European Patient Safety and Parallel Pharmaceutical Trade

– a potential public health disaster?

European Alliance for
Access to Safe Medicines

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Dedication

This report is dedicated to all European patients who deserve to benefit from more informed healthcare policy. In particular, this report is dedicated to my Hungarian wife Szilvia and her family whose health has suffered because of ill-informed healthcare provision.

Disclaimer

This report reflects the opinion of the author based on the evidence and commentary he has been able to evaluate between June and November 2007. Whilst every reasonable attempt has been made by the author to access all relevant information neither the author, the publisher or the European Alliance for Access to Safe Medicines (the Alliance) can be held responsible for any material omissions that third parties may believe, in their opinion, should have been included.

> "There is no right to strike against the public safety by anybody, anywhere, anytime"
>
> (Calvin Coolidge 1872–1933 ex-US President)

Author's note

Having graduated in medicine and psychology in the UK and then worked as a junior doctor, with the inherent pressures, I suppose I should have been prepared for anything.

But, when I read every day about the political, social and public health problems perhaps unique to Eastern Europe at that time, my frustration boiled over and I felt that, given my skills, I had to do something.

In 1989, turning my back on the conventional career path, I left my National Health Service (NHS) job to go to the former DDR to – figuratively and practically – help break down their wall. Some might label this professional stupidity but it seemed the right thing to do.

Some time later, it occurred to me that I would be in a far better position to put my talents to productive use if I had a more rounded professional background. I returned to the UK and completed my MBA at the London Business School. As it happens, this benefited more than just my professional standing – it taught me much about life.

Thus equipped, the bulk of my professional life has been spent assisting developing countries in Eastern Europe and beyond, helping them to develop pharmaceutical regulatory systems. I found that by far the best way to do this was to live within these divergent societies, working on a daily basis with the people experiencing the very real frustrations of new and rapidly changing systems. The correct balance between

technical/market dynamics and social healthcare is an extremely difficult one. It has always and will always remain my goal and my priority.

If my name is known to the reader, it will probably be as a result of the report I wrote for the Council of Europe (CoE), in 2006. I came to write that report by pure chance – after 7 years living and working full time in Russia for the EC and other international donors to develop rational health and pharmaceutical policy in that country, I was working to establish a pharmaceutical regulatory system in Kosovo (having done so previously in Bosnia Herzegovina) when the CoE contacted me. They had been alerted to the counterfeit medicine problem in the Balkans. Being there, on the ground, every day, this wasn't exactly news to me and I felt that by writing the report for the CoE I could strike a blow against those profiting from the misery of that region's citizens. It was another opportunity to fulfil my joint objectives of improving healthcare systems while helping society.

Jim Thomson and I have presented together on several occasions and it was in Prague, at the 3rd Global Forum on Pharmaceutical anti-Counterfeiting, that Jim first mentioned to me that he intended to establish the European Alliance for Access to Safe Medicines. Again, this resonated with my own professional objectives and, when the Alliance approached me to write a report on Parallel Pharmaceutical Trade (PPT), I immediately realised that both the time and the subject were right.

In its current form, Parallel trade is a clear and present danger to the safety of every European patient and presents the opportunity to contribute towards a Potential Public Health Disaster in terms of under regulated pharmaceutical trade in Europe, against the background of the growing threat of counterfeit, adulterated and diverted medicines and medical devices globally. Moreover, with other regions and markets looking at PPT as a potential means to provide patients with much-needed medicines, there was no way I could allow the opportunity to pass to present the benefit of my experience. The Alliance asked me to provide a summary of a couple of pages – in effect to help with a position paper. Happily, the Alliance quickly realised that there was an opportunity to produce a much more detailed analysis and recommendations. My report is the result. It is my fervent wish that everyone reading this report will appreciate the need to take the twin elements of rational markets and public health, and tune them into harmony with one another. It is my ambition to see that happen, and where better to begin than with Europe.

Dr Jonathan Harper, Budapest, Hungary

"Parallel trade is a clear and present danger to the safety of every European patient."

(Dr Jonathan Harper)

Jim Thomson

Three and a half years ago, when I became involved in campaigning for safe medicines, the environment was very different. One of the most striking things back then was how few pharmaceutical companies acknowledged the existence of counterfeit medicines. A few enlightened companies were trying to act but, even then, very few felt that patient groups had any constructive role to play. Over those three and a half years, things have changed. Pharmaceutical companies, by and large, have accepted that the global community has a major problem with counterfeit medicines. They have also accepted that it's a problem they can't solve on their own.

When your mission is to raise awareness of a little-known phenomenon (which mine was when I started out speaking about counterfeit medicines) you will travel almost anywhere if it means that maybe even one more person will be aware of the dangers. I have spoken in some very unusual places. I have also met some truly inspiring people, some of whom have faced and continue to face, severe personal danger, in their commitment to the health and welfare of others.

One of the less unusual venues was a high-level conference in Washington DC. I mention it because it also happened to be the first of the two major milestones along the road that led to the formation of the EAASM. At that conference, I shared the platform with Dr Jonathan Harper. This was around the time that the US was first considering legalising personal importation of prescription medicines. The theory was that patients would be able to import cheap medicines from Canada. Many of these medicines would have originated in 'Europe'. Back then, I think that most Americans believed Europe to be bounded by the M25. When Dr Harper stood up and presented his report on the Council of Europe surveys, the room emptied. I thought this was pretty harsh – it had been a good presentation. Of course what I hadn't realised was that those leaving the room were, variously, lobbyists, Senators' assistants and PR people – hustling back to the Hill to spread the word. The importation bandwagon slowed somewhat for a while.

The second milestone was passed almost exactly a year ago. I was discussing the state of the safe medicines campaign in Europe with a number of friends and colleagues. My argument was that, frankly, we in Europe have the environment we deserve. Elsewhere, in far harsher conditions, people have succeeded in making a difference. In Nigeria, India, China, Malaysia, abject markets have been improved because of one thing; action. However, I had spent a lot of time and effort talking and was growing tired and disillusioned. After about 20 minutes, one of those present said, "Jim, shut up and do something about it."

Many different people, organisations and companies have come to the EAASM table in the year since that initial discussion. We have gone from being an idea, to being a voice for patients. Around our table we have many of the leaders in the campaign for safe medicines. In fact, pretty soon, we're going to need a bigger table.

Our focus is, and will always remain, patient safety. We have a clear vision of what must happen to protect European patients from the dangers of counterfeit and substandard medicines. However, we know that we will only realise that vision if we have clear strategies and if our collective effort is of the very highest standard. From the beginning, one of our main concerns has been with the inherent risks of the current European distribution system. When the EAASM decided that the necessary first step in improving the distribution system would be to produce a definitive report on the current environment, I remembered the effect Dr Harper's work had had on that audience in Washington. Dr Harper agreed to produce for the Alliance an independent view of the patient safety implications

of the distribution system. This report is the result. It will make uncomfortable reading for some. Indeed, some parts of it will make uncomfortable reading for the very same pharmaceutical companies who are among my colleagues in the Alliance. I have two comments on that. First, I trust them to act on what Dr Harper has to say in any way that they can. Second, they realise that, sometimes, criticism is a small price to pay for being part of an inter-sectoral, independent, solution to a problem that poses the biggest single threat to global patient safety. We have all come a very long way in those three and a half years.

Jim Thomson, Chair EAASM

Bill Newton Dunn

Counterfeit and substandard medicines represent a real and increasing threat to the safety of all Europeans. A recent report by the European Commission highlighted this, stating, 'The number of counterfeit medicines seized by EU customs authorities at European borders rose from 500,000 pharmaceutical items in 2005 to 2.7 million items in 2006'. As a member of the European Parliament, I believe that we must look at this issue very carefully and thoroughly evaluate all the evidence available – including this report. Everything I have examined leads me to believe that the European Parliament needs to strengthen and enforce current legislation to ensure that every European citizen has access to safe medicines that maintain and improve people's health.

There are many stakeholders who have important roles to play in protecting patients from counterfeit and substandard medicines and the Alliance aims to bring these stakeholders together under one banner – patient safety. I am therefore delighted to support the Alliance's objective of excluding counterfeit and substandard medicines from Europe. As part of their campaign, the Alliance has commissioned this report by Dr Jonathan Harper on European Parallel Pharmaceutical Trade and Patient Safety. Dr Harper is a leading authority on counterfeit medicines and the European distribution chain, and his report is highly informative. I was particularly concerned to see that there were four Class 1 Medicine Recalls by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK in 2007. The fact that counterfeits are reaching patients through their pharmacists has motivated me to do everything I can to prevent future breaches of the supply chain.

The following report makes a number of recommendations that I believe could make a real difference to patient safety:

- strengthen regulation of the European pharmaceutical supply chain, particularly concerning parallel pharmaceutical trade
- enact regulation stating that repackaging and relabelling of medicinal products destined for parallel trade should be conducted under the supervision of the original trademark holder
- introduce regulations addressing the fact that parallel pharmaceutical trade undermines technological measures designed to ensure supply chain security
- implement measures to achieve real pharmaceutical Good Distribution Practice.

It is my sincere hope, and that of the Alliance, that this report will act as a call to action for all the stakeholders who can reduce the danger of substandard and counterfeit medicines across Europe. It is time to ensure that everyone, including Governmental bodies, are doing everything within their power to guarantee patient safety.

Bill Newton Dunn, Liberal Democrat MEP

Katherine Eban

Zyprexa, Plavix, Casodex, Lipitor.

These are familiar and in some cases life-saving drugs used widely throughout the world. But when tens of thousands of packs entered the legitimate supply in the United Kingdom and were handed to patients by their trusted pharmacist, they were familiar in name alone. The packaging looked real, as did the pills themselves. But they were counterfeit, containing at worst no, or at best sub-standard active ingredients. They had not been licensed, had not gone through the rigorous clinical trials that doctors and patients rightly demand and, most importantly, were in no way, shape or form what their packaging suggested.

Their arrival has not just harmed patients. It has degraded their trust and ripped apart outdated assumptions about the safety of Europe's drug supply.

Counterfeit medicines in Europe. Until recently, those words summoned up images from the past, a cinematic past depicted in the movie version of The Third Man by Graham Greene. Set in post-war Vienna, the unscrupulous war profiteer Harry Lime sells diluted penicillin to the military, victimising children who fall ill or die.

That was drug counterfeiting in Europe then: exceptional and fictional. Today, Europeans have arrived at a crisis point that is all too real.

The report by Dr Jonathan Harper shows that counterfeit drugs are widespread throughout the European Union. Among the report's findings: Last year, seizures of counterfeit medicine almost quadrupled from 2005. And between 2001 and 2005, 197 separate cases of counterfeit medicine were identified in Europe's drug supply.

Counterfeits have penetrated drug supplies once presumed to be safe, like the United Kingdom's and Holland's. And they have not been the work of a single profiteer able to exploit desperation. They spring from the burgeoning business of counterfeiting and enter the legitimate drug supply through the most routine mechanism of Europe's new economy: parallel trade.

Wholesalers in poorer southern European countries have effectively become the new Harry Limes of the European marketplace. They sell their dangerous wares upstream from lower-priced markets within the European Union to costlier ones. As counterfeits pour into health systems once considered sacrosanct, regulators such as the MHRA are virtually powerless to detect them. Mostly, these dangerous drugs announce themselves after-the-fact: once patients have taken them to potentially tragic effect. With restrictions on parallel trade set to lift for the new EU Member States, the situation can only become more dangerous.

With perfect fakes and hidden victims, how can Europe stem the tide? As of now, the MHRA has yet to tell the British public not only how much counterfeit medicine it recovered but, more importantly, how many 'dangerous doses' are still out there. Dr Harper argues that ideally, regulators should know and should be able to tell patients. However, Europe's convoluted distribution system makes this impossible. Today, Europe's citizens get medicine that may have passed through 20 different hands, through countries with different languages and licensing systems, sporadic reporting and minimal enforcement. For the Harry Limes of the new marketplace, it's a dream come true.

In the United States, some of our politicians naively assume that medicine from European and Canadian markets can be the solution to our price problem – safe affordable medicine from supply chains we can trust. Some have even gone so far as to suggest that counterfeit drugs are a good thing. "You may call them counterfeiters, I would call them entrepreneurs…. The net result for the consumer is exactly the same," a congressman from Minnesota stated during a congressional hearing in 2005.

The champions of so-called reimportation ignore two things. There is no such thing as a safe supply chain – or a counterfeiter you can trust.

I spent three years investigating America's drug supply, which many had assumed was the world's safest. The result was my book 'Dangerous Doses: A True Story of Cops, Counterfeiters and the Contamination of America's Drug Supply' (Harcourt, 2005).

What I learned was almost enough to drive me from the drugstore. America's medicine routinely passes through a grey market of middlemen, who buy and sell to one another in frenzied all-hours trading. This minimally-regulated trade has drawn narcotics traffickers and organised criminals, who handily obtained state licences as drug wholesalers. The result is that the supply we once trusted is now riddled with counterfeit, adulterated, mishandled and expired medicine.

What Dr Harper's report has identified is that Europe's parallel trade effectively replicates America's frenzied medicine auction – and is equally unsafe. In May and June of 2007 in the United Kingdom alone (which is presumed to have Europe's most tightly-regulated market) there were four separate cases of counterfeit medicines reaching patients through parallel distribution.

Dr Harper's report is a must-read for European lawmakers and American policy-makers would do well to take note: we have enough of our own counterfeit medicine, and should not be re-importing anyone else's.

Katherine Eban, author of *Dangerous Doses*

> "In the United States, some of our politicians naively assume that medicine from European and Canadian markets can be the solution to our price problem – safe affordable medicine from supply chains we can trust. Some have even gone so far as to suggest that counterfeit drugs are a good thing. "You may call them counterfeiters, I would call them entrepreneurs…. The net result for the consumer is exactly the same," a congressman from Minnesota stated during a congressional hearing in 2005."
>
> (Katherine Eban)

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EXECUTIVE SUMMARY

The timing and content of this report has been stimulated by a number of factors relating to EU pharmaceutical supply chain security concerns, the EC single European market consultation process and forthcoming closure of parallel pharmaceutical trade (PPT) new Member State derogation.

PPT refers to the process where pharmaceutical products that are available in one country are exported and resold in another country for a higher price by an intermediary. The practice occurs outside the manufacturer's or its licensed distributor's formal channels.

The subject of PPT in Europe is now courting increasing attention and controversy and there are no signs that the debate is about to end soon. Arguments for and against seem to continue to be delivered exponentially, in particular respectively from the European pharmaceutical parallel traders association and the research-based manufacturing industry. This situation is likely to escalate in view of the forthcoming closure of the PPT derogation agreement between the old and new Member States.

This report provides a critical examination of PPT in the EU/EEA and attempts to look at the issue from the point of view of ultimate patient safety and benefit. The subject of PPT is a highly complex topic involving the interplay of many factors against the background of tension in attempting to achieve a single EU pharmaceutical market.

To date, the main academic and policy arguments have focused on the economic issues of PPT, but the time has come to analyse the topic in a broader context, which involves a number of factors in addition to pure health economics. In order to make a full cost/benefit calculus of PPT, the factors that require examining include:

(i) the context of PPT in terms of contributing towards the achievement of the 'single European pharmaceutical market'
(ii) the concept of 'artificial partitioning of the market' with respect to European pharmaceutical trade, pharmaceutical purchasing and pharmaceutical consumption
(iii) the drivers of PPT that relate to EU healthcare subsidiarity, the national differences in European pricing and reimbursement systems and the economic incentives employed
(iv) the impact of the forthcoming new Member State derogation closure on overall EU PPT
(v) counterfeit medicines and European pharmaceutical supply chain security
(vi) the legal and regulatory situation applicable to PPT in terms of weaknesses and costs
(vii) the options open to the research-based pharmaceutical industry to circumvent PPT
(viii) the issues of medicines safety, ultimate patient safety and health consumer choice; and
(ix) the level of information available to stakeholders to enable informed opinion.

A note on conclusions:

Several conclusions can be made concerning the functioning of the European pharmaceutical market in general and European PPT specifically. In terms of general conclusions, the European pharmaceutical market can be said to be suffering from the 'Potential Public Health Disaster' syndrome of 'invisibility, biohazard and system failure', particularly with respect to distribution chain regulation and supply chain security. The EU has undergone a lot of recent stress as a result of its enlargement process which impacts

on the way the European pharmaceutical market works. The EU has made some progress in attaining its objective of achieving a single European pharmaceutical market in certain areas, but there are still many pre-existing and emerging challenges to confront.

These include the need to: (i) rationalise the divergence and inefficiencies in the European pharmaceutical pricing and reimbursement system; (ii) effectively manage European pharmaceutical supply chain complexity and security with adequate attention to both the human and technological elements; (iii) have better European stakeholder coordination on drug safety; (iv) have better medicinal product safety reporting systems that motivate and allow full participation of all stakeholders; and (v) introduce some meaningful concepts and definitions concerning drug safety that all stakeholders can understand simultaneously, particularly the patient (or healthcare consumer).

Specific conclusions on the PPT business can be divided, respectively, into those in favour of and those against PPT. In favour of PPT are the arguments that: (i) PPT provides real health consumer savings; (ii) it provides a mechanism for European pharmaceutical price arbitrage; and (iii) that the new Member States have the right to participate in this system. The case in favour tends to rely on health economic arguments, however the available evidence shows that PPT provides marginal health economies at best.

The arguments against PPT cover several inter-related areas which can be summarised as follows:

(i) the value added goes largely to intermediary traders

(ii) the practice exploits the inefficiencies and rigidity in the European pricing and reimbursement system

(iii) PPT is not a driver of European pharmaceutical price convergence. PPT is driven partly by targeted incentives employed by national health purchasing authorities and results in the import of cost control systems from other countries

(iv) the existing legal and regulatory framework governing PPT in the EU/EEA is imprecise and implemented highly divergently at a national level

(v) PPT creates additional regulatory cost and burden both to regulatory authorities and original manufacturers which is out of scale in relation to the benefit that PPT arguably provides

(vi) PPT combines pharmaceutical manufacturing with the distribution business ('pseudo pharmaceutical manufacturing')

(vii) the PPT distribution network complicates the already highly complex European pharmaceutical supply chain (which has the potential to become convoluted further by the complex interaction between PPT and personalised medicine trading – ie, internet and mail order pharmacy). PPT in active pharmaceutical ingredients (APIs) has to be an area of major regulatory concern

(viii) the practice of repackaging and relabelling undermines supply chain security. There is increasing evidence that PPT acts as an entry point of counterfeit medicines into the legitimate pharmaceutical supply chain

(ix) PPT leads to product shortages in the exporting national market which undermines the requirement for ensuring continuous pharmaceutical supply

(x) the forthcoming PPT 'derogation closure' with the new Member States is likely to complicate the European supply chain further, increasingly undermining supply chain security, as well as adding to the escalating tensions between certain stakeholders

(xi) PPT can legally be circumvented by the original manufacturer

(xii) PPT adds to the existing weaknesses in the system of global drug safety

(xiii) in the absence of effectively implemented Good Distribution Practice (GDP), PPT is often managed as a non-transparent business activity

(xiv) PPT has the ultimate potential to undermine patient safety, while patients have little knowledge of the practice. In addition to the threat of counterfeit medicines, there are issues concerning the confounding of patient and dispenser with therapy.

It should be noted, however, that some criticisms can be made against the European research-based pharmaceutical industry in terms of contributing to 'artificial partitioning of the market' and lack of effort towards achieving a single European pharmaceutical pricing system.

From an examination of the areas covered by this report, it is possible to construct a calculus on the benefit or otherwise of PPT to the patient. Although some key areas of evidence are missing, a summary of the available evidence suggests that the practice of European PPT does not ultimately benefit the patient.

Finally, in the context of ultimate patient safety, a number of recommendations can be made both in terms of general pharmaceutical market functioning which impacts on the issue of European PPT, as well as specific recommendations that address the problem of European PPT in the context of pharmaceutical supply chain security.

General recommendations that impact on European PPT:

1. Create an EC action plan that achieves a real single European pharmaceutical market
2. Define and implement good pharmaceutical regulatory practice in Europe
3. Further conceptualise, define and address 'artificial partitioning of the market'
4. Achieve European national pricing and reimbursement system convergence and transparency
5. Rationalise and coordinate national demand and supply incentives employed to achieve cost-effectiveness of pharmaceutical consumption
6. Centralise European drug safety reporting system including database of 'product defects'
7. Adopt technological solutions to supply chain security issues
8. Define and institute the concepts of 'drug safety', medicinal 'product defect', 'pharmaceutical crime', 'counterfeit medicine' and 'supply chain security'.

Specific recommendations concerning European PPT and pharmaceutical supply chain security:

1. Formalise European consultation process on PPT
2. Rationalise and simplify the European pharmaceutical distribution system – the right of original manufacturers to secure their product supply chain
3. Full audit of the European pharmaceutical supply chain
4. Create a centralised European database and Geographic Information System of pharmaceutical distributors, which all stakeholders can access
5. Implement measures to achieve pharmaceutical Good Distribution Practice (GDP) in Europe
6. Review and codify EC case law on PPT
7. Strengthen regulation of the European pharmaceutical supply chain (with particular regard to PPT) at EC and national levels
8. Ensure that national Member State regulatory authorities have the capacity to regulate the supply chain and are implementing EC guidance and regulations on PPT fully
9. Prohibit 'de-boxing' – PPT undermines technological measures to secure supply chain security
10. For public safety purposes, restrictions can be potentially imposed on the freedom of movement of pharmaceuticals within the EU/EEA territory
11. Patient involvement and empowerment measures with respect to PPT and related drug safety
12. Further studies to obtain more evidence to inform policy.

INTRODUCTION

This report and its timing has been stimulated by a number of factors, namely: the increasing number of counterfeit medicine cases reported in the EU legitimate and illegitimate supply chains, recently instigated EC reviews (of the single pharmaceutical market and the problems of counterfeit medicines and PPT) and the forthcoming expiry of new EC Member State derogation from PPT.

The subject of PPT in Europe is now courting increasing attention and controversy and there are no signs that the debate is about to end soon. Arguments for and against seem to continue to be delivered exponentially and repetitively, in particular respectively from the European pharmaceutical parallel traders association and the research-based manufacturing industry.

To date, the main academic and policy arguments have focused on the economics of PPT; a subject still to be resolved, given that the methodology to make a satisfactory analysis is far from universally agreed and there are continuing major methodological disagreements between the academic institutions that study the topic.

Irrespective of pure economic arguments for and against PPT, there are many other issues of equal importance that should be brought into the equation (eg cost/benefit calculus) in order to enable an informed and evidence-based discussion of the benefits or otherwise of PPT in Europe.

In this regard, the ultimate question is, does the patient benefit from the practice of PPT?

This report attempts to look at the entire issue of PPT in Europe by providing an overview and analysis of: (i) the practice of PPT and reasons for its existence; (ii) the background of the single European pharmaceutical market; (iii) the current economic, trade, legal, regulatory and public health arguments; (iv) the European pharmaceutical distribution system and supply chain security, particularly with respect to the threat of medicines counterfeiting; and (v) the issue of new EC Member State derogation from PPT in the context of European supply chain security.

This report is written in a way that observes the issue from the perspective of the European patient.

"The subject of PPT in Europe is now courting increasing attention and controversy and there are no signs that the debate is about to end soon. Arguments for and against seem to continue to be delivered exponentially and repetatively"

European PPT: definitions, legal basis and regulatory framework

Definitions

Acceptable definitions and descriptions relating to parallel pharmaceutical trade come in a number of forms and are summarised as follows:

(i) Parallel pharmaceutical importation

'Parallel importation of a medicinal product is a lawful form of trade within the Internal Market based on article 28 of the EC Treaty and subject to the derogations provided by article 30 of the EC Treaty[1]. *Parallel imports* are products imported into one Member State from another and placed on the market in the destination Member State, outside the manufacturer's or its licensed distributor's formal channels. Parallel importation tends to occur when price levels for similar products between two Member States are significantly different, either as a result of national regulations or of manufacturers' policy. That creates an incentive for traders to buy products in the Member State where they are priced lower and sell them in the Member State where they are priced higher, at a price which allows the trader to make a profit.' *(EC Commission Communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted – COM/2003/0839 final, hereinafter called EC 2003 Communication).*[2]

(ii) Parallel pharmaceutical distribution

The European Medicines Agency (EMEA), in its Post Authorisation Guidance on Parallel Distribution document, uses the term *parallel import* for EU nationally-authorised medicinal products and the term *parallel distribution* for centrally-authorised medicinal products.[3]

(iii) Pharmaceutical parallel trade

'Parallel trade in the pharmaceutical industry refers to the process where pharmaceutical products available in one country are exported to and resold in another country for a higher price by an intermediary. Global parallel trade is not permitted. However, in Europe, it is legal for companies to parallel trade pharmaceutical goods between European Economic Area (EEA) countries as part of the EU's objective to integrate Europe into a single market. The standard route for parallel-traded drugs in Europe involves a trader or distributor purchasing drugs from one wholesaler and reselling them to a wholesaler in another country.' *(Datamonitor).*[4]

(iv) Drug re-importation

In the US, the term re-importation is used for parallel pharmaceutical trade. The one-sided terminology used in the US with respect to parallel pharmaceutical trade is perhaps not surprising in view of the fact that the US is the most expensive pharmaceutical market in the world for prescription medicines (thus the US is not an exporter of cheap prescription medicines). As the US is the largest developer of original innovative medicines, the high expense of prescription drugs in the US is perhaps understandable.

According to Datamonitor[4], 'it is technically illegal to import prescription drugs into the US from foreign countries, either commercially or for personal use, although there are two main exceptions to the rule. Firstly, a company can manufacture its drugs at foreign FDA-approved plants and import these products if they adhere to FDA standards. Secondly, drugs that are exported from the US which have been manufactured at an FDA-approved plant and approved in the US, adhering to FDA regulations and standards, can be reimported by the original manufacturer under proper controls and in compliance with regulations. This is often referred to as re-importation.'

For the purpose of this report, we use the abbreviation PPT, as the report addresses both the import and export of parallel traded products in the context of the EU/EEA as a whole and does not make a distinction between the parallel pharmaceutical trade practices resulting from EC central and national marketing authorisation procedures.

Legal basis

The legal basis of PPT in the EU is founded upon the fundamental principle of the free movement of goods (Article 28 EC, Article 30 EC and exhaustion of rights) of the EC Treaty. To support the application of this principle, there are laws on anti-competition (Article 81 EC and Article 82 EC) which restrict the action an Intellectual Property Rights (IPR) owner can take to limit PPT.

Article 28 EC states: 'quantitative restrictions on imports and all measures having equivalent effect shall be prohibited between Member States'. Article 30 states: 'Article 28… shall not preclude prohibitions or restrictions on imports, exports or goods in transit justified on grounds of… the protection of industrial or commercial property. Such prohibitions or restrictions shall not, however, constitute a means of arbitrary discrimination or a disguised restriction on trade between Member States.'

Regulatory framework

The current regulatory framework for governance of European PPT is based on:

1) EC-level pharmaceutical sector regulations and guidance is summarised as follows:

   (i) *Commission Communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted (COM/2003/0839)* – and which updates the original 1982 communication on the same subject

   The 2003 Communication states that parallel importation of a medicinal product is a lawful form of trade within the Internal Market based on Article 28 of the EC Treaty and subject to the derogations regarding the protection of human health and life and the protection of industrial and commercial property, provided by Article 30 of the EC Treaty. This Communication has been developed largely as a result of EC case law

   (ii) Directive 2001/83/EC on the Community code relating to medicinal products for human use (as amended by Directive 2004/27/EC)[5] – Article 76 Notification provisions; Article 81 Continuous supply provisions

   (iii) EMEA Post-Authorisation Guidance on Parallel Distribution. Release for Consultation. EMEA/Ho/2368/Rev 4 (19 July 2006)[3]

   (iv) Council Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[6]

   (v) Council Regulation (EC) No 953/2003 of 26 May 2003 to avoid trade diversion into the European Union of certain key medicines[7]

   (vi) Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)[8*]

2) Individual Member State interpretation of the EC regulations and guidance:

   In principle, it is incumbent on the Member State regulatory authorities to interpret and put in place their own national guidance in accordance with the provisions laid down at EC level. It is beyond the scope of this report to present a full listing of how, and if, individual Member States have put in place their own guidelines concerning the national regulation of PPT.

PPT and the context of the single European pharmaceutical market

In order to understand the issues surrounding European PPT, one should have an understanding of the background to the single European pharmaceutical market. The EC 1998 Communication on the Single Market in Pharmaceuticals from 1998[9] (hereinafter referred to as the EC 1998 Communication) addresses the issue of completing the single market so as to provide an environment which is favourable for pharmaceutical innovation and industrial development and also to improve patient choices in pharmaceuticals of the required quality, safety and efficacy at affordable cost.

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* Good Distribution Practice (GDP) is that part of quality assurance which ensures that products are consistently stored, transported and handled under suitable condition as required by the marketing authorisation (MA) or product specification.

The EC 1998 Communication states further that: 'The efforts undertaken for the completion of the Single Market in pharmaceuticals must take into account the particular features of this sector: a research-based global for-profit industry; the traditional functions of demand split between the patient; the prescribing doctor and social security institutions meeting most of the cost as third-party payers; little private market provision, and high consumer expectations that they will have access to the benefits of medical advances at affordable cost.'

These efforts must also be consistent with the principle of subsidiarity: Member States have exclusive responsibility in the field of healthcare: they view both the provision of health and its financing as key to social solidarity; and they have to meet public expenditure objectives, notably for the purpose of European Monetary Union. The EC 1998 Communication sets out 'the totality of the regulatory, social and industrial interests in play, in order to ensure that patients and consumers have access to the pharmaceuticals they need at affordable cost on the one hand and that appropriate incentives are available for innovation and industrial developments on the other.'

The EC 1998 Communication recognises the existence of the challenges (as interpreted and summarised as follows) in order to achieve a single European pharmaceutical market:

- *Macroeconomic conditions.* Significant differences exist between EU Member States in general macroeconomic conditions (especially per capita income and wealth)
- *Health systems.* Significant differences exist between EU Member States in health systems
- *Healthcare expenditure.* Differences in healthcare expenditure per capita between Member States appear to be greater than those in incomes per capita (probably due to significant differences in pharmaceutical demand)
- *Pharmaceutical expenditure.* Within the EU, this is highly skewed towards a limited number of major markets and hence the two largest (Germany and France) account for just over half the total EU market, and the largest four (Germany, France, Italy and the UK) account for nearly 75% of the total
- *Pharmaceutical pricing and reimbursement.* The EC 'Transparency directive'[10*] and differences between Member State pharmaceutical pricing and reimbursement systems
- *Pharmacoepidemiology.* Marked variances exist in the prevalence and incidence of major diseases, the medical practices and treatments that address these diseases and differing pharmaceutical demand patterns. The nature and extent of use of in-patent, out-of-patent and non-prescription medicines varies significantly among Member States. In particular, the use of generic products varies considerably according to how Member States arrange the financial incentives within their healthcare systems for the supply, distribution and use of generics
- *Pharmaceutical distribution.* The cost of pharmaceutical distribution, including wholesale and retail pharmacy distribution differ widely among Member States. Together with variations relating to medicines under indirect taxation rules, these costs impact on pharmaceutical budgets significantly
- *Pharmaceutical regulation.* Due to difficulties and complexity of interpretation, there is diversity in the ways in which pharmaceuticals have been regulated within different healthcare systems, particularly regarding regulation which is supervised by 'soft law' (ie, 'guidance' documents as opposed to 'regulations')
- *Legal issues.* There is concern about the interaction between European and national regulation of the pharmaceutical sector in general and the specific issue of PPT.

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* EC Directive 89/105/EEC of 21 December 1988 'relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems'.

The EC 1998 Communication summarises the incomplete agenda with respect to creating a single EU pharmaceutical market as follows:

'… whilst it is clear that the responsibility for the funding, management and organisation of the healthcare systems is one that is firmly within Member State competence, there are aspects to the operation of these systems that relate to a wider European Union agenda, notably in respect of the contribution that free movement of goods makes towards the creation of the Single Market. Of wider relevance still is an industrial policy concern that some of the mechanisms by which the financial viability of the healthcare systems is assured may unnecessarily distort the operation of the market leading to a reduction in the competitiveness of this sector in a global context.'

'The key remaining issues relating to the completion of the Single Market in pharmaceuticals are thus largely ones within Member States' competence. Member States and the Commission have a primary concern with the improvement of public health and with ensuring that patients and consumers have wide access to pharmaceuticals at affordable cost; these priorities have in turn to be reconciled with public expenditure objectives. Measures adopted for the completion of the Single Market must therefore be consistent with the principle of subsidiarity. Solutions will be found largely within the healthcare systems which are – and are set to remain – widely divergent.'

On the issue of EU PPT, the EC1998 Communication makes the following statement:

'To the extent that price fixing by Member States results in the establishment of widely divergent prices, conflict can exist between the operation of price fixing mechanisms and the Single Market. Wholesale intermediaries buy products in lower-priced parts of the European Union and sell them in higher-priced parts of the Union. In an effectively integrated market, the prices of tradable goods tend to converge towards a situation where arbitrage is no longer an issue; in this sector, since maximum prices are fixed in many Member States, the price convergence pressure on products already in the market will be towards lower prices, at least for out-of-patent products.'

Unless parallel trade can operate dynamically on prices, it creates inefficiencies because most, but not all, of the financial benefit accrues to the parallel trader rather than to the healthcare system or patient. However, parallel trade must equally be seen as an important driving force for market integration and, consequently, for achieving the Single Market. In as far as the market structure does not provide for the financial benefits of parallel trade to be passed on to consumers and taxpayers, this can normally be ensured through adequate national measures.

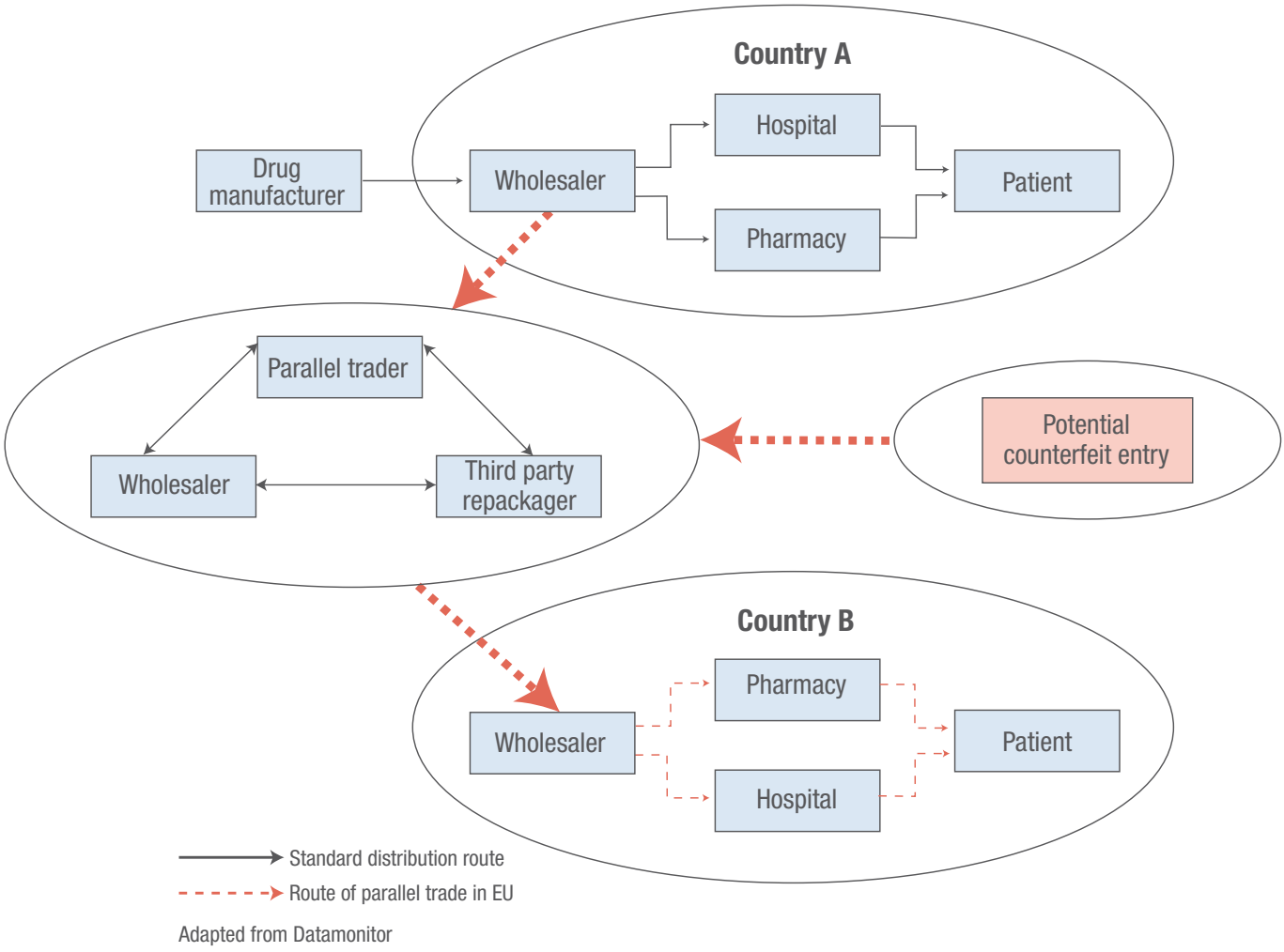
Parallel trade has also, to an important extent, been stimulated by price differentials created by currency fluctuations. European Monetary Union is therefore an important step in reducing the risk of price distortions. For those Member States that participate in the Euro, currency movements after market launch and the considerable effect that these fluctuations have had on parallel trade will be a thing of the past.

The concern about the interaction between European and national regulation of this sector (pharmaceuticals and parallel trade in pharmaceuticals) is not new. There have been a number of cases in the European Court of Justice seeking to establish whether price fixing by Member States is compatible with the free movement of goods in the European Union. The Court has noted that price control systems, although not in themselves contrary to the principle of free movement of goods, may nevertheless be considered as such when the prices are fixed at a level such that the sale of imported products becomes either impossible or more difficult than that of domestic products.'

The European pharmaceutical distribution system

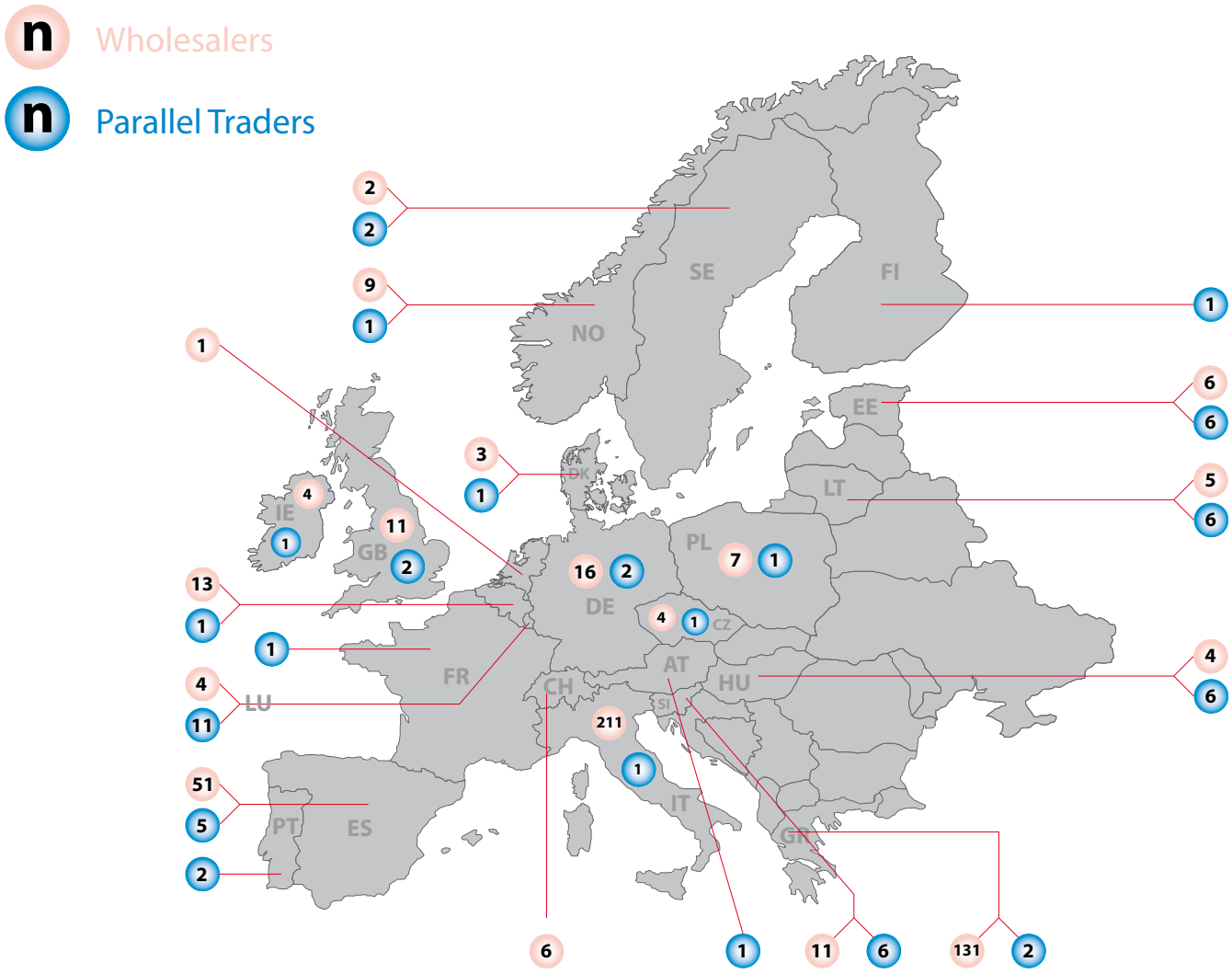
The European pharmaceutical distribution system for finished medicinal products (FPs) – notwithstanding the likelihood of the situation being complicated even further concerning trading of raw manufacturing materials (APIs, excipients, packaging and labelling) and intermediate production forms (Bulk Intermediate Products) that go to make up FPs – is extremely complex with an array of full-line cross-Europe pharmaceutical wholesalers, national full-line wholesalers, secondary wholesalers, short-line wholesalers/ pharmacy wholesalers and parallel traders. The variety of different business types involved in pharmaceutical trade is a menagerie.

Figure 1 – The parallel pharmaceutical trade system



Adapted from Datamonitor

Figure 2 – Mapping the European pharmaceutical distribution system



Source: European Association of Pharmaceutical Full-Line Wholesalers and
The European Association of Euro-Pharmaceutical Companies (EAEPC),

Figure 1 provides a simplified overview of how the European pharmaceutical system works. Figure 2 attempts to provide a map of the wholesalers and parallel trader in the distribution system. However, only the most well known companies are listed as there are very few records available.

The European pharmaceutical distribution system is made yet more complex by the rapidly increasing number of Member States; added complications are likely to intensify once the new Member State derogation from PPT expires. Arguably, the EU is expanding faster than its ability to cope with securing its internal and external pharmaceutical supply chains.

There is no obligation for any licensed pharmaceutical wholesaler to hold membership of any recognised association. Most short-line wholesalers and/or small parallel traders do not belong to any trade association. However, at European level there are currently two major associations for pharmaceutical wholesalers:

1. European Association of Pharmaceutical Full-Line Wholesalers/*Groupement International de la Repartition Pharmaceutique* (GIRP)
2. The European Association of Euro-Pharmaceutical Companies (EAEPC), which represents the European parallel pharmaceutical traders.

GIRP – the umbrella organisation of pharmaceutical full-line wholesalers in Europe. Founded in 1960, GIRP represents the national associations of over 600 pharmaceutical full-line wholesalers serving 32 European countries, including all major pan-European pharmaceutical wholesaling companies. Members employ approximately 140,000 people and distribute medicines with an annual value of over €100 billion.

'Full Members' are the national associations of pharmaceutical full-line wholesalers in each European country as well as three pan-European companies and a cooperative uniting six European countries. There are two other classes of membership – the 'Associate Professional Member' (full-line pharmaceutical wholesalers and members of their national association, who also wish to have direct representation) and the 'Associate External Members' (who may be companies or organisations whose business interests are related to the pharmaceutical industry and its distribution). These latter members do not need to be based in Europe.

Members of GIRP are required to: (i) carry a full range of products continuously; (ii) ensure continuous product availability to patients within a matter of hours; (iii) create and maintain quality standards that ensure the safety and integrity of the medicine when delivered to the retail pharmacist.

EAEPC – is the representative voice of pharmaceutical parallel distribution in Europe. Through national association or individual company membership it encompasses over 70 firms from 18 countries in the EEA. The EAEPC states that all products handled by their members have EU or national regulatory approval, are 100% safe and are sourced exclusively from, and sold to, EEA countries using authorised channels.

PPT activity in the EU/EEA

PPT in Europe appears to have commenced circa 1983/1984 following the publication of the first EC Communication in 1982 on the practice. Certainly, parallel pharmaceutical importation into the UK began in 1984.

The exact value of PPT within the EU is difficult to measure, though most current estimates put the extent of PPT in the region at between 2% and 3%. The following figures provide the best estimates which are derived and compiled from several sources:

Figures on European PPT

Figure 3 EFPIA data on European parallel pharmaceutical trade (EFPIA in figures 2007)

According to EFPIA, parallel pharmaceutical trade was estimated to amount to €4,100 million (value at ex-factory prices) in 2005.

Share of parallel imports in pharmacy market sales (%) 2005 :

Denmark	– 15.7%
Finland	– 1.9%
Germany	– 5.9%
Netherlands	– 11.5%
Norway	– 8.2%
Sweden	– 13.9%
UK	– 14.5%

Source: EFPIA member associations

Figure 4 Parallel trade rose substantially in Europe between 1998 and 2002, particularly in the UK, Sweden and Germany

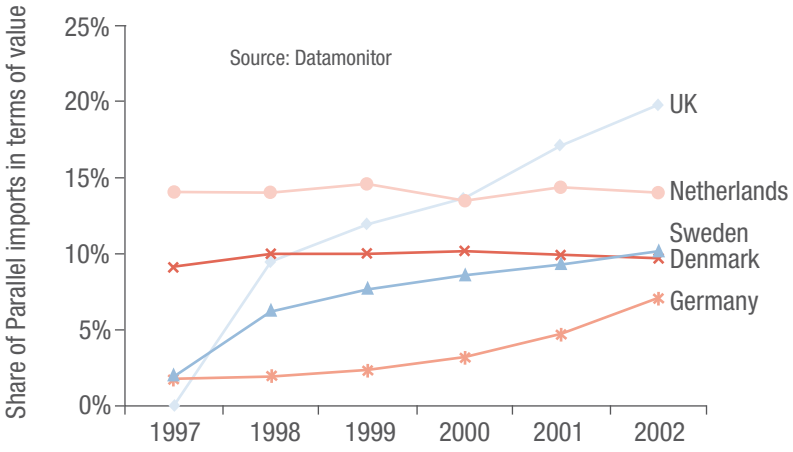
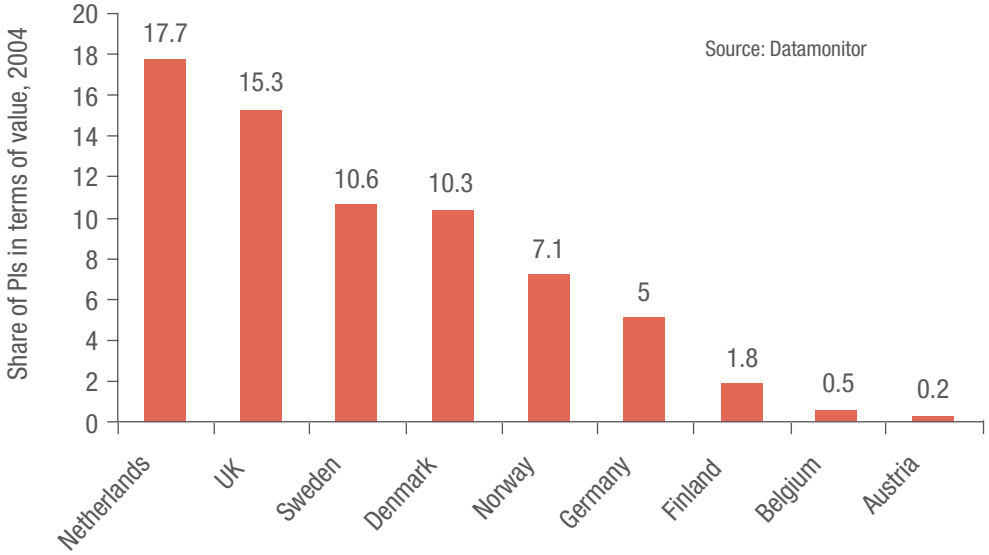


Figure 5 Parallel import penetration across selected European countries in terms of value in 2004



Parallel importation of pharmaceutical products appears to be concentrated in six EEA countries, namely: Denmark, Germany, the Netherlands, Norway, Sweden and the UK. These countries are typically considered to have relatively high drug prices compared with others in the EEA.

The UK appears, until recently, to have been the largest market for parallel importation:[11]

- 70% of parallel trade in the EU is into the UK
- parallel-traded medicines account for approximately 1 in 5 of prescriptions dispensed to patients
- it is estimated that 90% of UK pharmacists source some products through parallel trade
- market share of parallel-traded products increased from 11% to 17% (1999 to 2003), with a recent decline
- parallel importation in the UK is suspected to be higher than the data indicates.

However, according to Graham Satchwell (personal communication September 2007), one of the results of UK government changes about two years ago – reducing the prices the NHS pays for parallel-traded products, is that profits for parallel import traders into the UK have been diminished. In addition, the national 'quotas' that several pharma manufacturers have applied across Europe have tightened the market further. This has had two important consequences. Firstly, UK traders have looked to the other big European markets and examined, afresh, opportunities to sell there. In this regard, Germany has proven to offer great potential both in terms of market size and high sales price. Many UK parallel traders are now sourcing products for Germany, including products that were first destined by the manufactures for the UK; the UK has become an exporter as well as an importer.

A further consequence is more disturbing. The absence of products on the parallel trade market – due to shortages resulting from quotas – creates a demand that the unscrupulous will be keen to serve, irrespective of the provenance of the medicine concerned. Small-time parallel traders (and 'trader agents'), those in the 'murkiest' part of the sector, if desperate to obtain products from somewhere and unable to do so via normal sources are likely to turn elsewhere, rather than go out of business. This is a problem for UK and Germany (and other parallel trade consumer countries). Might even the recent spate of counterfeits in the UK be examples?

The main countries exporting parallel-traded pharmaceuticals tend to be concentrated in Southern Europe, such as Greece, Portugal and Spain – though France also is becoming an increasingly important source country. Yet, given the complexity of both the European pharmaceutical pricing and distribution systems, it is very hard to obtain an accurate picture of PPT product flows. It is certain that PPT, in terms of both import and export, occurs to greater or lesser degrees in all EU Member States (notwithstanding the derogation applying to the recently accessing Member States).

According to Datamonitor, 'analysis of the overall level of parallel trade in pharmaceutical products across Europe since 1998 has indicated that it rose substantially from 1998 to 2002. The growth was mainly seen in Germany, Sweden and the UK. Sweden's relatively low level of parallel import penetration prior to this is because parallel trade only became legalised when it joined the EU in 1995. Since 2002, it appears that the growth of parallel trade has slowed down and is stabilising, despite the accession of new central and eastern European countries in the EU on 1 May 2004. EU enlargement has not yet caused a rise in parallel trade, mainly because of the derogation that prevents parallel exportation of many branded drugs from eight of the new countries. However, the effect of derogation will erode over time and a gradual rise in EU PPT is expected as a result of the enlargement.'

Perhaps unsurprisingly, statistical data on EU PPT is weak. It is near impossible to determine the PPT figures for EU centrally-authorised (CP), mutually-recognised (MRP) and nationally-authorised (NP) medicinal

products, irrespective of determining where they come from and go to and at what price. However, in 2006 more than 140 million individual drug packages were parallel imported throughout the EU and a secondary wholesaler repackaged each and every one.

PPT derogation agreement between the old and new EU Member States

EU/EEA PPT has so far largely been excluded from the new EU Member States as a result of an accession treaty derogation. The legal basis for derogation with respect to PPT is summarised as follows by the EC 2003 Communication:

'… an industrial property right will be exhausted even in the case of a product which the owner of the industrial property right first markets in one Member State where protection exists, then markets it in another Member State where there is no such protection: the owner of the right cannot prevent the parallel importation of the product from the latter Member State to the former. An important, even if temporary, exception to this rule has emerged, during discussions on the G10 Medicines initiative, with the accession of the new Member States in 2004 and, in particular, the Czech Republic, Estonia, Latvia, Lithuania, Hungary, Poland, Slovenia and Slovakia. The Treaty of Accession provides for a specific mechanism whereby parallel imports from the above mentioned new Member States are prevented until the patent or supplementary protection of the medicinal product concerned expires in these Member States.'

A good summary of the PPT derogation issue is provided by both Datamonitor and OEBIG:[12]

'A derogation of the free movement of goods in the EU was included in the Accession Treaty with respect to pharmaceutical products for eight of the 10 countries that joined the EU in 2004. The conditions of the derogation allow a patent or SPC (Supplementary Protection Certificate) holder to prevent the parallel importation of pharmaceutical products in Member States if the products were exported from an accession Member State where there was no equivalent patent protection or SPC available when a patent or SPC for the pharmaceutical product was filed in an EU member state. Equivalent patent protection was introduced in these eight new Member States between 1991 and 1994. As a result, those products that have patents or SPCs filed prior to this are protected from parallel trade from these accession states. Given that it typically takes at least 10 years for a drug to reach the market after the patent for the product has been filed, the majority of branded products already launched in the EU are likely to be protected from parallel trade from most of the new accession countries because of the derogation.' *(Datamonitor)*

'Because of concerns of the pharmaceutical industry, the Accession Treaty includes a derogation to limit exports from the new EU Member States, when intellectual property rights differed at the time of the market launch of a pharmaceutical. The G10 High Level Group also recommended governing parallel imports between EU Member States. The derogation provides, that holders of SPCs, which had been granted in the EU-15 before product patents were available in the new EU Member States, may prevent exports from the new Member States. Furthermore, parallel importers have to notify patent holders of their intention to import a pharmaceutical 30 days prior to their application for a parallel import product licence, thus pharmaceutical companies have the chance to take legal action if they feel that the derogation of the EU Accession Treaty is violated.' *(OEBIG July 2006, p316).*

Parallel pharmaceutical trade in the context of global pharmaceutical trade

There are no international agreements on PPT, with the exception of the agreements applying to the EU/EEA common market. Without full international pharmaceutical regulatory harmonisation it is not possible to contemplate international PPT, irrespective of the arguments advocated for PPT in terms of providing cost savings. The ICH[13] process and the WHO credibly attempt to introduce commonly agreed international pharmaceutical regulatory standards, but how these standards are adopted throughout the world is a major issue of concern and has not been resolved.

The United States government, against the background of high drug prices, is examining the issue of re-importation as a mechanism to provide cheaper drugs to its population. Irrespective of the financial arguments in favour of re-importation, there are legitimate concerns for drug safety reasons about the introduction of PPT between the developed countries of the world and thus this subject is being highly debated in the US and Canada. In the developed world, which countries can trust the drug supply of another country against the background of global supply chain insecurity?

If the developed world has problems with PPT, then what about the situation in developing countries? It is rather frightening that international bodies such as the UN Conference on Trade and Development (UNCTAD) are advocating PPT as a mechanism for achieving competitive drug pricing and arbitrage in the various Africa sub-regions. If the developed countries of the world have a problem with trusting drug price arbitrage via PPT, then what is the situation likely to be in African States which arguably do not have the rigorous regulatory structures in place as exist in the developed countries of the world?

The EC May 2003 Regulation[7] to facilitate differential pricing between the EU and the rest of the world is considered by some observers to be an option for encouraging PPT, including reducing the concerns of the research-based pharmaceutical industry with this practice. The EC regulation in theory provides anti-diversion measures against specific pharmaceutical products and requires manufacturers to reduce their essential medicines export prices to developing countries by '75% off the average ex-factory' price in OECD countries, or 'at the cost of production plus 15%'.

Although in theory global PPT may provide savings and be a force for global region and sub-region price harmony, the best evidence shows that the costs outweigh the benefits. How for example, is it possible to enforce EU regulatory guidance internationally? In the absence of a secured global supply chain with common international regulatory standards and enforcement practices, it is not at all clear how PPT can work as a mechanism for global pharmaceutical price arbitrage.

In the US, the concerns surrounding PPT are summarised as follows by Datamonitor: 'If drug importation were legalised, the responsibility of monitoring the quality of the imported drugs would fall upon the US government. There is essentially little incentive for foreign governments to commit their limited resources to ensuring the quality of exported drugs destined for the US. To support this assumption, the HHS Task Force found that in many countries there is currently a lower level of protection to ensure the quality of exported drugs, because each government's main priority is ensuring the safety of drugs for its own citizens. As a result, the FDA, as the national drug regulatory agency in the US, would be expected to take up the role. It is expected that substantial investment, including additional personnel, would be required to establish the infrastructure of an effective drug importation monitoring system that could ensure imported drugs meet FDA standards'.

EU single pharmaceutical market development and convergence – achievements and challenges

This section of the report summarises the recent achievements and future challenges of creating a real single EU pharmaceutical market so as to place European PPT in context. From a detailed analysis of the EC 1998 Communication and the progress made to date on achieving a single EU pharmaceutical market, one can see that PPT in Europe is a major symptom of a greater problem that exists within the heart of the EU pharmaceutical market.

The EC 1998 Communication on the single EU pharmaceutical market states that 'the continued differences between the European markets lead to excess costs (such as higher marketing costs, higher distribution and administrative costs) and, in some cases, to excess production capacity, that could be off-set by a better operating (single) market.' The EC states further that, 'the operation of the Single Market in pharmaceuticals remains the most important of the uncompleted parts of the agenda for establishing the European Union as a firm base for pharmaceutical innovation and sustainable industrial development'.

What has the EC and EU free market achieved in single EU pharma market convergence since 1998?

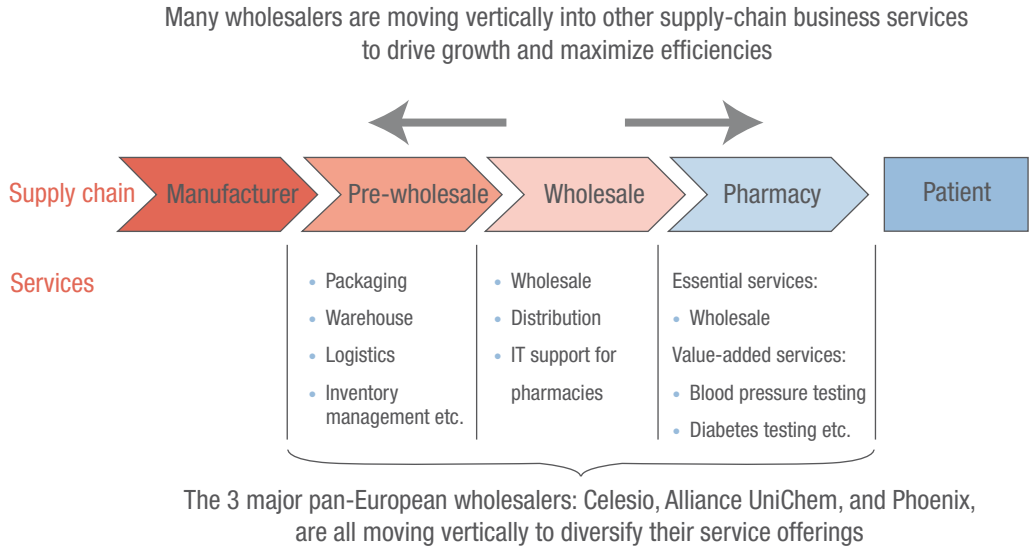
Pharmaceutical legislation and regulation. The business of pharmaceutical regulation is to ensure that the patient receives safe and effective medicines. Pharmaceutical products, by their nature, require a high level of regulation from manufacturer to consumer. A good summary of the history of EU pharmaceutical legislative development and the EC *Pharma Review 2001* process is provided by the article 'New Medicines Legislation' on Euractiv.com.[14]

Against the background of EU accession, the EC has made several achievements in the area of developing and integrating pharmaceutical legislation and regulation as a result of EC Pharma Review 2001. It has, *inter alia*, adopted the basis of a community code for medicinal products for human use, updated and, to some extent, rationalised the EU marketing authorisation procedures (Centralised procedure – CP, Mutural Recognition Procedure – MRP and National Procedure – NP), introduced stronger pharmacovigilance, regulation of herbal medicinal products, updated clinical trial regulation and introduced guidelines for new technologies and enforcement of intellectual property rights. The EC is currently conducting a review of the Marketing Authorisation 'variations procedures' (so as to potentially address the issues of 'artificial partitioning of the market' and the need to rationally update new medicinal product information based on clinical experience).

Pharmaceutical pricing and reimbursement. The business of pharmaceutical pricing and reimbursement is to ensure that patients receive cost effective medicines. In terms of achieving convergence of pharmaceutical pricing and reimbursement between the EU Member States, there has been limited success. However, Greece provides a recent example where pricing and reimbursement system rationalisation has been achieved.

Free market forces. In terms of free market forces applying to the business of pharmaceutical distribution (independent of the market forces applying to the business of PPT), there is a trend towards European pharmaceutical distributor vertical integration, which is summarised, in the following figure provided by Datamonitor.

Figure 6 – Wholesalers are vertically integrating into offering pre-wholesale and pharmacy activities



Source: Datamonitor

To what extent this trend rationalises the European pharmaceutical distribution system is hard to say. For example, the EU Member States have varying rules on pharmaceutical distributor manufacturing and the right to establish pharmacy chains. To what extent and how this consolidation process affects EU PPT and supply chain security and rationality remains to be seen.

What are the current challenges in creating a single EU pharmaceutical market?

The evidence suggests that since the date of the original EC 1998 Communication on the single EU pharmaceutical market there has been limited progress in attaining this goal. At the same time, the EC has recognised that at the beginning of the 21st century Europe is now facing new public health, scientific and economic challenges:

- the globalisation of the sector and the increasing internationalisation of the value chain
- the smooth functioning of the internal market in a widening Europe
- advances in science and technology.

Thus, the EC has recently launched a consultation document entitled *The future of pharmaceuticals for human use in Europe*[15] with the intention of reviewing the functioning of the single EU pharmaceutical market. This document is aimed at encouraging a public debate on the future of pharmaceuticals in Europe and thereby enabling the EU to better understand stakeholders' views on the key challenges and how they should be tackled. The consultation document highlights several areas that require attention:

- the coexistence of different and divergent national pharmaceutical pricing and reimbursement schemes
- the safety of medicines within the EU internal market (eg, the recent 'Vioxx case', the failed clinical trial in the UK and the issue of 'rational and effective pharmacovigilance')
- counterfeit medicines and supply chain security
- PPT
- EU pharmaceutical industry competitiveness
- emerging technologies, eg, regenerative and personalised medicine and nanobiotechnology.

In terms of achieving a single EU pharmaceuticals market, there are other areas that also need addressing and which also take into consideration our existence in the age of a global market:

- artificial partitioning of the European single pharmaceutical market
- overall coordination of pharmaceutical regulation (ie, achieving the correct balance between centralisation and decentralisation of regulatory activities in the EU)
- addressing regulatory gaps and areas where there may be over or under regulation (eg, the under regulation of pharmaceutical distribution)
- EC-level management of the EU pharmaceutical system in terms of supply chain security (eg, do we have a map of European pharmaceutical distribution?)
- internet pharmacy (and other related new trading models)
- the diversity of pharmacoepidemiology between EU Member States
- EC assistance for potentially accessing countries to rationalise their pharmaceutical markets
- EC assistance for less developed countries of the world in terms of strengthening their pharmaceutical regulation.

As the pharmaceutical market becomes more global, it is in the interest of the EC to assist less developed parts of the world with a view to guaranteeing pharmaceutical supply chain security worldwide. The EC should have some obligations in this respect. As Vice Commissioner Verheugen has stated recently: "the current legislation in developed countries often sets different standards for medicines sold on the whole market and those exported to third world countries. This is also true for the EU. This is unacceptable."

Artificial partitioning of the European pharmaceutical market – who is partitioning it?

The concept of 'artificial partitioning of the market' with respect to the single European pharmaceutical market was coined by the EC 2003 Communication, which states that artificial partitioning occurs when 'the trademark proprietor has placed an identical pharmaceutical product on the market in several Member States in various forms of packaging and/or under a different trademark and the size of the packet marketed in the Member State of exportation may not be marketed in the Member State of destination for various reasons.'

'Furthermore, the European Court of Justice (ECJ) has also ruled that even when one of the many sizes of the product marketed in the Member State of destination is also marketed in the Member State of exportation, this is not enough to justify the conclusion that repackaging is unnecessary. Partitioning of the markets would still exist if the importer were able to sell the product in only part of his market.'

'Artificial partitioning of the market' may not necessarily be directly attributed to and intended by the proprietor of the trademark but rather to such factors as those mentioned by the ECJ: a rule authorising packaging only of a certain size or a national practice to the same effect, health insurance rules linking the reimbursement of medical expenses with the size of the packaging, or well-established medical prescription practices based, *inter alia*, on standard sizes recommended by professional groups and health insurance institutions.

Some examples of 'artificial partitioning' problems, with respect to patient safety issues created by the pharmaceutical industry, are levied as follows by an independent pharmacy public health official and expert (personal communication September 2007):

- medicines are manufactured at different sites with different compositions (eg, colouring substances, shapes etc). It is, therefore, difficult for patients to understand that it is the same product as that directly imported
- they often have different names in different countries – as an example, in one of two recent adverse drug reaction (ADR) reports Lipitor was called Sortis, while in the other Nexium was called Esopral. With generic substitution, at least its generic name and status is manifest.

Clearly, industry practice is not helping the creation of a single European pharmaceutical market or in a way that benefits the European consumer. Arguably, the industry response, in terms of providing products that confuse professionals and patients, is due to the rigidity and incoordination of the divergent pharmaceutical pricing and reimbursement systems. The concept of 'artificial partitioning of the market' is a good one, but was developed as a one-sided affair. Aside from industry pricing and marketing practices being adapted to local circumstances, the artificial partitioning of the European pharmaceutical market has also been driven by the divergent and rigid public financing, pricing and reimbursement systems that exist in EU Member States. At the same time, this situation can be exploited potentially by unscrupulous intermediaries, as described by a Canadian Health policy expert, Mike Tremblay[16] as follows, with reference to experiences in the US:

'The Treaty of Rome stipulations that bestow on Member States control over their health systems appear to have been extended to include oversight of the pharmaceutical industry and its products through national pricing controls. It is open to question, however, as to whether pricing control of medicines by national authorities is compatible within the context of the EU as a whole. Certainly, marketing authorisations, which do fall within Member State competence and are perhaps compatible with their authority to protect human health, should not be confused with subsequent pricing policies by these same Member States. Indeed, it may be that these pricing policies, as a cost divergence between Member States, create exploitable opportunities for trade in counterfeit medicines. This is comparable to the situation in the US, and may incentivise counterfeiters and rogue traders to exploit these price differentials.'

The drivers of parallel pharmaceutical trade: subsidiarity, health economics and health financing

This section of the report provides an overview of the EU Member State pharmaceutical pricing and reimbursement system, health economic policy incentives that drive the PPT business, a summary of the major academic health economic reports on PPT and finally a brief comparative examination of EU Member State pharmaceutical prices.

Healthcare provision: subsidiarity, healthcare expenditure and effective healthcare delivery

The principle of subsidiarity means that Member States have authority for providing and financing national healthcare. According to the EC 1998 Communication: 'Member States have exclusive responsibility in the field of healthcare; they view both the provision of health and its financing as keys to social solidarity; and they have to meet public expenditure objectives, notably for the purpose of European Monetary Union.'

There is increasing tension in controlling healthcare expenditure and delivering effective healthcare services concurrently. All EU Member States are facing problems with spiralling healthcare costs, which they are seeking to minimise by controlling prescription drug expenditure.

However, there are clear inefficiencies in the cost effective delivery of healthcare between the EU Member States as highlighted by a recent report – the 2007 EuroHealth Consumer Index.[17] The report surveys and statistics outlined three groups of countries in terms of providing effective healthcare:

- a first group of nations performing very well, separated only by tiny differences
- a middle group of adequate performers, with rapid improvers such as Estonia
- a third group of poor performers - mainly new member states, such as Hungary.

The correlation in the EU between national GDP and effective health care delivery is clearly not linear for a number of reasons as outlined by the EuroHealth Consumer Index report, not least of which is divergence and disparity in drug financing policy.

Overview of EU Member State pharmaceutical pricing and reimbursement

In order to understand why we have PPT, it is firstly necessary to have a basic understanding of the pharmaceutical pricing and reimbursement system in the EU and how the system varies considerably between Member States.

Pharmaceutical pricing and reimbursement in the EC is governed by the 1988 'Transparency Directive'[10] relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance. The EC states that 'competent national authorities are free to make their own decisions on the pricing and reimbursement of pharmaceutical articles, provided that these decisions are made in a transparent manner and do not create barriers to trade. Member States therefore play a key role, as do the national competition authorities. However, they need to be transparent in the decisions they take in that national context.'

A summary of EU pharmaceutical pricing and reimbursement – the system and stresses

Surveying, Assessing and Analysing the Pharmaceutical Sector in the 25 EU Member States: ÖBIG (Österreichisches Bundesinstitut für Gesundheitswesen) July 2006, p316[12]

'Within the framework of the EU Transparency Directive 89/105/EEC, pharmaceutical pricing and reimbursement systems are national affairs. Consequently, these systems may differ widely throughout the 25 Member States.

The pharmaceutical pricing and reimbursement systems are often very complex, being customised to the specific economic and health needs of a country, and often having a long tradition.

Furthermore the systems are adjusting continuously as Member States are in the process of reviewing their healthcare systems, searching for strategies to increase the efficiency of pharmaceutical services, or keeping their pharmaceutical budget under control.

These efforts often lead to a reaction by other players in the market such as pharmaceutical manufacturers, wholesalers, doctors, pharmacies or patients. Examples of these reactions may be changes in pricing strategies or in consumption patterns. In return, authorities might respond to these developments for example by means of new cost containing measures, thus creating a 'pendulum' of action and counter action.

These developments lead to comprehensive and up-to-date information being rather hard to gain, but nonetheless very important in order to monitor the conditions of competition in pharmaceutical markets. The demand for accurate information is further accelerated by the enlargement process of the European Union as the pharmaceutical systems in the ten new Member States are still in the process of adjusting to community provisions.

The DG Competition of the European Commission has therefore identified the need for comprehensive and detailed information on pharmaceutical systems in the EU Member States, allowing them to identify similar cost drivers and policy measures, to maintain the monitoring and enforcement of competition rules by the Commission'.

EC summary of the problems with the EU pharmaceutical pricing and reimbursement system

'There are important differences between Member States, both in levels of prices and in levels of consumption (volumes). These differences can be explained by a number of factors, including: divergent medical cultures and prescribing patterns, price discrimination by pharmaceutical companies to reflect the differences in the ability to pay, and conjunctural factors such as inflation and currency fluctuations. One of the factors in these differences appears to be the extent to which Member States rely on price control as the main means for controlling aggregate costs – or whether a wider range of policies are used (including demand controls and efforts to influence prescribing patterns). Because total expenditure on pharmaceuticals has both a volume and a price component, relying on price-fixing to control expenditure does not necessarily deliver a lower aggregate spend on pharmaceuticals or a lower per capita pharmaceutical budget.'[9]

The EC G10 Pharmaceutical Forum[18] has stated: 'The price negotiating systems and reimbursement structures in a number of Member States can lead to significant delays (in products being made available on the market). This is not only a problem within those Member States, but it can also result in citizens of one Member State having access to new medicines months, or even years, in advance of those in other Member States.'

'On the non-regulatory side, and despite efforts currently carried out under the EC G10 Pharmaceutical Forum, different national pricing and reimbursement schemes still coexist, leading to market fragmentation, parallel trade, disparities in prices and time-to-market delays. In certain countries, medicines are not even made available due to administrative requirements and poor economic rewards. A lack of transparency and harmonisation with regard to pricing, reimbursement and relative effectiveness remains a challenge.'[15]

Health economic policy incentives for PPT

In the absence of a unified EU health policy, a number of divergent incentive measures are put in place by Member States to encourage cost effectiveness in pharmaceutical purchasing, prescribing, dispensing, use and consumption. These can generally be categorised into supply and demand policy measures. Datamonitor states: 'In addition to the price differential that drives parallel trade, there are a number of national incentives to encourage pharmacists and/or payers to procure parallel imports', and 'governments of EU countries may adopt new initiatives to encourage the use of parallel imports, as part of their efforts to curtail spiralling healthcare costs.'

The rationality or irrationality of the measures employed is open to debate (both from academic and practical perspectives). Healthcare and pharmaceutical economics in Europe is a fraught business and is an employment industry in itself. To understand the system requires ability to review commercially published reports such as Scrip's report series on *'Pharmaceutical Pricing & Reimbursement in Europe'*[19] written by leading academics on the topic.

A useful and informative summary of the issue of health economic policy incentives currently employed by the Member States is provided by Datamonitor in the following box:

Incentives for parallel importation in the six main parallel importing countries

INCENTIVE	DENMARK	GERMANY	NETHERLANDS	NORWAY	SWEDEN	UK
Clawback (or indirect benefit to payer)*	No	No	Yes	No	No	Yes
Financial incentive to pharmacy	No	No	Yes	Yes	Yes	Yes
Parallel import quota	No	Yes (7%)	No	No	No	No
Financial benefit for consumer	Possible	None	None	Possible	Possible	None

* Clawback – indirect financial benefit to the payer through a mechanism where the payer captures a share of the discount that a pharmacist receives from the wholesaler.
Source: adapted from Kanavos et al, October 2005

- The high level of parallel import penetration in the UK and Netherlands is driven by financial incentives for pharmacists
- Denmark and Sweden have different incentives that drive parallel importation
- Parallel importation in Germany is driven by imposed quotas
- UK parallel importation fell in 2005 because of Pharmaceutical Price Regulation Scheme (PPRS) price cuts

The high level of parallel import penetration in the UK and Netherlands is driven by financial incentives for pharmacists. 'The high price differential of drugs in these countries compared with many other European countries, along with the financial incentive for pharmacists to procure drugs from the cheapest possible source, have been the key drivers of parallel importation in these countries.'

The following box provides an overview of the PPT incentives employed by the health financing authorities in the UK, Netherlands, Norway, Denmark, Sweden, Germany and France as well as the EMEA (information provided by Datamonitor and GIRP):

Overview of PPT incentives employed by health financing authorities in various EU Member States

UK

'In the UK there is a financial incentive for pharmacists to procure parallel imported products because they are not subject to fixed profit margins, unlike many pharmacists in other European countries. Under the payment system for pharmacists, the Department of Health reimburses a pharmacy based on the NHS price list and deducts a clawback (typically around 10%) to take into account the discount a pharmacist obtains from buying the drug from a wholesaler. The clawback is based on the assumed discount that a pharmacist obtains, which is determined annually by authorities. The system means that a pharmacy can retain any discount above the set clawback level, except for a selection of high-cost products (for example, vaccines and cold storage products) that are in the 'zero discount' list.'

'IMS Health reported that parallel importation in the UK fell in 2005, after a relatively stable period between 2002 and 2004. This was associated with the 7% PPRS price cut of branded prescription drugs that came into effect on 1 January 2005. This effectively reduced the price differential of drugs in the UK compared with many other European countries – a key factor that affects parallel trade.' *(Datamonitor)*

'In the United Kingdom a claw-back mechanism is closely linked to parallel trade. In this respect the percentage amount taken by the government through the claw-back mechanism is highly dependant on the fluctuations in the volumes of parallel trade.' *(GIRP)*

Netherlands and Norway

'A similar financial incentive exists for pharmacists in the Netherlands and Norway. In Norway, the financial benefit is split 50:50 between the government and the pharmacist (Kanavos *et al*, April 2005). In the Netherlands, the pharmacist can retain a third of the price difference, while the government captures two-thirds of the difference through the clawback system.' *(Datamonitor)*

Denmark and Sweden

'In Denmark and Sweden there are different incentives that drive parallel importation. In Sweden, for example, pharmacists have the right to substitute a prescribed product for a generic or parallel imported product. In Denmark on the other hand, pharmacists are required to inform customers if there are cheaper parallel imported products available above a particular threshold of savings. Although there is no direct financial incentive for pharmacists to dispense parallel imported drugs, there is one for patients, as their co-payments for prescription drugs are percentage-based. Consequently, the savings from parallel imported products accrue to the payer and the customer rather than to the pharmacist.' *(Datamonitor)*

Germany

'Parallel importation in Germany is driven by the imposed quotas. Between 1998 and 2002 there was a substantial rise in parallel importation from approximately 2% to 7%. This was driven by a number of government initiatives. This included the introduction of a minimum sales quota of parallel imported pharmaceutical products for pharmacists. In 2002, the quota was set at 5.5%, rising to 7% in 2003 (Arfwedson, 2003). The quota level can be renegotiated to take into account the availability of parallel imported drugs. If pharmacists fail to meet their quotas, they are penalised by having their reimbursement levels reduced (Kanavos et al, June 2005).' *(Datamonitor)*

'In Germany, pharmacies are obliged by law to dispense a set percentage of parallel imported products to patients and wholesalers by jurisdiction to have all parallel imported products on stock.' *(GIRP)*

France

'The French authorities even issue licences for those whose business is limited to the export of medicines from France. Exporting licences (distributeurs en gros à l'eportation) are granted by the Agence Française de Sècurité Sanitaire des Produits de Santé (AFSSAPS), which belongs to the French Ministry of Health. The detailed requirements are laid down in French legislation (Code de la Santé, Art. R 5106 §7).' *(GIRP)*

EMEA

'Even for centrally registered EMEA products, which have already received a central marketing authorisation, a procedure has been established by the EMEA granting an additional 'parallel distribution' authorisation to parallel traders who wish to bring innovative medicines registered through the centralised process to the national markets.' *(GIRP)*

Health economic studies of PPT – an examination of the arguments

The debate surrounding the benefit or otherwise of European PPT to healthcare purchasers and patients has led in recent years to a number of academic health economic studies on the subject and which have been funded by various stakeholders. There is clearly some debate about the savings that payers and patients obtain through PPT and conclusions may arguably be influenced to suit whichever stakeholder is funding a particular study. The following box and table summarise the key findings from the main studies.

Summary of economic studies on European PPT

The York Health Economics Consortium study (YHEC) (West and Mahon May 2003)[20], funded by the European parallel traders association (EAEPC), found evidence that parallel imports have indirect competitive effects by forcing down the price of their domestically-sourced counterparts and that direct and indirect savings from the parallel trade of pharmaceuticals have helped contain mounting public healthcare expenditure in many European countries.

The Imperial College London study (ICL) (Szymanski, 2004),[21] funded by the UK Economic and Social Research Council, found that despite the fact that the UK national health service is effectively the largest parallel importer of patented medicines in Europe, the net benefit of this to the UK economy is negative. That is, the savings made by the health service are outweighed by the greater costs imposed on the overall UK economy.

The London School of Economics study (LSE) (Kanavos et al, January 2004),[22] funded by a research-based pharmaceutical company, concludes that there are no direct benefits to patients and recommends a re-evaluation of current practice by policymakers.

The University of Southern Denmark study (USD) (Enemark et al, June 2006),[23] funded by the European parallel traders association (EAEPC), on the economic impacts of pharmaceutical parallel trade in the EU, concluded that PPT generates considerable direct, as well as some indirect, savings to both patients and health insurers.

"There is clearly some debate about the savings that payers and patients obtain through PPT and conclusions may arguably be influenced to suit whichever stakeholder is funding a particular study."

Table 1 Summary of the economic impact of PPT, based on the YHEC, LSE, ICL and USD studies
(adapted and updated from original Datamonitor table)

	YHEC	LSE	ICL	USD
Date published	May 2003	January 2004	March 2004	June 2006
Countries covered	Denmark Germany Netherlands Sweden UK	Denmark Germany Netherlands Norway Sweden UK	Finland Sweden UK	Denmark Germany Sweden UK
Data sources	Various, including: national statistics agencies, pharmacy bodies, parallel traders	IMS sales data for six classes of drugs	Department of Health	Various, including: national statistics agencies, pharmacy bodies, parallel traders (similar methodology to YHEC study)
Savings to health insurer	Denmark: $20m Germany: $241m Netherlands: $34m Sweden: $46m UK: $250m	Denmark: $4m Germany: $22m Netherlands: $24m Norway: $1m Sweden: $5m UK: $70m	n/a	Denmark: $18m (indirect savings $10m) Germany: $181m (indirect savings n/a) Sweden: $57m (indirect savings $20m) UK: $296m (indirect savings n/a)
	Total: $591m	**Total: $126m**	**Total: $448m**	**Total: n/a**
Savings to patients	n/a	Some savings in Denmark and Sweden	n/a	n/a. The total estimated savings for health insurers combines estimates also for patient savings
Financial benefits to pharmacy	Denmark: n/a Germany: n/a Netherlands: $6m Sweden: n/a UK: $176m	Denmark: $0m Germany: $0m Netherlands: $8m Norway: $1m Sweden: $0m UK: yes, but undefined	n/a	n/a
	Total: $182m	**Total: $9m**	**n/a**	**n/a**
Financial benefits to parallel trader	n/a	Denmark: $9m Germany: $122m Netherlands: $54m Norway: $15m Sweden: $23m UK: $583m	n/a	n/a
	Total: n/a	**Total: $806m**	**Total: $896m**	**Total: n/a**
Total value	**n/a**	**$941m**	**$1,344m**	**$552m (+$30m indirect)**

n/a = not available
Sources: Datamonitor, April 2006; West et al, May 2003; Kanavos et al, January 2004; ESRC, 2004; Enemark et al, June 2006.

Of all the studies conducted so far, the LSE study has to be considered to be the most credible in terms of addressing the entirety of issues relating to the economic benefits or otherwise of European PPT. A summary of the LSE report, that attempts to look at all factors from the respect of all stakeholders, is provided in the following box:

The economic impact of PPT in European Union Member States: a stakeholder analysis
(Kanavos et al, January 2004)

Hardly any evidence is found on price competition or price convergence between locally sourced and parallel-imported products over the 1997–2002 period in the six study countries. Therefore, the hypothesis that PPT stimulates price competition and drives prices down in destination (importing) countries over the long-term is rejected. There is also very little evidence lending support to the argument that parallel trade stimulates (price) competition among exporting and importing countries. Thus, the arbitrage hypothesis of price equalisation or price approximation is also rejected.

- A survey has shown that a number of low-price countries (Greece, Spain and France) are introducing measures to account for the extent of parallel exports from their territory. By contrast, traditionally high-price countries seem to have mature policies, which also enable them to benefit somewhat from this activity (especially the UK, the Netherlands, Germany, Sweden and Denmark).
- The lack of sizeable direct benefits to health insurance organisations, the limited price competition in individual markets, the existence of reported product shortages in some member states, and the size of absolute and relative profits accruing to parallel traders, may force policy makers to re-evaluate the rationale behind parallel trade. This implies taking into account the dynamic impact it may have on patients in some Member States and on the research-based pharmaceutical industry in terms of location, manufacturing and research.

In Europe, the financial gains made from PPT accrue mostly to parallel pharmaceutical traders, as highlighted by the findings of two separate studies published by the ICL and the LSE in 2004. These studies found that only a small portion (in some cases none) of the financial savings were passed onto consumers or payers. Although parallel pharmaceutical traders make the greatest financial gain from the practice, health insurers do capture some of the savings, although the value of this varies from country to country. The latest study by USD attempts, through the use of an intricate methodology, to identify the savings that may be made indirectly through the competition parallel imports bring against locally-sourced products.

Datamonitor states that 'in an unregulated market and where there is no product differentiation, economic theory would predict that the competition would exert a downward pressure on prices. However, there is no conclusive evidence as yet that PPT has led to a convergence of drug prices between countries, even in Europe where there is a significant level of PPT. This is attributable to two factors. Firstly, PPT exerts a minimal competitive pressure on drug prices globally because it occurs at a low level. Secondly, the pharmaceutical industry is distinct in that, in most countries, the prices of drugs are regulated by governments and regulatory authorities. As a result, the normal economic dynamics of competition have not caused drug prices to converge. Going forwards, Datamonitor does not expect that any significant price convergence in Europe or globally will be seen as a result of these factors.'

Further analysis of the economic costs and benefits of PPT is provided by a recent policy paper produced by the London School of Pharmacy,[24] excerpts from which are provided in the following box:

The costs and benefits of medicines parallel importing in the EU

The main importers of parallel traded medicines in the EU are the UK, Germany and other smaller northern countries such as the Netherlands and Sweden. Chiefly, the main exporters have been southern European countries, such as Greece and Spain, which have traditionally had low imposed pharmaceutical prices coupled with relatively high overall levels of domestic medicine consumption. The costs and benefits of such trading are difficult to calculate. This is in part because relevant factors are constantly changing. For example, Dutch authorities have recently moved in various ways to restrict the level of discount being retained by pharmacists dealing in both parallel traded and generic medicines.

The costs and benefits of parallel trading in medicines are also uncertain because of more technical economic considerations. For instance, a hidden benefit of parallel trading might, its proponents suggest, be that it tends to depress all medicine prices in recipient countries. But any such possible effects are difficult to quantify accurately. In fact, there could be compensatory price increases associated with parallel trading that are also hard to identify, together with long-term macro-economic disadvantages that studies confined to health sector expenditure analyses alone will not record. Regulatory costs should also be accounted for, along with any gains for, or harm to, end-point medicine consumers.

The body of evidence available suggests that parallel trading is currently saving healthcare providers in the EU between €500m and €1bn a year, in a total pharmaceutical market worth approaching €150bn. This is an appreciable figure. But the costs of parallel importing to the research-based pharmaceutical industry in Europe and the wider economy are significantly higher. Much of the income lost by innovative companies as a result of EU parallel trading in medicines is transferred to parallel traders, drug wholesalers and pharmacy service providers, rather than healthcare-funding agencies.

In respect of this issue it is particularly important to note the findings of the publicly-funded (ESRC) investigation by Professor Szymanski of Imperial College, that despite the UK NHS being effectively the largest parallel importer of patented medicines in Europe, the net benefit of this to the UK economy is negative. Savings made by the NHS are outweighed by the greater costs imposed on the overall economy.

Trick or Treat? Opportunities for European action on health improvement, pharmaceutical innovation and the threat of medicines counterfeiting, School of Pharmacy, University of London, 2006

Thus, in summary: the evidence from the various health economic studies on the economic benefit or otherwise of PPT to date is inconclusive. The two studies funded by the European parallel traders association (EAEPC) do not examine the financial benefits to the parallel trader. The University of Southern Denmark (USD) study attempts to look at the indirect financial benefits of PPT in two countries using an intricate methodology. The available economic evidence, which is often highly conflicting, suggests that PPT provides marginal health economic benefit at best.

There is no conclusive evidence that PPT has led to a convergence of drug prices between European countries which can be attributed to two factors. Firstly, PPT exerts a minimal competitive pressure on drug prices because it occurs at a low level. Secondly, the pharmaceutical market is distinct in that the prices of drugs are regulated by authorities. As a result, the normal economic dynamics of competition have not caused drug prices to converge.

Irrespective of the health economic considerations of PPT, many other factors not included in the health economic studies described above need to be considered in order to make an ultimate full evidence-based analysis of the benefits or otherwise of PPT to the patient.

EU Member State pharmaceutical price comparisons

There seems to be a large degree of confusion over pharmaceutical prices and the Pharmaceutical Purchasing Power Parity (PPPP) of individual Member States. This is perhaps unsurprising in view of both the high level of complexity and variation that exists in the national pharmaceutical pricing and reimbursement systems and the manufacturer and wholesaler pricing strategies that take advantage of these differences. It is extremely difficult to obtain a clear picture of the real pharmaceutical pricing situation in Europe.

It may be the case often that pharmaceuticals are more expensive in the newer Member States compared with the old ones. Although the accession states have a GDP per capita well below the average seen in the old 15 Member States prior to the EU enlargement in 2004, the prices of branded drugs in these countries are not necessarily the cheapest in the EU. According to IMS Health, the average price of the 19 leading drugs per tablet is higher in Latvia, Lithuania and Poland than in France or Spain. So it is equally likely that there will be parallel trading of innovative medicines from Southern Europe's low price, high-volume markets to some of the new accession countries.[25]

The impact of the new Member State PPT derogation closure on European PPT and prediction of future trends

How will derogation closure potentially benefit the new Member States? Notwithstanding the right of the new Member States to enter into PPT once derogation seizes, some representatives are in favour of PPT because they believe that it will benefit their local economy (ie, increased export market and creation of new Member State PPT traders). Others want it from an import perspective because they consider pharmaceutical prices within their country to be more expensive than prices in some of the old Member States.

In the context of the debate about new Member State PPT derogation, the tension is reflected well by the following question recently posed by a Polish Member of European Parliament for which an answer is provided by an EC representative.

"According to IMS Health, the average price of the 19 leading drugs per tablet is higher in Latvia, Lithuania and Poland than in France or Spain. So it is equally likely that there will be parallel trading of innovative medicines from Southern Europe's low price, high-volume markets to some of the new accession countries."[25]

European Parliament question posed by Polish MEP on PPT, and response from the EC

Polish MEP question

"In accordance with Community law, Poland recently introduced provisions authorising the parallel distribution of pharmaceuticals. Contrary to popular opinion, the price of many medicines in Poland is higher than in the 'old' Member States. Parallel distribution appears to be a good method of introducing competition in the market for proprietary products. Such competition should bring savings for the Polish Government and, at the same time, for the general public."

EC response to the question posed by Polish MEP

"The Commission is aware of the supply quota systems put in place by several pharmaceutical companies. Under those systems, pharmaceutical companies unilaterally allocate a quota of medicines to their wholesalers. In principle the quota covers domestic demand for the medicines in question in a particular Member State.

The European courts have held that such unilateral supply quota systems are not within the scope of Article 81 of the EC Treaty when there is not enough evidence that they are the result of an agreement with wholesalers. However, another type of practice aimed at curbing parallel trade such as 'dual pricing systems' – which, as you know, are systems where prices differ according to whether the product is for local consumption or for export to the other Member States – has been held to infringe Article 81 in, for example, the Glaxo-Wellcome decision of May 2001.

The Greek national competition authority has initiated proceedings against restrictions on parallel trade on the basis of Article 82, which prohibits the abuse of a dominant position. There are also parallel civil litigation proceedings pending in Greece, dealing with the same matter. The Commission is monitoring these developments closely.

Article 152 makes clear that the organisation and the delivery of health services and medical care are the responsibility of the Member States. The competent national authorities are free to make their own decisions on pricing and reimbursement for pharmaceuticals, provided that these decisions are made in a transparent manner and do not create barriers to trade.

The Commission understands that in Poland the price of reimbursable pharmaceuticals is subject to a Ministry of Health decision following representations from the industry. In discharging that duty, the Polish authorities could and do use prices in other EU Member States – including low-price countries – as a reference point."

The following analysis of the impact of derogation closure on EU PPT is provided by Datamonitor:

'There were fears in the pharma industry that the accession of the 10 new Member States to the EU on 1 May 2004, would result in a substantial increase in parallel trade from these Member States to the western Member States because of the low prices of drugs in these countries. However, a rise in parallel trade has failed to materialise. Very little increase in parallel trade in Europe has been observed since the expansion of the EU. There are three main reasons behind this:

1. the volume of drugs available for parallel exportation – low levels available in many accession countries due to small populations and relatively small pharmaceutical market size
2. the derogation applied to accession states – prevents the exportation of patented pharmaceutical products from eight of the new member states to the original 15 members
3. the price differential between the accession states and the old Member States of the EU – it is not universally true that prices in the accession states are the cheapest in the EU.'

Datamonitor adds that 'in the future, parallel distributors may turn to the accession states to obtain drugs as the effect of the derogation is eroded and further restrictions on their drug supplies are imposed by drug manufacturers, such as Pfizer's dual pricing strategy introduced in Spain in 2005. However, going forwards, the effect of the derogation will be eroded as new products are launched, which is likely to contribute to a gradual increase in parallel trade.'

What can be concluded from the above? In summary: once derogation closure occurs it is likely that we will see a rise in European PPT, but this is also likely to result in an escalation of tension between the EU research-based manufacturing industry on the one side and healthcare purchasers and pricing and reimbursement authorities on the other, as well as further confusion and complexity for the EU pharmaceutical distribution system against the background of increasing supply chain security concerns.

The difficulty in making general predictions on future trends regarding European PPT is described here by Professor David Taylor:[24] "Some commentators argue that PPT will decline naturally as and when Europe becomes more homogenous. However, this could take decades, particularly if the Union continues to expand. In an increasingly diverse and, in some respects, harsher social environment, trading in low-cost medicines could become more intense. Further, some interests may plan to introduce in selected Member States laws requiring pharmaceutical companies to fulfil orders of any size, regardless of local market requirements. This could, ostensibly, be aimed at ensuring that medicine shortages do not occur, but would in fact serve to increase the volume of pharmaceutical parallel trading in Europe."

Counterfeit medicines and pharmaceutical crime – is Europe really safe?

The security of PPT needs to be considered in the light of the growing global problem and threat of counterfeit medicines.

Overview of the counterfeit medicine problem

The World Health Organisation (WHO) estimates that counterfeit medicine sales range from around 1% in developed countries, such as the EU Member States, to over 10% in developing countries and that medicines purchased over the internet from sites that conceal their physical address are counterfeit in over 50% of cases.[26] The US-based Centre for Medicines in the Public Interest predicts that counterfeit drug sales will reach US$75bn globally in 2010, an increase of more than 90% from 2005.[27]

There is, therefore, concern over an increasing global threat from medicines counterfeiting and pharmaceutical crime. In order to provide a mechanism for global coordination to tackle the problem, the WHO in 2006 introduced its IMPACT global initiative[28] addressing the five areas of: technologies, legislation, enforcement, regulation and risk communication. A year earlier, in 2005, the Council of Europe had undertaken a large survey and analysis of the counterfeit medicine situation[29] with respect to estimating the scale of the problem, the legislative, regulatory and trade problems and made recommendations concerning measures required to address them. The European Parliament is now calling for action on counterfeit medicines[30] and the EC has also commissioned a full investigation of the counterfeit medicine situation (in conjunction with a full investigation of PPT, as the two topics are highly related).[31]

A good overview of the counterfeit medicine problem in Europe is provided in *Counterfeit Medicines & Pharmaceutical Crime in Europe: Invisibility, Biohazard & System Failure* (Chapter 1) from the 2006 publication *Coincidence or Crisis? Prescription Medicine Counterfeiting*.[32] The following box provides a summary of some of the key points:

Do counterfeit medicines exist in Europe?

The evidence from the Council of Europe Survey Report suggests that counterfeit medicines exist practically everywhere in Europe and are not just confined to Eastern Europe. The first real evidence for the presence of counterfeit medicines on the European market appeared circa 1998 and since then the number of cases reported has been steadily increasing.

Undoubtedly there is a large 'invisibility' factor that masks the real extent of the presence of counterfeit medicines in Europe. This is due to a number of reasons, not least of which are the very nature of medicinal products (counterfeit medicines are invariably harder to detect compared to other types of counterfeited products), the lack of a commonly agreed and employed definition of counterfeit medicines (if we do not know how to define something then it is difficult to record and estimate its presence) by European States and a lack of awareness (in the case of several relevant authorities as well as the general public) of the threat that counterfeit medicines poses, even if they exist at all.

Pharmaceutical/chemical brokers and traders

Although brokers and traders play an important role in the supply of Active Pharmaceutical Ingredience (APIs) and Bulk Intermediate Products (BIPs), there is little in the way of substantive evidence to say that they are a major contributory factor to the supply of counterfeit medicines. However, brokers, as facilitators in the international commerce of medicines, are well placed to participate in the diversion of medicines – including counterfeits – as they lie outside of the pharmaceutical regulatory system and remain invisible to authorities. Brokers are not directly subject to national legislation and they operate at an international level without being mentioned on bills and or held as a responsible party in the strict legislative sense. Brokers appear to be the only intermediaries in the pharmaceutical supply chain not subject to authorisation and regulatory control, which has to be a major point of concern.

Public health impact and pharmacovigilance

The types of Adverse Drug Reaction (ADR) associated with the inadvertent use of counterfeit medicines can relate to one or more of a number of problems depending on the type of counterfeiting practice employed. Counterfeit medicine associated ADRs may be due to, but not limited to, inappropriate API dose (absent, insufficient or excess dose) and quality problems (product contamination, excipient problems).

Under reporting of possible counterfeit medicine related ADRs is likely to be significant when one takes into account the well known problem of ADR under reporting even for authorised medicinal products. A weakness in the existing European pharmacovigilance system is that it is not explicitly geared to detection of 'drug ineffectiveness'. The direct impact of the inadvertent use of counterfeit medicines on public health in Europe by an unsuspecting public is thus difficult to determine based on known currently available data.

While it is extremely unlikely that inadvertent consumption of counterfeit medicines in Europe is related to major mortality (unlike the situation that exists in some countries in Asia and Africa), it is certainly possible, if not probable, that counterfeit medicines make a not insignificant morbidity contribution (via, for example, ineffectiveness, inappropriate/mislabelling and no possibility for batch recall).

An overview of recent stakeholder commentary, and sample of comments, on the problem of counterfeit medicines in Europe is provided in the following box:

Member of European Parliament, Francoise Grossetete: "Counterfeiters are using repackaging as an opportunity. As our borders become increasingly permeable, there will be more pirating, more fakes and more counterfeiting. Europe needs to equip itself with the means to successfully combat these illegal practices."

German Federal Ministry of Health (BMG): "When dealing with counterfeit drugs we are not only dealing with intellectual property – it directly impacts on the health of our citizens. Until now, there have only been a limited number of cases within Europe. WHO recently announced that in the EU it is below 1%. Nevertheless, a huge increase in numbers indicates that it could become a substantial problem even for Europe, in the very near future."

European Commission (EC): "The EU has made great progress in harmonising pharmaceutical legislation and marketing authorisation. However, there is now an urgent need to take care of the distribution channels and to ensure that these products can be safely distributed to the consumer in a safe manner. Improvements in legislation, customs and intellectual property still need to be made."

"We need understanding from the public and especially from those potential consumers. If the public is well informed then the counterfeiters will be less successful in selling their products."

European Medicines Agency (EMEA): "The European Medicines Agency does not have the responsibility at all for counterfeit medicines. Legally speaking, it is the national competent authorities of the Member States who have the full responsibility of supervising distributors, manufacturers and licensing of medicines. They have come together in an informal club called the Health Surveillance Club. They have created a working group with the European medicine enforcement officers, who are working very actively in this field. Thus, informally much is going on. However, this is not sanctioned by European legislation."

European Generics Association (EGA): "The lack of auditing of certain partners in the legitimate supply chain can be viewed as an omission in the total system of quality control against counterfeit medicines. The area of the supply chain that is most vulnerable to counterfeits entering the stream of commerce is with secondary wholesalers, and not through transactions between legitimate manufacturers and the primary distributor."

European Federation of Pharmaceutical Industries and Associations (EFPIA): "Examples reported by research-based pharmaceutical companies highlight a series of safety and quality problems arising from the handling of pharmaceutical products by parallel traders, in addition to logistic problems and regular product shortages in some countries where medicines simply do not find their way to patients in need. This raises not only serious safety issues in terms of patient consumption, but also acts as an obstacle in case of product recalls. At the extreme end of the spectrum, there is also the risk of unlawful counterfeit medicines reaching patients under the guise of parallel imports. Recent incidents in the UK have indeed highlighted the risk of counterfeit medicines finding their way into the legitimate supply chain through parallel trade."

"Counterfeiters are using repackaging as an opportunity. As our borders become increasingly permeable, there will be more pirating, more fakes and more counterfeiting. Europe needs to equip itself with the means to successfully combat these illegal practices."

Facts and statistics on counterfeit medicines in the EU

According to the EC:[33, 34]

- counterfeit medicines increased by 1000% between 1998–2004
- in 2003, 100 million counterfeit articles with a value of $1bn were seized at external EU borders
- between 2001–2005, 197 cases of counterfeit medicines were identified in the pharmaceutical supply chain
- 170 counterfeit medicines were identified in illegal distribution channels over the past five years in the EU Member States
- 2,711,410 counterfeit medicines were seized at EU borders in 2006 – a rise of 384% on the previous years' articles seized (560,568) and the highest increase in seizures for all categories.

Counterfeit and substandard medicines are a real and intensifying threat to European patient safety and need to be addressed by all stakeholders. For example, in terms of finished medicinal products, 1,647 million packs of medicine were sold in Germany in 2002. If, as the WHO estimates, 1% of these medicines were counterfeit, then a staggering 16.4 million packs of counterfeit medicines were sold in Germany in that year.[35]

There are no available statistics for counterfeit APIs in the EU. In view of real and serious weaknesses in the global regulation of API trading, the statistics for fake or adulterated APIs being traded in the EU are likely to be truly frightening. As the French Agency for Environmental and pubic health protection states, 'counterfeited APIs may enter the supply chain early on'. The real and serious threat posed by fake and adulterated APIs was described by the Council of Europe 2006 report, and has been very recently highlighted by a sobering article published in the New York Times.[36] A major problem is that we have a far from accurate picture of the scale of API adulteration and counterfeiting and its impact on the rest of the pharmaceutical supply chain.

However statistics can be misleading, particularly when it comes to discussing public health issues. It is not the absolute scale of a problem but its existence and growth that should be of concern, particularly when it pertains to public health. Drug safety should be a zero tolerance business. Although the WHO estimates the prevalence of counterfeit medicines in Europe to be 1%, the EC has witnessed a rapid rise in the detection of counterfeit medicines over the past two years, particularly as a result of the actions of some informed and proactive EU Drug Regulatory Authorities (such as the UK's Medicines and Healthcare products Regulatory Agency – MHRA) and customs authorities' increasing awareness of the problem. Estimating the scale and impact of counterfeit medicines is a fraught business; an analogy can be made with estimating the size of an iceberg.

"There are no available statistics for counterfeit APIs in the EU. In view of real and serious weaknesses in the global regulation of API trading, the statistics for fake or adulterated APIs being traded in the EU are likely to be truly frightening."

Pharmaceutical crime practices

The box below presents a classification of pharmaceutical crime practices.[29] These are highly diverse with no shortage of creativity shown by counterfeiters, particularly in the case of API counterfeiting. All of these practices reportedly occurred in Europe:

TABLE 2 MEDICINE COUNTERFEITING PRACTICES	
1.	**Finished medicinal products**
1.1	*Identical copy* – identical formulation with packaging and labelling that is hard to differentiate from the original
1.2	*Pure counterfeit* – altered/replaced ingredients with similar packaging (but either no/different/wrong dose API or excipient)
1.3	*Hybrid counterfeit* – re-use of components/refilling (eg, genuine containers [ampoules, bottles, vials, syringes] and packaging with substitute or no API)
1.4	*Illegal relabelling/repackaging* – genuine formulated product falsely repackaged/relabelled as being from the original manufacturer and intended for the same or diverted to a different market than originally intended by manufacturer (also includes use of fake pricing labels and products claiming wrongly to be an original product eg, use of well-known name or trademark)
1.5	*Diversion and illegal trade* – of genuine medicinal products with genuine packaging and labelling (whether or not through the internet)
1.6	*Unpackaged medicinal products* – eg, wholesale/retail of medicinal products without the primary authorised packaging
1.7	*Placing a non-authorised medicinal product on the market* – exploitation of regulatory weaknesses concerning regulation of personalised medicine trade within the EC borders
1.8	*False documentation* – eg, granting a Certificate of Suitability (CoS or CEP)* by regulatory authorities without the given company being audited, false CEP, incorrect status on import documentation
1.9	*False MAA* – entire marketing applications is sold and used; their contents do not have any relationship with the actual operations involved in the manufacture of the API or dosage form
1.10	*Waste/expired product re-entering the market* – includes repackaging and relabelling of expired products
2.	**Active pharmaceutical ingredients and excipients**
2.1	*API procurement from uncontrolled/non-GMP origin* – done by some authorised FP manufacturers because uncontrolled API source is cheaper
2.2	*Illegal API relabelling/repackaging* – unauthorised API material may also be shipped in containers labelled with the name of a different API
2.3	*'Ghost API manufacturing plant'* – API (possibly not produced via the registered manufacturing process) not manufactured by the 'registered producer' is sold to FP MAH (who may be unaware of this fact, as API label mentions only the authorised manufacturer; a broker/trader may play a crucial role in this practice)
2.4	*'Ghost API supplier'* – MAH purchases API willingly and knowingly from a different manufacturer than that specified in the MA (in this case the manufacturing process will normally differ from that described and authorised in the MA)
2.5	*'Paper curtain'* – API manufacture performed through different process than that specified in the MA (a double documentation system may be used at the manufacturing site: one hidden set containing the true data and another set containing faked data that comply with authority requirements and regulations; such documentation systems may even be in place at a site where the API is not manufactured at all)
2.6	*'Authorised facades'* – manufacturer/trader with approved CEP and DMF supplies API material from a large number of unauthorised manufacturers (all labelling mentions only the authorised manufacturer. This set up is believed to be widespread regarding API material imported from China and possibly also India. In addition forged CoA and other forged documents will also be used in such situations)
2.7	*Illicit intermediate production* – unauthorised API materials from obscure sources are blended with the registered API material

* CEP (also known as CoS) is the Certificate of Suitability of European Pharmacopoeia monographs and is intended to demonstrate that the purity of a given substance produced by a given manufacturer is suitability controlled by the relevant monograph(s) of the European Pharmacopoeia.

Identification of counterfeit medicine cases in the European PPT system

In spite of the obvious risks presented by the additional complication of PPT in the European pharmaceutical supply chain, until recently there was no 'real' evidence to suspect that the European PPT system in any way presented an opportunity for counterfeit medicines to enter the legal European pharmaceutical distribution system. In fact, the ability to discuss whether PPT was actually a threat to supply chain security was actively discouraged by some senior European regulatory and public health parties.

However, in the last few months, four cases of counterfeit medicines arising in the parallel pharmaceutical distribution system, and requiring batch recalls, have been officially reported by the MHRA in the UK (see table below).[37]

TABLE 3 PARALLEL-TRADED PRODUCT BATCH RECALLS MADE BY THE UK MHRA SINCE MAY 2007

24 May 2007 | Class 1 Drug Alert (action now – including out of hours): Counterfeit parallel distributed product – Zyprexa tablets 10mg (olanzapine) The MHRA in conjunction with the European Medicines Agency EMEA, and with assistance from Eli Lilly and Company Ltd, are recalling any parallel distributed stock of lots A200127, A216454 and A229505 (and lot variants) of olanzapine tablets 10mg branded as Zyprexa following the discovery of counterfeit tablets in the legitimate supply chain.
25 May 2007 | Class 1 Drug Alert (action now – including out of hours): Counterfeit parallel distributed product – Plavix tablets 75mg film coated tablets (clopidogrel) We are recalling any parallel distributed stock of lots 3098 and 6Y098 (and lot variants) of Clopidogrel tablets 75mg branded as Plavix following the discovery of counterfeit tablets in the legitimate supply chain.
01 Jun 2007 | Class 1 Drug Alert (action now – including out of hours): Counterfeit parallel imported product – Casodex tablets 50mg (bicalutamide) We are recalling any parallel imported stock of lot 65520 (and lot variants) irrespective of livery of Bicalutamide tablets 50mg branded as Casodex following the discovery of counterfeit tablets in the legitimate supply chain.
04 Jun 2007 | Class 1 Drug Alert (action now – including out of hours): Counterfeit parallel distributed product – Waymade plc – Plavix tablets 75 mg Film Coated Tablets (clopidogrel) We are recalling any parallel distributed stock of certain batches of Plavix 75mg film coated tablets following the discovery of counterfeit tablets in the legitimate supply chain

In addition, there have been 10 cases of counterfeits found in the UK legitimate supply chain since August 2004, of which five were found on pharmacy shelves and had been dispensed to patients.

There may well have been previous cases of counterfeit medicines appearing in the legitimate supply chain as a result of PPT, but this is almost impossible to claim retrospectively. A leading UK pharmaceutical security expert, Graham Satchwell has summarised the problem and potential of uncontrolled pharmaceutical trade allowing counterfeit medicines into the legitimate supply chain (several of which could have arisen via PPT) through the following real case studies:[38]

Real counterfeit medicine cases in the UK to 2003 reported by a leading UK pharmaceutical security expert

A sick business – counterfeit medicines and organised crime

The following cases are all a matter of record. This short list is not comprehensive, but represents those cases that are known to the author, Graham Satchwell. All have been discovered by the authorities by accident; none had been detected as a result of any proactivity. This begs a question over the quality of checks and searches.

1 In 2003, a dealer in Kent bought a consignment of AIDS drugs from a dealer in Essex, which when raided was revealed to have incriminating documents plus half a tonne of cannabis on the premises. Police dropped the cannabis charges when the dealer claimed that he knew nothing about it! Some of the AIDS drugs, which had circulated the world before coming back into the UK as parallel-traded items and being stored with cannabis in Essex, were being sold by the dealer to NHS hospitals.

2 In 1998, counterfeit Losec was parallel-imported and spotted by the parallel importer as not appearing genuine. Some 6,000 bottles had been bought from a licensed dealer in Italy.

3 In 1999, Eli Lilly & Co goods were delivered to Preston, Lancashire, and supplied to a patient who found that they had been damaged in transit and sent the damaged goods directly to Eli Lilly & Co to complain. On examination by Lilly they were found to be part of a larger consignment intended for the Red Cross in Russia. The Russian mafia was believed to be involved.

4 In 1994, a UK wholesaler found that 'good quality' counterfeit Zantac (a GlaxoSmithKline product) had been delivered to him in the UK from Greece. This was the fourth occasion on which this product had been seen in Britain.

5 In 2001, counterfeit Viagra tablets were discovered in Oldham. These had originated in Thailand. The offender was bailed and subsequently absconded.

6 In the mid-1990s, counterfeit Losec was discovered being distributed in North London.

7 In 2000, counterfeit Nubain – an injectable painkiller – was being counterfeited in Newcastle by an offender who was sentenced to five years imprisonment for criminal deception.

8 In the late 1990s, Humatrope, an Eli Lilly & Co product, was being manufactured illegally in a factory at Pilling near Liverpool. The offender was sentenced to five years in prison, though he maintained that he was forced to manufacture this product having been subject to assault and death threats by a Liverpool crime gang.

9 Counterfeit Dermovate was seen in many London pharmacies in the 1990s. Cynically advertised by the counterfeiters as a product that would 'lighten the skin', it contained steroids that could cause permanent damage to sensitive areas on the face.

As the title of the 2006 Stockholm Network publication asks, is this a *'Coincidence or Crisis'?* [32]

The recent cases of counterfeit medicines appearing in the legitimate supply chain through PPT were identified by the UK MHRA, arguably the European Drug Regulatory Authority (DRA) with the strongest regulatory capacity to deal with the threat of counterfeit medicines – in view of its strong market intelligence capability developed in recent years. How significant is the threat of counterfeit medicines appearing elsewhere in Europe through the legitimate supply chain as a result of PPT? Although the UK may be a major destination for PPT products, the fact is that the EU/EEA is a single market with no internal border controls. In the absence of a clear picture of internal EU PPT, we only have a limited idea of where PPT products end up. PPT products have the potential to change hands (up to 20 times in some cases) and be repackaged many times over.

Organised crime, counterfeit/diverted medicines and the illicit drug business

Little doubt exists now that organised crime is involved in the insertion of counterfeit and diverted medicines into the European supply chain, exploiting regulatory weaknesses in Europe's pharmaceutical administrative system. It is a natural extension of the illicit drug trade.

Frailties in cooperation between the authorities responsible for illicit drug and authorised medicines control is a point for serious concern as was highlighted in a recent article entitled *'Deadly Trade'* published by the journal *'World Pharmaceutical Frontiers'* in 2007.[39] To what extent organised crime has entered the PPT business is hard to determine in view of major European administrative coordination problems. The absence of global cooperation on the twin subjects of illicit drugs and counterfeit/diverted medicines is well illustrated by the United Nations International Narcotics Control Board 2006 annual report.[40]

Protecting the EU borders: customs, drug importation and counterfeit medicine seizures

Irrespective of the weaknesses concerning governance of pharmaceutical GDP inside the EU territory, the regulatory safety of PPT is also strongly dependent on the EU's ability to protect and control its own borders with respect to importation of APIs, excipients, Bulk Intermediate Products (BIPs) and 'finished' medicinal products. The trading control and regulation of medical devices is also an imported related subject for discussion.

The following analysis was recently provided by the author on pharmaceutical import, export, transit regulation and customs control:

> A number of important weaknesses exist.
>
> In relation to import, export and transit controls on FPs, controls on APIs and bulk/intermediate products (BPs) are much less stringent and also inconsistent in Europe. As a result of the single EU market, there is limited requirement for trade controls between Member States, thus APIs (and FPs) that have illicitly entered one State can then be easily disseminated throughout the EU.
>
> The storage of pharmaceuticals in a bonded warehouse/free zone is inconsistently legislated for in European States.
>
> Existing certification schemes in Europe are often inadequate with large scope for documentation fraud (a 'reliance on paper' can be said to be important, but in comparison, the US Food and Drug Administration uses this and other methods to corroborate data – eg, the use of e-data).
>
> The actual factors and approach adopted by European States in medicine customs risk analysis and control is highly variable. Risk factors applying to medicinal products (eg, specific drug class or custom tariff code) are not employed universally by authorities. Very often, customs will rely heavily on information or intelligence provided by the rightholder. The types of control carried out by customs are often not related specifically to medicinal products, with the exception of narcotics and psychotropics as a result of obligations under UN conventions.
>
> As a result of the single EU market, weaknesses in the trade control system of one Member State can provide a critical weak point in the entire EU pharmaceutical regulatory system. Thus although some Member States, with strong regulatory and control systems, may assume that they have no counterfeit medicine problem on their territory, this assumption may well be false.
>
> *Coincidence or Crisis (Chapter 1): Counterfeit Medicines & Pharmaceutical Crime in Europe: 'Invisibility, Biohazard & System Failure'*

In the opinion of a leading European research-based manufacturer, sanofi-aventis, "we are not as well protected as we think in Europe. In Europe we need to keep an eye on too many disorganised import networks. There are all sorts of illegal imports".[41]

According to the EC customs authorities, 'the percentage of seizures by EC customs of fake and adulterated medicines, while not very high (1.5% of all seizures), is rapidly increasing. The data is not alarming; it is terrifying. The first statistical data for the year 2006 shows a 380% increase in seizures of fake and adulterated medicines. There is clear indication that the problem is growing. There is also the issue of cooperation with China in ensuring global pharmaceutical supply chain security for example, although

recent information soon to be published indicates that it is India and the United Arab Emirates that are the main sources of counterfeit drugs. However, we believe that European customs has been improved today. Customs is part of the solution to the problem. We do have the means and the legal basis. However, it is not perfect and much needs to be done.'

The EC customs have faced a number of problems in controlling the import of APIs, Bulk Intermediate Products (BIPs), (ie. half finished medicinal products) and finished medicinal products into the EU territory. For example, concerning Intellectual Property Rights EC customs state "these are to a large extent, in the hands of the Member States". Thus, customs has to rely on different legal bases in different Member States in order to implement legislation. "This is a problem requiring action." A further problem has been the customs coding and risk assessment of medicinal products (not just for high risk finished medicinal products, but also for APIs and BIPs).

However, the recent introduction of new legislation on the enforcement of Intellectual Property Rights (IPR) (including relevant customs actions),[42] that deals with civil enforcement of IPR, has assisted the EC customs with its battle against counterfeit medicine imports. Furthermore, changes to the customs codes have greatly assisted EC customs: "now for the first time we have a community-wide legal basis for risk analysis." The results of this new legislation are impressive. Statistics from the customs authorities indicate that the amount of fake medicines stopped at the external border of the EU are alarming and are challenging our system. At the same time EC Customs confirm that the use of regulatory and enforcement strategies pays off.

The first directive on the enforcement of IPR, Directive 2004/48/EC,[42] deals with 'civil enforcement' of IPR. It was hastily passed before the Fifth Enlargement of the EU on May 1, 2004. It did originally include criminal sanctions provisions, but this rather controversial part was omitted in order to be able to meet the May 2004 deadline.

Recently a proposal for an EC directive on 'criminal measures aimed at ensuring the enforcement of intellectual property rights',[43*] (being the second directive on the enforcement of intellectual property rights, it is sometimes called IPRED2 – Second Intellectual Property Rights Enforcement Directive) has been approved by the European Parliament in its first reading. EU wide penalties are foreseen, and thus this new directive when it comes into force can be considered to be a major step forward in combating counterfeit medicines and pharmaceutical crime.

The EU directive on criminal measures aimed at ensuring the enforcement of intellectual property rights is a proposed directive aimed "to supplement Directive 2004/48/EC of 29 April 2004 on the enforcement of intellectual property rights (Civil enforcement)" (Source: Justification for the proposal, COM(2005) 276 final, July 12, 2005). The directive was proposed on July 12, 2005 by the Commission of the European Communities.

* A proposed directive to "supplement Directive 2004/48/EC of 29 April 2004 on the enforcement of intellectual property rights (civil enforcement)" (Source: Justification for proposal, com(2005) 276 final, July 12, 2005). The directive was proposed on July 12, 2005 by the Commission of the European Communities.

The capability of EU authorities to tackle the problem of medicine counterfeiting

The Council of Europe's report has highlighted many administrative weaknesses associated with the prevention, detection and elimination of counterfeit medicines from the European market.[29] Mike Tremblay has summarised the administrative problems relating to these issues succinctly, as follows, including highlighting the problem of 'regulatory denial':[16]

Finding common ground: policy imperatives For Europe

"Regretfully, much medicines regulation focuses on regulating the medicines themselves, and documenting approval of companies to engage in the medicines trade. This means that systemic problems that cut across the regulatory rules may fail to register as priorities because they fall outside the regulator's formal jurisdiction, and may be a concern for industry or another regulatory body or agency. A simple example involves distinguishing between the regulator's licensing of companies to import medicines, and national customs enforcement of importation: the former enables the latter to act, while the latter is responsible for detecting criminal conduct by those licensed by the former. A third body may be required to enforce regulatory compliance, and a fourth may deal with recovery of payment for the medicines. In the meantime, commercial partners in the pharmaceutical supply chain continue to be confronted with rogue traders and must improvise their own disparate solutions.

This regulatory denial is unhelpful in dealing with problems that are emergent and in the early stages of becoming major. This denial is highlighted when concerted action across borders is required and international agreements are lacking. In Europe, the situation is complicated by the requirements of the single market, the open border with free movement of goods, and where existing European Union (EU) medicines regulation fails to adequately frame counterfeiting in a EU context. A similar situation exists between Canada and the USA.

The absence of comprehensive and reliable data on the prevalence of counterfeit drugs also means that regulators, rightly from their perspective, can deny the existence of a major problem. The lack of good information makes it more difficult to justify raising the priority of counterfeiting. That there have been no major scandals and health catastrophes in any European Member State is taken by regulators as evidence that the system is working – the situation is no different in other countries where discussion on counterfeiting is muted, and so the denial is reinforced by whatever poor-quality empirical evidence exists. This, in turn, does not justify urgent action by lawmakers. But, more than that, poor data undermine proper understanding of the potential scope of the global medicines counterfeiting 'industry'.

The failure to pool information and knowledge and adopt common definitions and data means that differences between national regulators will continue to frustrate attempts at a coherent response to the problem at an EU or international level."

Coincidence or Crisis? Prescription Medicine Counterfeiting (Chapter 3)

Thus, Europe potentially has a problem with counterfeit medicines because of weaknesses in its administrative system.

Recent European initiatives to combat medicines counterfeiting and pharmaceutical crime

Given that there is now a realisation by the Council of Europe, the European Parliament and the EC that the issues of pharmaceutical crime and counterfeit medicines need addressing, actions are now being taken. The EC has recently launched an assessment of the counterfeit medicine situation in the EU, which is related to its assessment of PPT. The Council of Europe is pursuing its approach to developing a European Convention on Counterfeit Medicines and Pharmaceutical Crime. How the EC and Council of Europe initiatives on counterfeit medicines and pharmaceutical crime will eventually interact remains to be seen.

Global pharmaceutical supply chain security

What is pharmaceutical supply chain security, why do we need it and why is it necessary for it to be organised at a global level? Because we live in the age of a global pharmaceutical market where production and trading of APIs, BIPs and final dosage forms (finished medicinal products) crosses the world's borders, a finished medicinal product placed on the EU market is probably manufactured at several intermediary stages in several different countries as a result of the globalisation of the business. Thus, it is important to have global pharmaceutical supply chain security in order to protect European patients. A valid comment on this issue is provided by Satchwell[38] who succinctly summarises the situation as follows:

> "The WHO, when discussing the many deaths that have resulted from counterfeit and substandard medicines, clearly identifies the dangers that come from repackaging. It states: 'Because of a lack of regulation and enforcement, the quality, safety and efficacy of both imported and locally manufactured medicines in many developing countries cannot be guaranteed. Subsequently, smuggling and illegal importation of drugs are often rife. Substandard and counterfeit drugs are then not only sold in these countries but also exported or re-exported.' This is an important point – it is wrong to assume, when goods can easily be offered for sale from the remotest places, that export from poorer countries of the world to Europe will not take place.
>
> The situation is worsened by the fact that medicines exported from many industrialised countries are not regulated to the same level as those domestically consumed, while export of drugs to developing countries via free trade zones is increasing. Relabelling of products to mask details of their origin is also known to occur.
>
> The WHO fact sheet points out that 'some policymakers now believe that drug regulation represents an unnecessary barrier to trade and should be reduced to a minimum. Pharmaceuticals, however, cannot be considered a standard commodity since consumers and prescribers are unable to assess their quality, safety and efficacy and the results can be harmful to patients' health."

The issue of supply chain security is highly interconnected with the issue of counterfeit medicines as illustrated by the following comment from a major European pharmaceutical wholesaler (Celesio AG): "The British authorities (UK MHRA) identified five (counterfeit medicine batch) cases between 2004 and 2006. Counterfeit medicines were being delivered through the usual channels to patients. As pharmaceutical traders we have to work within the existing channels because one counterfeit medicine is one too many."[41]

The EC now recognises that it has a problem with regulation and oversight of the European pharmaceutical supply chain. The following box provides a commentary (by the author of this report) on how counterfeit medicines can enter the legal pharmaceutical distribution system:

> **The entry of counterfeit medicines into the legal pharmaceutical distribution chain**
>
> 'Evidence exists that counterfeit medicines appear in the legal distribution chain at all stages. The reasons as to how they get there are probably several and include insufficient distribution controls, multiple ownership and levels in the distribution chain, illegal trading by legal wholesalers and pharmacies, unregulated repackaging, substandard control practices by participants, documentation weaknesses and forgery, poor traceability requirements, and the relative ease of switching of legitimate to counterfeit API. In some countries, wholesalers and pharmacists report to different regulatory bodies which makes regulation of the legal distribution chain more problematical.'
>
> *Coincidence or Crisis: Counterfeit Medicines & Pharmaceutical Crime in Europe: 'Invisibility, Biohazard & System Failure'* (Chapter 1)