 5bn EUR. It is estimated that the annual profits of parallel traders in the EU are of the order of 400-500 m EUR. There are around 100 companies[131] engaging in parallel trade in the EU, employing approx. 10 000[132] persons. Market share of parallel traders is approx. 5% in the EU, with 15% each in the UK and in Denmark, approx. 13% in Sweden, approx. 10% in the Netherlands, approx. 7-8% in Germany, and approx. 2% in Finland..[133]

With few exceptions, parallel traders usually fall within the definition of SME.

5. Retailers/pharmacies

Pharmacies typically retail the medicinal products for prescription drugs. There are approx. 150.000 pharmacies in the EU. With some exceptions, notably in the UK, the large majority of pharmacies are SMEs.

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125 Eurostat (2005)

126 For the purpose of this report, parallel traders are qualified as distributors. Note that, in regulatory terms, parallel traders are obliged to obtain a "manufacturing licence" for their activities.

127 Case 181/82, *Roussel*, ECR 1983, 3849.

128 Case C-264/01, *AOK Bundesverband*, ECR 2004, I-2493.

129 Approximative shares of relabelling: UK: 85%, Skandinavia: 50%; Germany: 70%.

130 Europe Economics, Safe medicines through parallel trade (2008), p. 2.

131 DE: approx. 25; UK: approx. 55; Scandinavia: approx. 10 – 15 ; Concerning UK, 14 companies account for approx. 50 – 60% turnover (80 – 85% volume) of parallel trade.

132 DE: 2 000 – 3 000; UK: 3 000 – 5 000; Scandinavia: 1 000 - 1 500.

133 Source: EFPIA, The pharmaceutical industry in figures (2008), p. 5. In the public consultation, these figures were largely confirmed.

Annex 2 – Compliance costs for policy options under specific objective n°1 – estimations and calculations

1. Policy option n°1/1a (all products)

1.1. Example of costs for tamper-proof feature:

The costs for compliance depend very much on the technique used. According to industry estimates, a tamper-proof feature costs in average approx. 0.06 EUR per each of the 29.7bn packs dispensed per year.

Annual costs are thus 1 069m EUR.

To this add the adaption of the packaging lines, which have to print the feature on the packaging. While there have been numerous conflicting sources from within industry on the estimated numbers of packaging lines in the EU, it can be estimated that approx. 15 000 packaging lines (**e**) are operated by EU manufacturers of medicinal products. The costs for adapting a packaging line to mass serialisation are approx. 150 000 EUR (**f**).

Today, approx. 40% of all dispensed packs (and the respective packaging lines) already contain an advanced tamper-proof feature.

One-off costs for a tamper-proof feature are thus 1.35bn EUR.

1.2. Example of costs for serialisation:

Manufacturers (one-off costs)[134]

The setting-up of the database is estimated to cost approx. 3m EUR (**a**) for a firm with a large portfolio (approx. 2 500, **b**) and approx. 1.5m EUR (**c**) for a firm with a small portfolio (approx. 1 200, **d**) of medicinal products.

To this add the adaption of the packaging lines, which have to print the serialisation number on the packaging. As set out above (point 1.1.) it can be estimated that approx. 15 000 packaging lines (**e**) are operated by EU manufacturers of medicinal products. The costs for adapting a packaging line to mass serialisation are approx. 150 000 EUR (**f**).

One-off costs for manufacturers

$$a * b + c * d + e * f = 11.55\text{bn EUR}$$

Manufacturers (annual costs)

Running costs are in particular devising serial number, its packaging, and printing devices, etc. Costs to implement and run a serialisation number would be approx. 0.02 EUR (**g**) per pack during the first 5 years of operations. These costs reduce to

[134] All estimations are based on industry information submitted during the public consultation.

0.005 EUR (**h**) per pack in the post first 5 years. Each year, 29.7bn packs (**i**) are dispensed in the EU.

Annual costs for manufacturers (over period of 10 years):[135]

$$\frac{g*i*5+h*i*5}{10}=371\text{m EUR}$$

Pharmacies (one-off)

For pharmacies labour cost of scanning of the products has not been considered, as this would be done when the product is dispensed (for example, while the patient pays the product).

On the control side, a scanner to read the serialisation number costs approx. 1 500 EUR per item (incl. software) (**e**). It is assumed that 30% of all 150 000 EU pharmacies (**g**) are already equipped with a scanner[136].

$$e*g*70\%=157.5\text{m EUR}$$

Shops (one-off):

There is limited information about the number of retailers selling OTC medicines. Estimations range as high as 1.5m. As none of these retailers is equipped with scanners today, one-off costs would be approx. 2.25bn EUR.

Savings:

- Fragmentations of product coding require companies to adapt the packaging to each national territory of the Community market. In the public consultation the difficulties created by a lack of harmonisation were repeatedly highlighted: Costs created by a lack of harmonisation in this respect are estimated to be presently as high as 1bn EUR per year (**f**) for EU industry.

- Facilitated recalls: The 100 large companies (**b**) are faced in average with approx. 2.5 recalls per year (**c**). The other 3 600 companies account for approx. 100 recalls per year (**d**). The handling and losses of a recall are calculated by industry to be 2m EUR (**e**) per recall. Industry estimates, that certain authenticity features allow for savings of the handling of 30%

- Facilitated handling of product returns: Apart from recalls distributors and retailers/pharmacists return products for various reasons, such as expiration of the product and damages of the packaging. Approx. 1% of products are returned per year. Handling of these returns is very burdensome and costly for industry. According to industry estimates, certain authenticity features would allow for savings in this area of 1bn EUR (**g**) per year.

135 For the purpose of the calculation, it is assumed that the number of dispensed packs remains stable.

136 During the public consultation, it was highlighted that many pharmacies use already today scanner technique. This holds in particular for Germany (25 000 pharmacies), which uses scanning techniques for invoicing medicinal products.

- A better access to data: As in any market, it is crucial to have reliable market data. Today, industry spends approx. 800m EUR per year to obtain market data (**a**). For the sake of this calculation, it shall be assumed that certain safety features could reduce these costs by 40%.

Savings:

$$a * 40\% + (b * c * e * 30\%) + (d * e * 30\%) + f + g = 2.53\text{bn EUR}$$

2. Policy option n°1/1b (prescription only)

2.1 Example of costs for tamper-proof feature:

About 3 000 of the packaging lines are used in the non-prescription sector. Existing compliance is approx. 40%. The prescription sector counts for approx. 50% of dispensed packages per year.

Thus, in applying the calculation above, annual costs would be approx. 534.6m EUR; one-off costs would be approx. 1.08bn EUR.

2.2 Example of costs for serialisation:

The costs for databases would not concern producers for OTC medicines: Thus, costs would only hit the approx. 2 000 producers with large portfolio and 700 producers with small portfolio. Costs for adapting packaging lines would relate only to approx. 12 000 non-OTC packaging lines. One-off costs would thus be 8 850m EUR.

Running cost regarding non-OTC would be, in analogy to above (6.2.) 185.5m EUR.

Regarding costs for pharmacies, etc., these would be essentially identical. However, retail shops would not be affected.

Annex 3 - Compliance costs for policy options under specific objective n°2 - estimations and calculations

1. Policy option n°2/1 ("Include "traders" into the scope of rules for safe distribution")

According to industry sources, it can be assumed that there are approx. 1 000 actors in the distribution chain which are not "wholesaler" as currently defined (**a**).

One-off costs for these players compose of the administrative costs for notification (cf. Annex 8), which are 140 000 EUR (**c**)

In addition, there are one-off compliance costs. They concern in particular alignment with the relevant provisions of the GDP, such as maintaining a quality system and record-keeping. It can be estimated that these one-off costs are approx. 5 000 EUR (**b**).

One-off cost for EU-industry:

$$a * b + c = \textbf{5.14 m EUR}$$

2. Policy option n°2/2

Strengthened enforcement means costs in terms of compliance costs (e.g. fees for inspections) and administrative costs.

Non-CoCP compliant GDP-inspections have to be brought up to CoCP-standards: Industry estimates that 80% of the current GDP inspections are not up to this standard. The fees for a CoCP-compliant inspection would be approx. 4 000 EUR (**d**), i.e. 1 300 EUR (**e**) more per inspection than a non-compliant inspection.[137] This fee is higher than that in point 1., as installations are typically more complex. Present administrative costs (**f**) and future administrative costs (**g**) are set out in Annex 8. It is assumed that inspections continue to be done in average every 3 years. There are 20 000 wholesalers in the EU (**h**).[138]

Increase of annual compliance costs for distributors

Situation today	**Policy option (100% of inspections at CoCP-standard)**
$\frac{h}{3}\left[(d - e * 80\%) + (d * 20\%)\right] + f = 23.53\text{m EUR per year}$	$\frac{h}{3} * d + g = 31.8\text{m EUR per year}$
Increase of annual costs: 8.27m EUR per year	

3. Policy option n°2/3a

137 Information from industry (EAEPC, FIRP) and competent authorities (MHRA).

138 This addresses only the wholesalers licensed already today. The Unlicensed wholesalers are addressed under point 1.

In terms of compliance costs, the estimation is based on the possibility of third-party-audits. This approach would contribute to the reduction of audits of the same plant by making the results of an audit available to a number of interested companies. There are 21 000 wholesalers[139] (**a**) and approx. 15 000 manufacturing plants (**b**) supplying medicinal products for the EU market. Approx. 90% of them are audited insufficiently frequently: every 5 years instead of every 3 years, which would be an appropriate interval. The costs for purchasing a third party audit are approx. 4 000 EUR (**c**). Costs for the audited are essentially costs for providing information etc. It is estimated that this requires 15 man-hours (**d**) with an average wage of 35 EUR (**e**).

Compliance costs – audit of suppliers, including supplying manufacturers

	Situation today (90% of companies audited every 5 years; 10% of companies audited every 3 years)	**Policy option (100% of companies audited every 3 years)**
Auditors	$\left(\frac{(a+b)*c*90\%}{5}\right)+\left(\frac{(a+b)*c*10\%}{3}\right)=$ 30.72m EUR	$\frac{(a+b)*c}{3}=$ 48m EUR
Audited party	$\left(\frac{(a+b)*d*e*90\%}{5}\right)+\left(\frac{(a+b)*d*e*10\%}{3}\right)=$ 4.03m EUR	$\frac{(a+b)*d*e}{3}=$ 6.3m EUR
Increase of annual cost total: 19.55m EUR		

4. Policy option n°2/4

The one-off cost to set up the database (**a**) would be 1m EUR. Experience with the database for G*M*P-compliance shows that annual costs to run the database (**b**) would be 100 000 EUR. There are 21 000 wholesalers[140] in the EU (**c**), which are inspected approx. every 3 years. The duration of updating the database (**d**) is approx. 0.5h (**e**), with an average labour cost of 29 EUR per hour (**f**).[141]

The annual costs which would be borne by industry are thus

$$\left(\frac{a}{10}\right)+b+\left(\frac{c}{3}*e*f\right)=0.3\text{m EUR}$$

139 Including unlicensed wholesalers.

140 Including unlicensed wholesalers. Note, that *manufacturers* owe by definition a distribution licence and are thus not included in this calculation.

141 Wages are lower than in the cost model in Annex 8, due to the different characteristics of the work.

Annex 4 - Compliance costs for policy options under specific objective n°3 - estimations and calculations

1. Policy option n°3/1

The "import for export" business generates revenues for the cargo business and the handling and warehouse business.

While the majority of general cargo is transported by sea, the transport of finished pharmaceuticals likely to be more evenly distributed between sea and air. This is due to the fact that many pharmaceutical products are relatively light and sensitive to storage conditions (relating to temperature) and time spent in transit, for which air travel is better suited. Pharmaceuticals are also high-value goods and insurance issues make it less risky for them to be transported by air. In addition (this is particularly applicable to individual importers), shipping cargo requires a minimum weight which makes it competitive to transport smaller consignments by air. Land transport makes up an almost negligible percentage of the transit of pharmaceuticals between non-EU countries through the EU.[142]

For this reason it is assumed that for the large-scale transit of pharmaceuticals, 50 per cent travel by air and 50 per cent by sea. For transport relating to individual importers for export, who are more likely to move smaller amounts, 60 per cent is assumed to travel by air and 40 per cent by sea.[143]

Transit volumes and revenues have been estimated separately for air and sea for the main hub air- and seaports in the EU. The revenue figures for both shipping and flying include all revenue generated by the movements: for forwarding agencies, airlines, airports, shipping lines and sea ports.

A. Sea Transit		
Figure	**Five main EU Ports**	**Source**
PT: estimated weight of pharmaceuticals transhipped through from outside the EU (1,000 tons)[144]	710	Estimate based on evidence from Hamburg, applied to Rotterdam, Antwerp, Hamburg, Amsterdam, Le Havre[145]
AR: average revenue per shipment of 10 tons[146]	€4,500	Typical sea route (Laos to Brazil) via EU of transited pharmaceuticals; opinion of Quality Director for EMEA: DHL Excel Supply Chain Cost from TransGlobal Express and PharmaExport Includes total revenue to all stakeholders (couriers, shipping lines, seaports) which would be lost.
Total revenue generated across all	€319m	

142 Opinion of Quality Director DHL Excel Supply Chain. It is competitive to transport a consignment of under 12 pallets by air.

143 Opinion of Quality Director for EMEA: DHL Excel Supply Chain.

144 Across the five main ports.

145 Choice based on Rotterdam Port Authority: Industry and Bulk Cargo; TransGlobal Express; Global Shipping; Antwerp Port Authority.

146 Average weight of shipment: 24 pallets at 417kg each.

ports [PT/10*AR]	

B. Air transit		
Figure	**Six main EU airports**	**Source**
PT: estimated number of transit movements of pharmaceuticals[147]	14,193	Estimate based on evidence from UK, applied to Frankfurt, Schiphol, Heathrow, Charles de Gaulle, Luxembourg, Milan[148]
AR: average revenue per movement[149]	€39,963	Typical route from India to Nigeria, based on evidence from MHRA[150] Average weight of 4,170kg per movement[151]
Total revenue generated across all airports [PT*AR]	€567m	

C. Handling and storage		
Figure	**Whole EU**	**Source**
NI = number of unauthorised importers	3,336	MHRA consulting with HMRC[152]
TC = total transport costs per firm per year	€408,150	Average of 45 transport movements of 5 pallets each per year per firm; 60% by air and 40% by sea. Details in Transit Calculations Annex
BW = bonded warehouse storage revenue per firm per year	€3,673	Total of €12,252,794 revenue lost across all 3,336 firms, based on 53% of all import-for-export pharmaceuticals being stored in warehouses. Costs from DTZ Consulting and Research (2005) "Benchmark study: Antwerp, Le Havre, Rotterdam"
VA = value-added per firm[153]	€716,578	60% of European wholesaler industry average.
EF = employment per firm	16	60% of industry average: Annual Business Inquiry (2007)

147 Across the six main airports.

148 Choice based on: De La Fuente Layos (2005) "Statistics in Focus: Transport", Eurostat publications; and opinion of Quality Director for EMEA: DHL Excel Supply Chain.

149 This is the total revenue generated by the movment. It is based on quotes from couriers (DHL; TransGlobal Express) and transport industry experts (PharmaExport; EMEA Supply Chain) and consists of all revenue to couriers, forwarding agents, airlines and airports (including handling and processing charges). It was not possible to separate the figure into these various components, but it is sufficient to represent the total loss of transport revenue resulting from the policy.

150 Medicines and Healthcare products Regulatory Agency, UK.

151 10 pallets at average 417kg each. More than 10 pallets not likely to travel by air.

152 UK Revenue and Customs.

153 Contribution to GNP. Made up of net profit and wages.

Total revenue generated across all importers	€3,764m	[TC+BW+VA]*NI
Total employment lost[154]	53,376	[EF*NI]

Total for policy option	
Total revenue lost from policy per year [A + B + C]	€4,651m

2. Policy option n°3/2

It is estimated that the number of wholesale exporters located in the EU (**a**) is 1 000.[155]

The one-off costs relate to the fees for the wholesale authorisation (2 000 EUR, **f**) and the one-off costs administrative costs related to it (**g**)[156]:

$$g + (a * f) = 2.35\text{m EUR}$$

In terms of annual costs, a Responsible Person ("**RP**") would be required at the importation site. A RP's annual salary (**b**) is approx. 35 000 EUR.[157]

The fee for wholesaler inspections (**d**) is 4 000 EUR. GDP inspections are schedules for every three years. To this add the administrative costs (**e**).[158]

The annual costs are therefore as follows:

$$(a * b) + \left(\frac{a * d}{3}\right) + e = 40.1\text{m EUR}$$

154 It is assumed that only employment will be lost among importers, not at ports or airports given small ratios of pharmaceuticals to all other cargo.

155 Based on the assumption that one third of the economic actors referred to under point NI in policy option n°3/1 have not wholesaler authorisation.

156 Cf. Annex 8.

157 Industry estimation.

158 Cf. Annex 8.

Annex 5 - Compliance costs for broad policy option n°4 - estimations and calculations

1. Policy option n°4/1a

Costs for authorisation (incl. the necessary inspection)

There are approx. 20 000 API production lines[159] (**a**) in 3rd countries and 700 manufactures with approx. 1 000 API production lines (**f**) in the EU.

Accompanying inspectors[160] takes approx. 24 man-hours (**b**) at costs of approx. 5 EUR per hour (**c**) in third countries – a rate justified by the fact that the large majority of these companies are established in India and China. To this add administrative costs in the EU (cf. Annex 8, **g**).

Fees for authorisation are 4 000 EUR for within the EU (**h**) and would be approx. 15 000 for plants outside the EU[161] (**i**).

Costs for subsequent inspections

The frequency of inspections would be approx. every 3 years. Fees for inspections are assumed to be similar to fees for authorisation.

It is assumed that, today 80% of all EU-API plants and 1% of all API plants in third countries are inspected by the EU.

Administrative costs for EU companies today (**j**) and with the policy option (**k**) are in Annex 8. For administrative costs for non-EU companies, refer to above.

Increase in one-off costs:

	Costs today	**Costs of policy option**
EU companies	Zero	$f * h + g = 4.84\text{m EUR}$
Third country companies	Zero	$a * i + a * b * c = 302.4\text{m EUR}$
Total increase: EU-companies:4.84m EUR; Third county companies: 302.4m EUR		

Increase in annual compliance costs:

Costs today	**Costs of policy option**

159 The number of production lines is essentially more relevant than the number of companies, as audits and inspections are usually made on the basis of active ingredient (i.e. its production line), not physical plant.

160 These costs are not reproduced in Annex 8, as they relate exclusively to the costs for third country manufacturers.

161 Taking account of costs for transfer of inspectors.

EU companies	$\frac{f*h*80\%}{3}+j=1.29\text{m EUR}$	$\frac{f*h}{3}+k=1.61\text{m EUR}$
Third country companies	$\left(\frac{a*i}{3}+\frac{a*b*c}{3}\right)*1\%=1\text{m EUR}$	$\left(\frac{a*i}{3}+\frac{a*b*c}{3}\right)=100.8\text{m EUR}$
Total increase: EU-companies: 0.3m EUR; Third county companies: 100m EUR		

2. Policy option n°4/1b

Costs for authorisation (incl. the necessary inspection)

There are approx. 1 000 API production lines (**a**) and 11 300 importers in the EU (**d**).

Fees for authorisation are 4 000 EUR (**b**).

Administrative costs (**c**) for authorisations are set out in Annex 8.

One-off costs would thus be:

$$(a+d)*b+c=59.532\text{m EUR}$$

Costs for subsequent inspections

The frequency of inspections would be approx. every 3 years. Fees for inspections are assumed to be similar to fees for authorisation.

It is assumed that, today 80% of all EU-API production lines but none of the importing sites are inspected by EU competent authorities.

Administrative costs for EU companies today (**d**) and with the policy option (**e**) are in Annex 8. For administrative costs for non-EU companies, refer to above.

Increase in annual compliance costs:

Costs today	**Costs of policy option**
$\frac{a*80\%*b}{3}+d=$ 1.3 EUR	$\frac{(a+d)*b}{3}+e=19.8\text{m EUR}$
Increase in annual costs: 18.5m EUR	

3. Policy option n°4/1c

Third-country manufacturers:

It is assumed that approx. 80% of the approx. 20 000 third-country API production line (**a**), i.e. 16 000 API plants, are not subject to regulation and enforcement of Community standard.

Accompanying inspectors[162] would take approx. 24 man-hours (**b**) at costs of approx. 5 EUR per hour (**c**). The frequency of inspections would be approx. every 3 years. To this add the fees for inspections by officials in the relevant third country (fees (**e**) are approx. 2 000 EUR).

Increase of annual compliance costs for third-country API manufacturers due to inspections (incl. administrative costs):

Costs today	$\left(\frac{a*b*c}{3}+\frac{e*a}{3}\right)*20\% = 8.16\text{m EUR}$
Costs (policy option)	$\frac{a*b*c}{3}+\frac{e*a}{3} = 40.8\text{m EUR}$
Increase in costs:	**31.84m EUR**

4. Policy options n°4/2a and n°4/2b

With regard to third country actors supplying the EU, notification by the approx. 34 500 third country manufacturers would cost them approx. 5 EUR per hour[163] and take approx. 10h. Costs would thus be 1.7m EUR.

There are approx. 700 manufactures (**a**) and 11 300 importers of API in the EU (**d**). Administrative costs are 4.2m EUR (cf. Annex 8).

5. Policy option n°4/3

Costs for a shared third party audit are in average approx. 12 000 EUR (**a**). This figure takes into account:

- the price differences between in-house audit and third party audit; and
- the fact that most audits would be performed in third countries (i.e. additional costs for transfer etc.)

There are approx. 21 000 API production lines (**b**) which would have to be audited every three years. Note that, according to industry information, audit is already widely undertaken. Industry suggests that, already today, 60% of all manufacturers (third country and EU), who place medicines on the EU market, audit sufficiently all their API-suppliers. Against this, it shall be assumed that 60% of all API supplier are sufficiently audited. With regard to third country manufacturers, they usually pass on costs for audit to the EU importer. On the basis of this, it can be estimated that

Additional annual costs for auditing (EU-) manufacturers and importers:

$$\frac{a*b*40\%}{3}\ 33.6\text{m EUR}$$

[162] These costs are not reproduced in Annex 8, as they relate exclusively to the costs for third country manufacturers.

[163] Cf. explanation for this rather low sum under point 1.

Increase of costs for the audited are largely to be born by API manufacturers in third countries, as EU-based API manufacturer are already audited regularly.

Annex 6 - Increase of counterfeit in the legal supply chain in the future: estimations and calculations

It is not possible to quantify how many counterfeit medicines enter the legal supply chain in the EU. Estimations could be based on extrapolations from national figures.

In view of the figures of counterfeit medicines detected in the Member States in 2007, and taking into account that these were 30% of all counterfeit packs detected, one could argue that there were in 2007 approx. 1.5m counterfeit medicinal products in the legal supply chain in the EU (**a_{2007}**), i.e. approx. 0.005% (i.e. 1 product out of 20 000) of all medicinal products.

On the basis of these figures, one could develop a baseline for the timeframe until 2020:

The "optimistic" baseline of non-action shall be that these are all the 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, **19.5m 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 (**a_{2020}**) the total number of counterfeit packs made available until then through the legal distribution chain as follows:

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

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 (**a_{2020}**) would be:

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

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

Annex 7 – Direct/indirect costs and other costs attributable to counterfeit in the legal supply chain: estimations and calculations

On the basis of the estimations above (Annex 6), one can establish the costs associated to non-action.

These costs depend as to whether the "optimistic", the "realistic" or the "pessimistic" baseline apply (cf. Annex 6).

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": $a_{2020} = \sum_{k=0}^{n-1} a_{2011}(1)^k = \mathbf{15m\ packs}$
- "realistic scenario": $a_{2020} = \sum_{k=0}^{n-1} a_{2011}(1+0.1)^k = \mathbf{35m\ packs}$
- "pessimistic scenario". $a_{2020} = \sum_{k=0}^{n-1} a_{2011}(1+0.3)^k = \mathbf{183m\ packs}$

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 EU[164]. 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 cancer.[165]

164 WHO (2005).

165 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 1.8bn EUR and 22bn EUR**.

- 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 31 EUR.[166] 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 93m EUR and 1.1bn EUR**.

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 used.[167] QALYs combine effects on life expectancy and quality of life within a single measure, with 1 QUALY 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 QALY.[168]

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 studies.[169] 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 60 000 EUR.[170]

On the basis of these assumptions, it can be estimated that the indirect costs of counterfeit medicines based on QALY are approx. 765m EUR 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 7.65bn EUR and 93bn EUR**.

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166 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.

167 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.

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

169 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.

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

Other quantifiable burdens:

- 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. 10m EUR. This would mean that a recall in the entire EEA-area costs business approx. 60–80m EUR.

- Costs for destroying seized counterfeit products which at present fall on the rightholder.

Annex 8 - Increase in annual administrative costs[171]

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Annual and one-off administrative costs for EU businesses discussed in the policy options					**Tariff (€ per hour)**		**Time (hour)**		**Price (per action or equip)**	**Freq (per year)**	**Nbr of entities**	**Total nbr of actions**	**Total cost (annually)**	**Total cost (one-off)**
Policy option in IA (present situation or policy option)	Type of obligation	Description of required action	Annual costs/one-off cost	Target group	i	e	i	e						
2/1 (policy option)	Notification	Filling forms	One-off	Traders	35		4,00		140,0		1.000			140.000
2/2 (present)	GDP inspection by competent authorities (CoCP compliant)	Filling forms, accompanying inspectors	Annual	Distributors	35		22,50		787,5	0,33	4.000	1.320	1.039.500	
2/2 (present)	GDP inspection by competent authorities (non-CoCP compliant)	Filling forms, accompanying inspectors	Annual	Distributors	35		15,00		525,0	0,33	16.000	5.280	2.772.000	
2/2 (policy option)	GDP inspection by competent authorities (CoCP compliant)	Filling forms, accompanying inspectors	Annual	Distributors	35		22,50		787,5	0,33	20.000	6.600	5.197.500	
3/2 (policy option)	Authorisation	Filling forms	One-off	Unlicensed Importers	35		4,00		140,0		1.100			154.000
3/2 (policy option)	Inspections	Filling forms, accompanying inspectors	Annual	Unlicensed importers	35		7,00		245,0	0,33	1.100	1.089	88.935	
4/1a (policy option)	Authorisation of EU incl. inspection	Filling forms, accompanying inspectors	One-off	EU API manufacturers	35		24,00		840,0		1.000			840.000
4/1a (present)	Inspection	Filling forms, accompanying inspectors	Annual	EU API manufacturers	35		24,00		840,0	0,33	800	264	221.760	
4/1a (policy option)	Inspection	Filling forms, accompanying inspectors	Annual	EU API manufacturers	35		24,00		840,0	0,33	1.000	330	277.200	
4/1b (policy option)	Authorisation, incl. inspection	Preparing, accompanying inspectors	One-off	EU API manufacturers and importers	35		24,00		840,0		12.300			10.332.000
4/1b (present)	Inspections	Preparing, accompanying inspectors	Annual	EU API manufacturers and importers	35		24,00		840,0	0,33	800	264	221.760	
4/1b (policy option)	Inspections	Preparing, accompanying inspectors	Annual	EU API manufacturers and importers	35		24,00		840,0	0,33	12.300	4.059	3.409.560	
4/2b policy option	Notification of EU manuf./importers	Submitting information	One-off	EU API manufacturers, importers	35		12,00		420,0		12.000			5.040.000

171 Wage rate is based on industry consultation with an overhead of 15%.

4/2b policy option	Notification of EU API distributors	Submitting information	One-off	EU API distributors	35		8,00		280,0		5.500	0	0	1.540.000

Annex 9 - Summary of responses to the public consultation document

1. Introduction

In response to the public consultation on "Key ideas for better protection of patients against the risk of counterfeit medicines"[172], the Commission received 125 contributions from stakeholders. Of these, 100 were from industry (pharmaceutical industry, distributors, suppliers of active ingredients, consultants), 15 from citizens, patient (groups), and academics, and 10 from health professionals, pharmacists and health insurers.

4 stakeholders (Eli Lilly, Bayer Healthcare, SICPA and Thornton & Ross Ltd.) requested their entire submissions to be treated confidentially. The other stakeholder responses have been published on the "pharmaceuticals - website" of the European Commission.[173]

Of the 125 stakeholder contributions, in terms of regions, 20 contributions were received from EU-wide associations, 30 from Italy, 14 from the UK, 9 from Germany, 4 each from France and Switzerland, 3 each from Poland and Ireland and the Netherlands, 2 each from Malta, and Denmark, 1 each from Austria, Sweden and Spain, and 18 from non-European third countries. 10 stakeholder contributions were global associations or could not be attributed in terms of region.

30 national and regional authorities profited from this stakeholder-consultation to inform the Commission of their views on the matter.

2. General remarks

2.1 Relevance

The initiative was unanimously welcomed by virtually all respondents who stressed that urgent and decisive action was needed, and that the problem of counterfeit is increasing exponentially.

Some respondents considered that the known cases were just the "tip of the iceberg", as in particular wholesalers and manufacturers are not keen on being related to counterfeit by media and the public. They argued that the problem is larger than anticipated and that discovery of cases is often pure luck. While it was repeatedly stressed that the situation could lead to "disaster", very little quantified information on the extent of the problem was given. One respondent (a wholesaler association) estimated that counterfeit packs represent "probably less than 1%" in one Member State.

A few respondents reminded of the need to stay rational and evidence-based – in particular regarding the lawful supply chain. One respondent argued that there is not

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172 http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2008/2008_03/consult_counterfeit_20080307.pdf

173 http://ec.europa.eu/enterprise/pharmaceuticals/counterf_par_trade/counterfeit_consult_2008.htm

necessarily increase in *counterfeits*, but increase in *surveillance*, including in the lawful supply chain.

While some respondents stressed that health considerations override the interest to mitigate compliance costs, others warned of an increase in bureaucracy and administrative burden. In this respect, it was opined that changes should not lead to an overhaul of the existing legal systems (rather, adapting some technical provisions) and that implementation times should be sufficiently long.

Some contributions highlighted the need to avoid unharmonised approaches across the EU. Others recalled that increased costs may be passed on to patients in second-round effects.

Various respondents highlighted the costs of counterfeit for industry and stressed that companies have anti-counterfeit strategies in place. In this context, the question was raised why industry should bear costs of counterfeit, rather than the society as a whole (i.e. the taxpayer). It was highlighted that, today, costs for destruction of counterfeit and recall of these products are in practice borne by the trademark owner.

The link to organised crime was stressed by several respondents.

2.2 Causes of problem

Practically all respondents agreed with the Commission's assessment of the causes of the problem and welcomed the comprehensiveness of the analysis, in particular the inclusion of aspects of active pharmaceutical ingredients ("**API**") quality/authenticity.

In particular, all respondents supported a "joint approach" with a bundle of measures, i.e. the look at different aspects. It was highlighted that U.S. FDA is following the same "multi layer" approach.

Finally, there was nearly unanimity that enforcement is a crucial element in the fight against counterfeit. This should entail the recall of licenses for non-compliant firms, penal sanctions, tighter checks at the outer borders of the EU and better information-sharing of customs authorities.

2.3 Other aspects

The public consultation was taken as opportunity to point at other, sometimes related aspects, such as the definition of "qualified person" (arguing that this person should be a pharmacist), the GDP guidelines (requesting a modernisation), pharmacies as buying groups, direct supply strategies (arguing that they encourage alternative sourcing, incl. internet purchase), the differing pace in Member States of approval of variations, the requirements for the "responsible person" (concerning wholesaling) and the illegal diversion into the EU of products destined for third country markets under favourable price regimes.

Several respondents highlighted additional aspects outside the scope of pharmaceutical legislation. These included, for example, assisting third countries with weaker regulatory/enforcement structure and a strengthening of criminal law measures against counterfeiters.

Many respondents pointed at the risks stemming from the *unlawful* supply chain, in particular internet pharmacies not complying with the requirements in the respective EU Member State(s). Some respondents entered a discussion as to whether internet pharmacies should be subject to a specific Community regulation and how. Others recognised that the main problem lies with dubious internet pharmacies established in third countries which are *de facto* accessible for EU-patients from within the EU but not controllable by Member States.

Some submissions raised possible links with the ongoing files "information to patients" and "pharmacovigilance".

3. Product protection measures and prohibition of their manipulation

3.1 Safety features

3.1.1 Technology

Regarding the present system of batch numbers, there was widespread agreement that batch numbers do not efficiently contribute to the fight against counterfeit, as the number of units within a batch can be enlarged and the number be replaced easily.

On the other hand, the vast majority of respondents pointed out that it would be premature, ineffective and even counter-productive to "prescribe" in secondary legislation (i.e. in a Directive adopted by the European Parliament and the Council) a specific safety/authenticity feature for medicinal products. The multitude of techniques and the need for flexibility was highlighted. Some respondents argued that the choice of a technology should be left completely to the manufacturer and that any technology has to be risk-adapted. Legislation should thus not be too prescriptive and further implementing legislation was needed.

On the other hand, several respondents stressed the importance to act quickly, as Member States are taking unilateral measures which would create considerable costs.

Finally, it was opined that any system would require thorough review after some years as well as a fall-back mechanism if it fails.

Turning to more concrete technologies, the following was observed:

3.1.1.1 Serialisation

There was almost unanimity that serialisation is in principle a useful technology to combat counterfeit. One respondent stressed that the tobacco industry is considering a similar technology.

On the other hand, the multiple technical and legal difficulties were highlighted. These would require a long period for implementation. The U.S. example shows this. Therefore, a stepwise approach (for example, first including certain high-risk products) would have to be considered (see below). On the other hand, some companies recalled that this approach would remove economies of scale.

Importantly, serialisation was highly supported by the research-based industry, but more critically assessed by the self medication and generics sector who argued that

their products had not been targeted by counterfeiters in the past and that costly product protection measures for those products would not bring additional benefits to the patient. Wholesalers and pharmacies showed a rather positive reaction to the concept of serialisation. This is crucial, as serialisation requires the involvement of many different actors.

Concerning verification, it was highlighted that pharmacies may use serialisation to facilitate inventory management.

Consumers should have a possibility to verify serialisation numbers via the phone or the internet.

Many submissions highlighted the international developments for example in the U.S. (in particular California) and in Turkey arguing that now was the ideal moment to build up a global harmonised approach.

Some submissions highlighted the data protection and competition issues which serialisation would rise.

3.1.1.2 Pedigree

Pedigree is a record of past ownership and transaction of a batch.

There were conflicting voices on the effectiveness of a pedigree. While some considered it as useful tool to back-trace (referring, for example, to similar aspects in the fresh meat sector), others argued that a pedigree does not add much to fight counterfeit.

In any case, it was widely stressed that a pedigree is a very complex solution and can only be considered as long-term aim – in particular if the system was to be automated. The U.S. example shows that very long implementation time is needed in order to address technical and financial obstacles.

Moreover, the high costs, which would be particularly burdensome for OTC-producers and SME, were highlighted. Several respondents recalled that a pedigree may affect negatively the throughput in warehouses.

Moreover, competition concerns were raised. The question as to who would have access to the pedigree database was characterised as “crucial”.

It was stressed that, in any case, use should be made of existing standards, such as the GS1 standard.

3.1.1.3 Others, incl. seal

Many submissions discussed the feasibility, effectiveness and efficacy of a seal in any form. Some criticised the concept of a seal as overly simplistic or “naïve”, adding costs without increasing security. Others criticised that efficient seals can only be verified by experts and that they would give a wrong feeling of safety. It was also stressed that the place where the seal is affixed (i.e. the product itself, the inner or the outer packaging) was crucial: A situation should be avoided where one “tracks cardboard, not product”.

On the other hand, a multitude of different concepts were presented which allegedly render counterfeit either impossible or uneconomical. These techniques included digital signature by asymmetric cryptography, colour-shifting dosages, watermark technology, chemical markers, flavour or aroma-adding, individual dosage level, DNA-coding, NIR-spectroscopy, electronic features, excipients tag, etc., etc.

It was stressed that seals were nothing new in the pharma sector and common practice in the food-and-feed sector. It was also highlighted that, in practice, a blister is a simple seal and that bottles often bear a seal "per se".

Some respondents stressed the need to ensure that a layperson (e.g. a patient) can identify the seal. Others, on the contrary, stressed that this would give a false feeling of security and that covert seals are preferable. Some highlighted that a combination of various technologies was needed.

The possibility of temperature-sensitive seals was considered to address also shortcomings in the cooled supply chain.

3.1.2. Scope

Many respondents discussed the scope of a safety feature. The large majority of respondents highlighted that an "intelligent", risk-based approach was needed for determination of the scope. For example, certain product groups should be primarily considered, such as injectables, expensive or high-volume medicines, or biotech medicines (which typically do not have a taste or colour).

The generics and OTC-producer challenged the argument that OTC products are equally affected by the problem. It was also argued that vaccines should be excluded in view of their peculiar distribution regime. The possibility of a "step-wise approach" was considered.

On the other hand, some respondents stressed that a limited scope would lead to confusion and that it would not allow exploiting scale effects. Moreover, it was argued that counterfeiters are very flexible and that it was difficult and even unrealistic to forecast a risk profile. The example of pandemic flue shows that risk profiles can change rapidly.

3.2 Prohibition of manipulation of safety feature

This item of the public consultation sparked many differing reactions and was the only item where views were fundamentally opposed amongst different stakeholders.

Holders of the original marketing authorisation stressed that it was vital that safety features (such as serialisation number or seals) which are affixed on the packaging cannot be removed or changed subsequently. They stressed that any effort in this respect was futile if the safety feature can be subsequently manipulated. Moreover, without a sealed package, there was a risk that a fake product is introduced into an (original) pack.

Many respondents pointed at the impact for re-packaging practices in the EU. This would concern, for example, re-packaging to ensure availability in small markets.

Moreover, respondents highlighted that parallel traders have to re-package or at least open the outer packaging in order to comply with the language and packaging regimes in the destination country. In particular parallel traders criticised that this key idea had been lobbied by the research based industry and would essentially be an attempt of putting parallel traders out of business.

Parallel traders also questioned the link between counterfeit and parallel trade. They argued that counterfeiters have no interest to pass via parallel traders who may, in the course of the re-packaging, detect the counterfeit earlier than a wholesaler. In this respect it was argued that, in fact, parallel traders provide for an additional safety net.

It was also argued that *if* safety features are contained on the packaging, parallel traders should be allowed to reproduce them and to reaffix them or to add their own safety features. In response to this, it was stressed that it was not realistic to require an originator to share safety-technologies with the many potential parallel traders.

In view of the potential negative impact on parallel trade, several respondents, including health insurers and some Member States authorities, highlighted its important role in ensuring intra-brand price competition for patented medicines thus leading to savings for health insurers and/or the exchequer. It was also argued that parallel traders are important to ensure a sustainable wholesale of medicines.

It was also stressed that OTC patients often wish to read the leaflet before purchasing the product, that pharmacists need sometimes to open the pack and that the possibility for patients with arthritic fingers to open packs should not be impaired. Finally, it was stressed that re-packaging is required for clinical trials.[174]

4. Distribution

4.1 General remarks

There was widespread agreement that today's distribution system constitutes a challenge in term of ensuring a counterfeit-free supply chain: There is a multitude of participants involved with an increasingly long distribution chain that changes often. In particular, the high number of interim traders ("brokers"), with little or no knowledge of the sector and the products was criticised. In this respect, several submissions stressed that "medicines supply is only as clean as its dirtiest link".

One interesting aspects, which had been raised by some respondents, was the idea to render reporting of counterfeit products obligatory for wholesalers.

4.2 Including more actors in scope of wholesalers

Against the background of these general comments, this measure was unanimously supported. The question focussed more on details and in particular on the question, which concrete actors should be included. In this context, distributors who only export, and brokers in third countries, were discussed.

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174 Note, however, that medicinal product for clinical trials are not within the scope of the Community Code for medicinal products (Article 3(3) Directive 2001/83/EC).

Some cautioned that a definition would have to be carefully drafted (also in view of the translations in the different official languages) and that mere transporting companies should not be included. Moreover, "trade" (i.e. transactions) within a company should not be covered.

It was outlined that not all actors can be subject to the same obligations and that a classification system for the different degrees of involvement was needed, so that inspections are adapted to the different actors.

On a different matter, one respondent highlighted that GDP should include rules on procurement of medicines.

4.3 Strengthen inspections

Here too, the important role of enforcement was highlighted. In this respect it was emphasized that the adoption of GDP as Directive would have limited impact, as it is already satisfactorily implemented in the Member States.

It was stressed that a better cooperation was needed, including avoiding duplication, coordination by EMEA, coordination at international level and strengthened inspections in third countries.

There were many suggestion how to render inspections more targeted and how to support them from the perspective of the Community legislator: Points raised concerned inspections of customs warehouses, revised Compilation of Community Procedures on Inspections and Exchange of Information ("**CoCP**") addressing, albeit in a flexible manner, wholesalers, obligatory CoCP also in third states, sunset clauses for GDP licenses and the possibility to restrict certain medicines to certain wholesalers and *vice-versa*.

It was stressed that administrative costs have to be considered and that, already today, inspecting competent authorities are sometimes understaffed.

One submission stressed that wholesaler certificates should be better protected against counterfeit.

4.4 GDP Database

This idea, too, was almost unanimously welcome as it would facilitate verification and bring an end to today's practice where wholesale licenses are simply copied to support alleged compliance.

Comments focussed on practical matters, such as who manages the GDP database and feeds it with data.

One submission suggested including in the database results of audits.

5. "Import for Export"

Here too, there was widespread support for the assessment of the problem and the measures envisaged. Existing difficulties, in particular in view of the recent case-law of the European Court of Justice, have been highlighted.

It was stressed that the food sector is considerably more advanced in addressing the issue.

Respondents highlighted in particular the need to have clarity with regard to "free zones" from the perspective of pharmaceutical law and rules regarding the interactions with customs. "Import" and "transit" should be defined for the purpose of pharmaceutical legislation.

Concerning substantial requirement, several respondents highlighted that a full batch analysis was not necessary if the exporting country had a functioning regulatory and surveillance system.

Several respondents recalled that large companies import their own products for export. They argued that, as there is a pharmaceutical quality system, re-testing should not be required.

Some respondents recalled that in practice, today, certificates from third country authorities are requested for imported consignments.

The importance to ensure correct storage conditions in customs warehouses was highlighted.

6. Active Pharmaceutical Ingredients (API)

6.1 General remarks

Regarding safety and authenticity, virtually all but one submission confirmed that the concerns set out in the public consultation document were justified and that the issue of counterfeit must not be restricted to the finished product.[175]

While one submission highlighted the need to also consider excipients, another submission called for an *ex*clusion of herbal substances from this debate.

6.2 API and enforcement, in particular in third countries

The unanimous view of the respondents was that Community provisions ensuring efficient enforcement are too weak, in particular with view to third country manufacturers. It was highlighted that, at present, the only very few Member States inspect outside the EU (these inspect approx. 20 plants per year).

With regard to checks by third country authorities it was argued that these work often with lower standards – in particular concerning exported substances. It was stressed that this situation has created a non-level playing field. One respondent estimated that a manufacturer who is Good manufacturing practices ("**GMP**") non-compliant saves approx. 25% of production costs. This situation is aggravated by strong competition in the active substances industry as well in the field of generic medicines.

[175] To characterise further the large approach, some submissions suggested referring to "rogue API", rather than "counterfeit API".

Some contributions argued that imports of API from countries with lower GMP standards should be banned and called for more aggressive and stronger enforcement. EMEA should get involved in inspections through coordination of work-sharing programs amongst Member States authorities. One submission contemplated a "European inspections team" for API. Moreover, duplication of controls by reliable third country inspections should be avoided and cooperation strengthened. This was particular relevant as inspections in third countries is not easily feasible for small Member States.

With regard of the quality of inspections, it was highlighted that these have to focus more on counterfeit aspects and that they should be based on a physical visit of the plant, rather than a check of documentation.

There were different appraisals of the contribution of GMP to combat counterfeit. Some considered GMP as "crucial". They argued that – while GMP-non-compliance does not make a product a counterfeit - counterfeit API are usually also severely GMP non-compliant. On the other hand, one submission argued that impaired quality has nothing to do with counterfeit.

Against the general claim of better enforcement, some respondents cautioned that manufacturer of medicinal products should continue to be held primarily responsible.

One respondent suggested that labelling of a medicinal product should include information on API.

More specifically, on authorisation and notification requirements the following was raised:

- Authorisation obligation: Many respondents did not explicitly address this point. Those who did supported an authorisation obligation in particular for third country manufacturer. This would lead to obligatory inspections rather than on inspections based on suspected "non-compliance".

- Notification obligation: Most respondents supported this point, highlighting that France has already introduced notification requirement for importers and distributors. Also, Italy is going to strengthen unilaterally its rules as of 1 January 2009. While respondents supported inclusion of distributors in the notification requirement, they spoke against a notification of each imported consignment.

6.3 Audits

Most respondents confirmed that audit is a very useful tool to increase compliance and to avoid "back-to-back" business. Only one respondent disagreed stressing that audits did not give an insight in the actual production process.

Some submissions reminded that auditors may be influenced by economical considerations. To address this, audits should be done by independent, qualified personal and Member State authorities should be somehow involved in the audit, for example through certification or accreditation.

Some submissions requested clear guidance as to the content of the audit and qualification of the auditor, while others stressed the need to maintain a flexible system, in particular concerning the frequency of audits.

A few submissions pointed at practical difficulties, such as access to the closed part of the drug master file. It was also stressed that the audited should agree to the audit.

It was highlighted that, currently, shared third-party audits are not very common. In order not to increase costs (in particular for SME), duplications of audits should be avoided, and an “audit database” was suggested.

One respondent stressed that package producers should be audited too.

7. Other aspects

Many respondents commented on the key idea, put forward in the public consultation paper, to apply “fingerprint techniques” in order to check the authenticity of the product. While this idea was in principle welcome, several submissions cautioned that it could not replace good process and supplier control. It was also stressed that technology evolves fast and that no definite technique should be fixed in Community legislation.