European supply chain complexity and confusion

The degree of difficulty in putting together a map of European pharmaceutical distribution illustrates the very problem: it is extremely difficult to regulate and secure the supply chain when we do not know where it is and who is doing it. Neither the EC nor EFPIA (European Federation of Pharmaceutical Industries and Associations) is able to compile an accurate map of European pharmaceutical distribution; this situation also makes it difficult for authorities and manufacturers to track a product. It should be possible, theoretically, to map the European pharmaceutical supply chain based on a compilation of registered distributors and the issuance of PPT import licences. In practice, however, this does not happen. No one has been handed responsibility for it.

The European pharmaceutical distribution system is extremely complex. It involves full-line European-level distributors, European-level parallel distributors, national full-line distributors, European- and national-level short-line distributors, national-level parallel distributors, pharmacy distributors, distributor manufacturers etc.

Complicating the situation further is the system's current complex and dynamic horizontal and vertical integration process. Different Member States have different rules and regulations for the allowance of pharmacy chains etc. The following box provides a recent overview (by the author of this report) on the topic of European pharmaceutical trade complexity:

European pharmaceutical trade complexity

'Trade globalisation, the dropping of trade barriers/restrictions and PPT have led to the legal pharmaceutical distribution chain in Europe becoming increasingly complex and involving many intermediaries; particularly downstream with the appearance of micro-distributors (ie, short-line wholesalers, secondary wholesalers and wholesaling retailers, small import/export firms etc). Arguably, the value added from PPT is dubious and only serves to complicate the European distribution system and make regulatory control more difficult.

While pharmaceutical trade liberalisation may provide consumer benefits, including greater choice and cheaper prices, it presents problems for the health regulatory authorities. Firstly, the jurisdiction of the latter is confined within State borders, and secondly the same authorities have understandable difficulties in applying the prescribed principles of medicines Good Trade and Distribution Practice (GTDP) to distributors below the level of the primary distributor. Criminal organisations and dishonest traders can easily take advantage of this situation.

The 'unregulated'/illegal distribution chain feeds off the legal distribution system via the practice of diversion; it undoubtedly plays a major role in the distribution of counterfeit medicines and is made up of a diverse range of players. These include secondary wholesalers and wholesaling pharmacies, and entities such as fitness and bodybuilding clubs, shops specialising in undercover goods of all types, illegal wholesalers and retailers (following internet bulk purchasing), sex clubs/shops, food supplement and cosmetic stores.'

Coincidence or Crisis: Counterfeit Medicines & Pharmaceutical Crime in Europe: 'Invisibility, Biohazard & System Failure' (Chapter 1)

Why do we have two European-level pharmaceutical trader associations, one for full-line European-level authorised wholesalers (GIRP) and another for European-level parallel traders (EAEPC)? Of course, the EAEPC serves as a lobbying body *for* PPT. In some cases there is crossover of membership between the two associations, however GIRP seems to have a strong position *against* PPT. GIRP states that its members are not allowed to repackage and enter into manufacturing, while EAEPC members are permitted to do so. What is the reason for this?

In Europe we have a single European-level association for the researched-based pharmaceutical manufacturing industry (EFPIA), one European-level association for the generic manufacturing industry (EGA) and one for the self-medication manufacturing industry (AESGP), all of which clearly represent different pharmaceutical sector businesses. One should therefore question why there is a need for the business of pharmaceutical distribution to have two different European-level associations.

GIRP comment on the necessity for two separate European-level pharmaceutical distribution associations

"I would like to emphasize that the profession of a full-line wholesaler is very different from the one of a parallel trader. A full-line wholesaler has a public service function to take care of the safe, adequate and continuous supply of all medicines to pharmacies (and in some countries also to hospitals) in order to ensure the availability of medicines for the patients in the Member State. The licence covering full-line wholesalers does not permit them to make any adjustments to the outer pack of a product as this activity requires a manufacturing authorisation. On the other hand, parallel importers who adjust the pack to the national requirements have a manufacturing authorisation for this activity. Full-line wholesalers treat parallel-imported products as different from those of the original manufacturer. The parallel-imported product is stored separately, ordered under a different number and becomes the manufacturer's product."

(Statement to the author by the GIRP Director, July 2007)

Analogy with the pharmaceutical distribution situation in the US

Is it only the EU, in the developed world, which has a problem controlling pharmaceutical distribution? One only has to look at recent occurrences in the US concerning a minimally-regulated and confused pharmaceutical distribution system and confused regulatory supervision, and how that situation allowed counterfeit medicines to enter the pharmaceutical supply chain easily. A complicated and multi-layered pharmaceutical supply system with inconsistent and uncoordinated regulation can lead not only to human public health disasters but also undermines the whole system of publicly-funded pharmaceutical financing. The situation was described saliently in the book *Dangerous Doses*.[44] EU authorities have a lot of scope to learn from US experience.

Pharmaceutical Good Distribution Practice (GDP) in the EU

In the context of the EU pharmaceutical regulatory system in general, regulation of distribution is very weak. Regulation of distribution is currently governed by GDP guidelines written several years ago,[8] although there is an indication that the EC intends to update them in the near future.* However, guidelines do not constitute 'hard' regulatory procedure. There are problems in the EU with the observance of GDP guidelines, which the following box highlights:

* Article 84 of Dir 2001/83/EC: The Commission shall publish guidelines on good distribution practice. To this end, it shall consult the Committee for Proprietary Medicinal Products and the Pharmaceutical Committee established by Council Decision 75/320/EEC (1).

Observance of GDP in Europe

'Even in European States that have strong pharmaceutical regulation there is cause for concern in the legal distribution chain. A recent study by the Dutch Health Care Inspectorate revealed several major shortcomings in the application of Good Distribution Practice (GDP) by legitimate parallel and 'full range' distributors.

The findings from the 2004 Dutch Health Care Inspectorate Study of Distributors revealed that GDP is not universally observed. In many cases, the distributor does not adequately check the trading authorisation of its customers. Moreover, almost all distributors lack a formal system to identify and intercept counterfeit medicines. In several cases, actual infringements of current legislation were observed. For example, some distributors had purchased pharmaceuticals from persons without the necessary authorisation to sell them. Similarly, a number of wholesalers were found to have supplied pharmaceutical products to persons who were not authorised to trade in them.

A further finding is that insufficient safeguards exist to ensure the proper destruction of medicines. In most cases, it was not possible to demonstrate that products returned for destruction had actually been processed in the incinerators as required.'

Coincidence or Crisis: Counterfeit Medicines & Pharmaceutical Crime in Europe: 'Invisibility, Biohazard & System Failure' (Chapter 1)

Several European drug regulatory authorities, both the EMEA and national DRAs, recognise that they have a problem with interpreting and implementing existing rules, for both medicinal products and medical devices:

- The EMEA states that, 'there are problems with the implementation of existing rules today. Furthermore, the control of the supply chain of medical and diagnostic devices is completely left to the discretion of the Member States. With the exception of Belgium, no other Member States have established any control or requirement with regard to the distribution of medical devices.'
- The Italian Ministry of Health has stated recently that, 'it is our task as European legislators to ensure that the business distribution networks are as safe as the products themselves. There is room for improvement. Similar problems and issues come up with active pharmaceutical ingredients, we need to have the same standards for them as for the medicine itself.'
- However, an anonymous national DRA states, 'we do not have harmonised legislation within the EU. Therefore, we do not have the wherewithal to do this job.'

Parallel Pharmaceutical Trade and Good Distribution and Manufacturing Practice

Parallel Trader Association Good Distribution and Manufacturing Practice Guidance

The European PPT association (EAEPC) has introduced guidelines to ensure the regulatory compliance of its business via the introduction of 'Good Parallel Distribution Guidelines for medicinal products'[45]

The EAEPC parallel pharmaceutical trading guidelines cover the important issues of: maintenance of the integrity of the supply chain, the need to have a Qualified person (for quality assurance), Control of incoming stock, Re-labelling/Repackaging, Final release, Storage conditions, Transport conditions and Inspections (GMP), Pharmacovigilance, Changes in the original marketing authorisation, Withdrawal of original marketing authorisation, Customer complaints, and Recalls.

In many ways, the GDP document drawn up by the PPT business is more comprehensive than that originally designed by the EC for pharmaceutical distribution in general. While the efforts made by the EAEPC to draw up regulatory guidance should be congratulated, there is potentially a big difference between association designed guidance and authority enforced practice – for many reasons the regulatory guidance and enforcement should arise from the side of the regulatory authorities.

However, irrespective of the concerns over regulation of the pharmaceutical distribution system, it is not clear how regulatory authorities oversee the parallel pharmaceutical trading business with respect to pharmaceutical Good Manufacturing Practice (GMP).

Good Distribution Practice experience with respect to PPT

The problems of ensuring European pharmaceutical GDP are likely to be exacerbated seriously by the practice of PPT. The author of this report, in 2006, summarised his opinion on the regulatory problems concerning PPT with respect to repackaging, relabelling and documentation printing which are presented in box A below. Further evidence, analysis and opinion on how PPT can potentially cause drug safety problems is provided by other sources in boxes B, C and D:

(A) Regulation of packaging, labelling, documentation printing and parallel importation

'Increasing supply chain complexity is associated with evermore prevalent repackaging and relabelling practices, and which are sometimes multiple for one product. Regulation of medicines (re) packaging, (re) labelling and printing is not performed consistently across European States. Of concern is the probable existence of unregulated or illegal packaging, labelling and printing facilities.

Legal provisions governing PPT in the EU tend to rely on existing provisions governing import licensing and marketing authorisation. As the regulation of finished medicinal product PPT is not determined at EU level, there is broad scope for Member States to interpret their own procedures for governing PPT.

The existence of a significant level of PPT within the EU, in the absence of adequate controls on repackaging and relabelling, can inadvertently facilitate entry of counterfeit medicines from one Member State into another. Re-(exchangeable) finished medicinal product packaging and labelling practices are highly prevalent across all European States.

Although known cases of counterfeit medicines have arisen in the European parallel trading system, the extent to which the practice of PPT in itself is a facilitating factor for the dissemination of counterfeit medicines throughout Europe has not been sufficiently studied to draw any firm conclusions. What is clear though is that PPT is reliant on a significant amount of repackaging, relabelling and printing and contributes to the increasingly complex pharmaceutical distribution system in Europe.'

Source: Coincidence or Crisis: Counterfeit Medicines & Pharmaceutical Crime in Europe: 'Invisibility, Biohazard & System Failure' (Chapter 1)

(B) EFPIA dossier on problems created by PPT

EFPIA has a dossier that contains over 1,350 examples of logistic, health and quality issues found in parallel-traded products circulating in the European market. These issues include:

- 50 examples of out-of-stock situations as a consequence of irregular new orders from parallel traders, involving life-saving products (eg. to treat heart diseases or cancer)
- 700 examples of regulatory and quality issues, most of which represent serious health concerns, ie. wrong dosage, wrong usage instructions, wrong expiry date, opening of originally sealed bottles, misleading information in the leaflet, wrong warning statements, side effects missing, incorrect declaration of active substance on both leaflet and carton, wrong language, untidy cutting of blisters damaging the cavities, etc.
- 600 examples of trademark issues, including debranding, importer name more prominent than manufacturer, sticker not allowing to read trademark or manufacturer name, etc.
- three examples of counterfeit products that have, or are believed to have, been distributed through the parallel trade route (legal action still open). Reimbursement frauds are also being investigated.

Furthermore, serious difficulties in recalling parallel-imported products have been noted, while concerns have also been raised on the compliance of parallel traders with cold chain parameters to be respected in the distribution of certain drugs.

Source: two surveys conducted by EFPIA among its member companies and associations, end of 2003 and July 2005

(C) Social Market Foundation (UK policy think tank) opinion on PPT

'The complexity of how these goods are supplied create possible consumer issues by (i) introducing the risk of human error via repackaging of imported medicines and (ii) making it more difficult to crack down on counterfeiting medicines. Some sources estimate that a product can change hands 20 or 30 times before it reaches the patient. This can make it difficult to track and recall batches of drugs when there are concerns about their safety. The pharmacist, who is the last part of the supply chain before medicines reach the patient, sometimes has very little information available to them in making an assessment about the integrity of the pack. This is because many of the features applied by the manufacturers to ensure product security (such as tamper-proof sealing) may be lost.'[11]

(D) US Center for Medicine in the Public Interest opinion on supply chain security, PPT and counterfeit drugs

'Last year more than 140m individual drug packages were parallel imported throughout the EU — and a secondary wholesaler repackaged each and every one. This means that, literally, parallel traders in Europe open 140m packets of drugs, remove their contents and repackage them. But these parallel profiteers are in the moneymaking business, not the safety business. And mistakes happen. For example, new labels incorrectly state the dosage strength; the new label says the box contains tablets, but inside are capsules; the expiration date and batch numbers on the medicine boxes don't match the actual batch and dates of expiration of the medicines inside; and patient information materials are often in the wrong language or are out of date.

The result is that drugs purchased from a British pharmacy to an unknowing American consumer could come from EU nations such as Cyprus, Estonia, Greece, Latvia, Malta or Poland. In fact, parallel-traded medicines account for about 20% (one in five) of all prescriptions filled by British pharmacies. In the EU there is no requirement to record the batch numbers of parallel imported medicines, so if a batch of medicines originally intended for sale in Greece is recalled, tracing where the entire batch has gone (for example, from Athens to London through Canada to Indianapolis) is impossible. Caveat Emptor is bad healthcare practice and even worse healthcare policy. Safety cannot be compromised, even if the truth is inconvenient for these parallel traders – these profiteers masquerading as pharmacists.

But there is a more insidious problem with parallel trade – it provides a convenient pathway for criminals to insert counterfeit medicines into the legitimate supply chain. With huge profits, counterfeiting is increasing at a phenomenal pace. The Center for Medicine in the Public Interest estimates that counterfeit-drug commerce will grow 13% annually through 2010. Counterfeit sales are increasing at nearly twice the rate of legitimate pharmaceutical sales.

Illegal drugs are a money machine. In 2010, it's estimated that fake drugs will generate $75bn in revenues – a 92% increase from 2005. And the risks of detection and prosecution are low. Authorities are concerned. The EU recently released statistics on counterfeit-drug sales in Europe. Canadian authorities have made some high-profile arrests. But overall, the results of enforcement have been marginal.

Two years ago the FDA claimed that counterfeit drugs were being used to fund global terrorism, and recent news that North Korea has gone into the business of manufacturing and selling counterfeit drugs has further proved the growing danger of counterfeit medicines entering the legitimate pharmaceutical supply chain via parallel trade.

The largest counterfeit market with close proximity to the EU free trade zone is Russia, where approximately 12% of drugs are said to be counterfeit. Now that the Baltic nations of Latvia, Lithuania and Estonia have joined the EU, the WHO has warned that there is increased risk of counterfeits entering the supply chain.'

US Center for Medicine in the Public Interest, 2007

Observations and actions by key distributors and manufacturers on rationalising and obtaining better control of the European pharmaceutical distribution system

There is clearly a need to introduce measures to rationalise the European pharmaceutical distribution system. In terms of updating EU GDP (and converting it into harder law) and in a way that takes account of the increasing supply chain security threats, the box below provides observations made by a major pan-European full-line wholesaler:

Updating European GDP: observations made by Celesio AG (European full-line wholesaler and GIRP member)[41]

'Celesio suggests a common industry standard made up of four parts: safe distribution; transparency in the supply chain; a programme against counterfeiting; and proper communication.

Safe Distribution. It is necessary for all distributors to be certified through an independent auditor and regularly checked. We should only be working with such certified companies. Doctors and hospitals should only be supplying themselves with products from these certified suppliers. In addition, they should have a choice of such certified suppliers.

Transparent Supply Chain. Information transparency must be achieved through inventories of sales reports. Everyone should have an anti-counterfeiting system, 'certified' being the key word. There needs to be an early warning system so that everyone in the supply chain can be warned in good time, when counterfeits appear. We also have to work with authorities like the police and customs. We have a safe supply coalition and we will introduce it very soon.

Certification Program. The certification authority should be a neutral regulatory authority. It should hand out a quality-seal, which would apply to the whole supply chain, producers, wholesalers, middlemen and pharmacies. As far as patient safety is concerned we are suggesting a first step, which should contain certain elements. Firstly, every supplier should meet GIRP standards. Secondly, there should be official documentation of each licence. There should be a certified training programme for staff in recognising fakes.

Proper Communication. There should be a blacklist of companies that are trying to sell pharmaceutical products without a licence. This would be most effective. As a company with corporate social responsibility, we believe this is the minimum we can do in a business where we are dealing with human health.'

At the same time, some members of the European research-based pharmaceutical industry – in view of their frustrations with the obvious unsatisfactory state of European pharmaceutical supply chain security, arguable non-transparency of the European PPT business and debatable undermining of their national pricing policies (due to artificial partitioning of the European pharmaceutical market) – are unilaterally implementing their own measures to secure the distribution of their products. The following box summarises this situation:

Recent initiatives by the European research-based pharmaceutical industry to secure its supply chain and simplify the pharmaceutical distribution system

Pfizer has initiated a trend by introducing unilateral measures to secure its supply chain directly to patients. According to Pfizer, "a research-based manufacturer should be able to secure its supply chain through mechanisms such as sole distributorships if necessary."

The following press statement from mid-2007 summarises the situation concerning ways in which other European research-based pharmaceutical manufacturers are following Pfizer's lead in this tactic to secure product distribution:[46]

'Eli Lilly and Novartis are the latest pharmaceutical giants to consider restricting the number of distributors they use to supply their products to chemists and doctors, despite claims this will stifle competition. The drug companies say the controversial move is necessary to combat counterfeit drugs. But some industry experts claim their true motivation is to tighten control and prevent a wave of cheap imports.'

'The UK Office of Fair Trading (OFT) is investigating limiting the number of distributors. Sanofi-aventis this week became the latest big pharma to restrict the number of wholesalers that distribute its drugs. From November it will nominate three pharmaceutical wholesalers, UniChem (part of Alliance Boots), AAH Pharmaceuticals and Phoenix, who will be allowed to distribute the company's drugs to pharmacies.

"The OFT is examining whether such deals are anti-competitive, and is to report in the summer of next year. Some pharmaceutical wholesalers claim that what the drug companies are really trying to do is stamp out parallel trade. This happens where medicines that are sold in other European Union countries at a cheaper price are imported to the UK and sold at a discount. UK Members of Parliament have also expressed concern that limiting suppliers could lead to medicine shortages or delays in delivery.'

'Usually, drug companies sell their drugs to wholesalers, who then compete to sell drugs to pharmacies and doctors. Pfizer, the world's biggest drugs company, prompted a row in September 2006 when it announced that UniChem would be the only company allowed to distribute its drugs in the UK. Since then, AstraZeneca announced that UniChem and AAH Pharmaceuticals would exclusively distribute its products, but has put off implementing its plan until next year. It is thought that AstraZeneca and sanofi-aventis may escape OFT censure as they have both chosen more than one distributor. A spokeswoman for Lilly said: "Lilly is considering a number of options about how we warehouse and supply our medicines, and we observe our industry colleagues' decisions with interest. We expect to be able to make a decision later this year."

The role of technology in European supply chain security

Technology plays an important role in securing the supply chain, particularly in view of the increasing threats of medicines counterfeiting and diversion. Technological measures to secure the supply chain consist of (i) product and packaging security (authentication) and (ii) product verification (track and trace) procedures. At a global level, these issues are being addressed by the WHO IMPACT Technology Working Group.[28] The following box provides views (of the author of this report) on medicinal product security and traceability:

Medicinal product security and traceability (pedigree tracking) systems

'Current security and traceability systems are generally regarded as being weak in their capacity to counteract the increasing sophistication in original packaging (and dosage form) forgery and to cope with the increasingly complex distribution system. Particularly worrying is that, compared with finished medicinal products, security and traceability systems for APIs and Bulk Intermediate Products are, arguably, practically non-existent. With regard to product security, several companies are now examining the possibility of introducing systems that consist of one or more overt, covert or forensic features, including trace substances, more unique closure systems and infra red spectrographic methods. Concerning traceability, proposals include the introduction of authentication technology for rapid identification at pharmacy-level, internet-based track and trace, mandatory paper or electronic pedigree, bar coding and radio frequency identification tagging (RFID).

Currently absent in Europe, however, are unified and harmonised regulatory guidelines that can assist manufacturers in defining a common minimal security and traceability standard and that can assist European regulatory authorities in their task.'

Coincidence or Crisis: Counterfeit Medicines & Pharmaceutical Crime in Europe: 'Invisibility, Biohazard & System Failure' (Chapter 1)

In Europe, research-based manufacturers are implementing various technology-based product and packaging authentication measures and various medicinal product verification systems are being tried and tested in several EU Member States (eg. in Belgium, Italy and Portugal). While product and packaging authentication measures understandably need to be the dictate of the manufacturer, the need to have different and various product verification systems in Europe is open to debate.

In the immediate-to-medium term, it is clear that high technology based medicinal product traceability systems (such as RFID), will not work in view of both the high cost and lack of a commonly agreed approach to medicinal product verification by EU Member States. There is a need in the EU to gain coordination concerning the choice and implementation of product verification systems, however, ultimately technology is not a replacement for human systems of guaranteeing supply chain security.

New models of pharmaceutical trading – internet and mail order pharmacy

The challenge of providing effective pharmaceutical distribution regulation in Europe is now complicated further by the rapid growth of internet and mail order pharmacy. In addition, the EC has to tackle the problems of 'unlicensed medicines' and medicines advertising. The following box provides a commentary (by the author of this report) on these issues:

Internet and mail order pharmacy, unlicensed medicines and medicinal product advertising

Unquestionably, the internet poses a significant risk for the dissemination of counterfeit medicines, as there is little regulation of internet medicines sales in Europe. The internet, as well as mail order, offers an easy way to illegally distribute prescription only and unlicensed medicines to consumers and websites also offer Bulk Intermediate Products for sale. Internet pharmacy is possibly the leading type of 'spam' worldwide with an emphasis on the retail of cheaper, lifestyle or unauthorised prescription medicines.

While there is an internet and mail order supply (without the need to obtain a prescription) and demand for these types of medicines, plus a lack of public awareness of the risk of purchasing drugs through unregulated sources, this type of business will continue to thrive. Unregulated internet and mail order pharmacy of prescription drugs are a serious threat to public health and undermine the entire pharmaceutical regulatory framework. Under existing European legislation, health and pharmaceutical regulatory authorities are very often powerless to investigate and control this type of business.

Coincidence or Crisis: Counterfeit Medicines & Pharmaceutical Crime in Europe: 'Invisibility, Biohazard & System Failure' (Chapter 1)

The US and Canada are currently the biggest markets for internet pharmacy sales and this causes considerable regulatory problems as many foreign internet pharmacies operate in a regulatory void. There are a considerable number of rogue internet pharmacies operating throughout the world. For example, a high percentage of internet pharmacies claim to be of Canadian origin, when in fact they could be based anywhere else in the world.

In the context of the impact of internet and mail order pharmacy on European PPT, Datamonitor states that 'in addition, the consolidation of wholesalers and the emergence of mail order and internet pharmacies may exert greater pressure on parallel distributors and thus restrict parallel trade in Europe. The emergence of mail order and internet pharmacies could also cause parallel trade to take a different route. It is feasible that these pharmacies could sell directly to consumers based in other EEA countries, resulting in cross-border parallel trade on the individual rather than commercial level.'

The growing trend of internet pharmacy challenges the traditional model of pharmaceutical distribution and, in many ways, can be seen to be a rationalising force on the existing EU pharmaceutical distribution, prescribing and dispensing system, in spite of the obvious weaknesses that currently exist in its regulation. However, the introduction of personalised medicines trading through the increasing trend of mail order and internet pharmacy is likely to have a complex interaction with the business of PPT which will make the job of regulators much harder. Exactly how PPT interacts potentially with internet and mail order pharmacy is yet to be addressed and fully studied.

The legal and regulatory situation applicable to PPT: weaknesses and costs

There are many potential weaknesses and costs in the EC legal and regulatory system pertaining to PPT, which has been developed through a long and continuing process of European case law. This section of the report attempts to analyse the deficiencies in the legal and regulatory framework applicable to European PPT and to provide an analysis of the regulatory costs of supervising PPT and ensuring regulatory compliance. A full and evidence-based analysis requires a comprehensive and well-designed survey of stakeholders, particularly national DRAs, original manufacturers, wholesalers and pharmacists with input from legal and regulatory experts. However, the analysis provided here is based on the author's personal assessment of the situation.

The legal situation

In spite of the initial EC legislation laying down the fundamental principle of free movement of goods, and EC laws on anti-competition, the legal situation concerning PPT is heavily contested and PPT regulation is consequently based on constantly changing case law and EC jurisprudence interpretations. This is not a satisfactory situation from the point of view of many sector stakeholders. In this context, a summary of the EC 2003 Communication FAQ is provided that summarises the problem from the perspective of the EC:

'… not every issue regarding parallel imports has been addressed by the Court. As the internal market develops, new questions keep emerging and old answers need further clarification. While all parties pursue their legitimate interests in the framework of the internal market, respect of what has already been achieved and close cooperation among Community institutions, national authorities and economic operators continues to provide the solid basis for the resolution of all outstanding issues.'

'So, have all problems been finally resolved? Not quite. Even though the Court has addressed a great number of issues and despite the Community legislation that deals with general issues regarding the marketing of medicinal products, there can by no means be any 'definitive' guide to parallel imports. New questions keep emerging and old answers need more clarification.'

Weaknesses in the European pharmaceutical regulatory system pertaining to PPT

Parallel pharmaceutical traders are required to hold a pharmaceutical wholesaling authorisation issued (in accordance with Article 77 of Directive 2001/83/EC, as amended) by the competent authority in the member state in which they are located. As a manufacturing operation, all repackaging/re-labelling requires a pharmaceutical manufacturing authorisation issued by the competent authority in the country of destination. Holders of manufacturing authorisations are obliged to follow Good Manufacturing Practice (GMP) guidelines, employ an EU Qualified Person and are subject to periodic inspection by the competent authority. A summary of the regulatory hurdles that have to be met by parallel pharmaceutical traders are below (as described by the European PPT association):

'Every parallel traded product has in fact been approved twice – its producer obtains a marketing authorisation to place it first on the market and then each parallel trader requires an abbreviated marketing authorisation to sell it. In addition, any trader that repackages or re-labels parallel trade has a manufacturing authorisation, employs a legally-responsible EU Qualified Person, and is subject to Good Manufacturing Practice regulations and periodic government inspection.' European Association of Euro-Pharmaceutical Companies (the European parallel pharmaceutical trade association [EAEPC]).

Within the EC/EEA, there are several shortcomings in terms of the adequacy of legal interpretation, regulatory provisions and their effective implementation with respect to the regulatory management of PPT.

With respect to the UK PPT regulatory situation, Satchwell[38] has highlighted the problems of inadequacy of both the necessary system and funding for GDP inspections (irrespective of the need for GMP inspections) of parallel pharmaceutical traders, and has further highlighted a major conceptual problem with respect to regulating PPT in the context of drug safety. If the UK, which has arguably the strongest drug regulatory authority in Europe, has a potential problem with the regulation of PPT, then what is the overall European situation likely to be?

A number of weaknesses in terms of the adequacy of legal interpretation, regulatory provisions and their effective implementation with respect to the regulatory management of PPT exist and which are summarised as follows (based on an analysis and legal interpretations of EC 2003 Communication):

- *An uncertain and vague legal framework based on imprecise case law and legal interpretations.* The principle EC PPT regulatory documents are the EC 2003 Communication[2] which is based on case law and legal interpretations, and EMEA guidance for parallel distribution of centrally-authorised products.[3] EC pharmaceutical regulatory directives only cover the regulation of PPT indirectly. There are many shortcomings and vagueness with respect to the guidance laid out by the EC 2003 Communication, so it is perhaps no surprise that EU national DRAs may have a problem with PPT regulatory oversight
- *Ambiguities of interpretation of EC rules lead to divergent practices between Member State DRAs.* There is often confusion about which practices should be compulsory and which should be interpreted in the best light of the EC guidance available. Interpretation of EU rules based on a communication provides significant scope for deviation at national levels and requires considerable time for national DRAs to be able to interpret the rules. Some national DRAs attempt to provide their own detailed guidance (eg, UK MHRA), while others do not
- *Definition of the term 'similarity of a medicinal product' for the purposes of PPT.* The EC 2003 Communication often uses interchangeably the terms 'the same', 'very similar', 'sufficiently similar' and 'essential characteristics'. For example, 'when the product concerned is the same or very similar to a product already authorised for sale in the Member State into which it is to be imported'. The current definition of 'sufficiently similar' is based on case law. The EC Q&A on the subject does not sufficiently clarify in spite of court rulings. Greater clarity on definitions is required
- *There is a potential regulatory problem when in spite of differences in excipients or other product features, a product is deemed to be 'sufficiently similar' for the purposes of PPT.* The legal interpretation does not take full account of pharmaceutical regulatory and supply chain security issues.[A] The fact that a parallel-traded medicinal product does not, according to the EC 2003 Communication, have to be identical in all respects to the product already marketed by the manufacturer is an invitation for medicine counterfeiters and diverters
- *Problems relating to different authorised pack sizes in PPT product originator and destination Member States.* Repackaging is complicated by the fact that there are often different pack sizes for the same medicinal product authorised in different Member States. This relates to the issues of 'artificial partitioning of the market'[B] and national variances in pharmacoepidemiology. There may be often very good public health reasons, sometimes dictated by national regulatory requirements, for having different pack sizes. As the EC 2003 Communication states, there are circumstances, however, (eg. difference in language), whereby certain alterations in the form of packaging are considered necessary for the marketing of the medicinal product in the Member State of destination, in other words, in order to avoid the artificial partitioning of the Internal Market
- *Definition and interpretation of "repackaging and relabelling" and clarification of the term "effective access".*[C] Current EC guidance on repackaging and relablling is not sufficiently clear. Relabelling and repackaging can have a similar adverse impact on "effective access" as can the practice of not relabelling or repackaging. Different 'rules' apply for nationally authorised (NP), Mutual Recognition

Procedure (MRP) authorised and Centralised Procedure (CP)[D] authorised medicinal products. The current rules are divergently interpreted by Member State DRAs and parallel traders and thus this situation compromises product security and patient safety. There is no clarity on the rules for 'deboxing', 'underboxing' , 'overboxing' and relabelling (to the extent that these practices actually benefit the patient)

- *Repackaging adversely affects the original condition of the product.* According to the EC 2003 Communication 'Repackaging should not adversely affect the original condition of the product'. The original condition of the product surely also includes product security features (packaging security and anti-tampering features). Repackaging and relabelling removes product security features introduced by the original manufacturer
- *Repackaging and relabelling regulations are not sufficiently clear.* The current rules are interpreted divergently by Member State DRAs and parallel traders and, thus, this situation compromises product security and patient safety. There is no clarity on the rules for 'de-boxing', 'underboxing', 'overboxing' and relabelling (to the extent that these practices actually benefit the patient)
- *Assessing whether repackaging is necessary.* A subjective element is introduced into the procedures for ensuring supply chain security. The EC 2003 Communication states 'whether repackaging is objectively necessary according to the conditions explained below is, in any case, to be assessed on the basis of the circumstances prevailing at the time of marketing of the medicinal product in the Member State of destination'. Pharmaceutical regulation is about precision. Such a statement leaves a lot of scope for divergent interpretation
- *PPT provides scope for an additional margin of human error in guaranteeing supply chain security.* PPT adds an additional margin for human error in guaranteeing supply chain security. The concept of 'adverse effects on the original condition of the product' as stated in EC 2003 Communication, admits to the possibility of increased human error as a result of repackaging. For example, in the changing of pack sizes and providing new Patient Information Leaflets (PILs)
- *Requirement for regulatory supervision of repackaging.* The EC 2003 Communication states that there is a need to have regulatory authority supervision of repackaging. There is a question as to whether this happens in practice
- *Absence of the need to have repackaging authorisation from the original manufacturer.*[E] In view of the EU pharmaceutical supply chain security deficiencies it is surprising that the original manufacturer does not have the right to provide repackaging authorisation. It is not impossible in the current situation that a repackaged product could be illegitimate
- *Parallel pharmaceutical trade introduces manufacturing into the drug distribution business.* In the EC, as is the case elsewhere in the developed world, normally it is a requirement to have separate licenses for manufacturing and distribution of medicinal products. However the business of PPT seems to be able to combine the two separate processes into one without regulatory supervision.
- *Legal and regulatory interpretation of the ability of Member State authorities to stop or restrict parallel imports.*[F] This is a difficult point for national authorities to interpret
- *Delays in implementation of the few EC directive provisions relating to PPT.* Delays in national implementation of EC 2004/27 EC with respect to PPT provisions is highlighted by the EC as being a problem
- *Notification procedure between Trade Mark (TM) holder and PPT trader.* The EC 2003 Communication is very vague on this issue: 'both parties, nevertheless, must make sincere efforts to respect each other's legitimate interests'. In the context of pharmaceutical regulation some clarity is required
- *Weaknesses and complications in pharmacovigilance obligations and communication.* Pharmacovigilance supervision of PPT products (particularly, when the original product is withdrawn from the destination

market) is weakened due to the absence of a legal requirement for PPT traders to report suspected product defects

- *Batch recall of medicines.* PPT compromises the ability for regulatory authorities to implement batch recall of medicines in the case of suspected product defects
- *Regulatory requirement for guaranteeing pharmaceutical supply.* The PPT system undermines public health in terms of the assurance of guaranteed pharmaceutical supply (ie. products intended for the supply of one country are parallel traded to another)
- *Withdrawal of the original reference product.* Regulatory and legal interpretation problems may occur when the original 'reference' product is withdrawn from the PPT product destination market[G]
- *Adequacy and understanding of product presentation and required information on 'repackaging' that allows a dispenser and patient/consumer to understand the difference between an original product and a PPT product.* The current regulatory and legal situation with respect to what information should be required to allow consumers to make an informed choice between an original or a PPT product is vague, if at all, existent. For example, EC 2003 Communication states that there are reasons to allow PPT traders to diversify their packaging according to whether the product is dispensed directly to a patient through a pharmacy or whether the product is dispensed in a hospital setting.[H] PPT by its nature allows trade between the hospital and consumer sectors which further complicates supply chain security.
- *Exhaustion of intellectual property rights, PPT and European pharmacoepidemiology.* The legal principle of 'Community exhaustion' limits the rights of original manufacturers to place medicinal products as when they may see fit with respect to the highly varying pharmacoepidemiology in Europe. There are very often good pharmacoepidemiological reasons why a medicinal product may be placed at different times in different EU Member State markets.

The EC has recognised recently that there may be shortcomings in the regulation of PPT and, thus, has implemented a thorough study on the issue. This is based on (i) concerns that there is limited harmonised legislation and regulation of PPT for both nationally authorised products (parallel import) and for centrally authorised products (parallel distribution), (ii) the opinion of the Member States group of legal experts (EMCOLEX) and (iii) increasing reports on medicinal product quality defects within the EU territory.

What are the costs of supervising PPT and ensuring regulatory compliance?

Health economic analysis of PPT has to take into consideration the regulatory costs associated with the PPT practice. There are a number of costs associated with supervising PPT and ensuring regulatory compliance both on the side of regulatory authorities and also on the side of both the original manufacturer and the parallel trader. The costs involved are both financial and the added administrative burden.

1) Drug Regulatory Authority Costs

   As the EAEPC states, 'every parallel traded product has in fact been approved twice - its producer obtains a marketing authorisation to place it first on the market and then each parallel trader requires an abbreviated marketing authorisation to sell it.' At the same time, a manufacturing authorisation should also be issued and supervised according to GMP standards.

   PPT causes extra workload for DRAs in terms of the need for regulatory compliance and supervision which can be summarised as follows:

   - *Difficulties of interpretation of EC rules that are not based on hard law.* The current EC rules for governance of PPT are based principally on a Communication derived from case law and the EMEA guidance document for centrally authorised (CP) products. The Communication guidance is imprecise and leads to difficulties of interpretation at the EU Member State level.

- *The need to provide extensive regulatory clarification for what should be a marginal regulatory activity.* The EMEA guidance document on parallel pharmaceutical distribution is quite extensive in relation to the scale and added value that PPT brings to the European community. Regulating PPT diverts resources from more important regulatory activities directed at what should be considered as the normal system of pharmaceutical development, production and supply
- *Licensing of parallel traders.* As distributors of medicines, parallel pharmaceutical traders require a licence to operate. This requires regulatory resources to examine licence applications and subsequent issuing and supervision of licences. A parallel imported medicinal product is subject to a licence granted on the basis of a 'proportionally simplified' procedure (compared to the full marketing authorisation procedure for original products). This involves a number of tasks: confirming that a product imported in parallel is indeed the same or sufficiently similar to the 'reference product', PIL conformity and language assessment, packaging approval etc. The EC 2003 Communication FAQ states 'national authorities are entitled to confirm that a product imported in parallel is the same or sufficiently similar to the one already authorised for circulation in their market'. How this process of 'entitlement to confirm' by national regulatory authorities works in practice is open to debate.
- *PPT distribution chain supervision (GDP and GMP compliance) including supervision of repackaging and relabelling (manufacturing compliance).* There is a regulatory obligation to supervise and oversee pharmaceutical distribution; PPT obviously adds an additional regulatory burden to supervising and overseeing the regular pharmaceutical manufacturing and distribution chain. Furthermore, the EC 2003 Communication states that 'repackaging should be carried out under the supervision of a public authority to ensure that the product remains intact (ie. ensuring GMP compliance).' Does this occur in practice?
- *Liaison between drug regulatory authorities.* Close liaison is required between the relevant competent authorities to obtain the necessary information to ensure that only those products which fully comply with the stringent criteria for parallel import are granted a licence. There is a requirement for EU national DRAs and the EMEA to liaise concerning the origin of a PPT product, its 'sufficient similarity' to 'the reference product' and the issuing of a PPT product licence. With respect to the CP procedure there is an additional burden of informing the EMEA.[I]

2) Original manufacturer costs: additional costs are incurred by the original product manufacturer to meet their regulatory obligations concerning product safety and traceability, protection of their IPR, and communication with authorities and PPT traders concerning their products which are parallel traded.

   - *Repackaging and trademark compliance checking.* The original manufacturer has to check compliance of the repackaging proposed by the parallel pharmaceutical trader.[J] Ensuring that the original manufacturer TM is not defamed in a way that undermines the product reputation and patient safety and satisfaction.[K]
   - *Safety and traceability costs.* Obligations regarding quality defect reporting, pharmacovigilance reporting, recall and withdrawal of products. To the extent that PPT also potentially undermines the product security features incorporated by the original manufacturer, then this places an additional burden on the original manufacturer.

3) Parallel trader costs: there is a significant regulatory compliance cost to the parallel pharmaceutical trader which is incurred above the regulatory compliance cost of a full-line wholesaler. A parallel pharmaceutical trader can be considered to be a manufacturer in addition to a distributor, although the EC rules are vague in this respect. This is a pharmaceutical regulatory issue which requires urgent attention.

- *Obtaining a PPT product licence.* This requires submission of a regulatory dossier under the PPT 'simplified procedure'. The parallel importer is accordingly required to submit all relevant information. A separate application is required for each presentation of a medicinal product.
- *Product licence fee.* In the case of a centrally authorised product (CP), a licence fee is payable to the EMEA, while for a nationally authorised product a licence fee is payable to the destination country DRA. This fee is highly variable between countries[L].
- *Medicinal product trademark holder notification costs.* It is a legal requirement to notify the TM Holder with respect to the intended parallel trade of a product and also supply samples of the product and its packaging.
- *Specific manufacturing requirements.* Conversion of an original product to a parallel traded product requires repackaging, relabelling, exchange of original PIL with a new PIL and attention to braille requirements; processes which obviously must incur a not insignificant cost towards the final product price. A manufacturing licence to conduct this process is required, but to what extent that pharmaceutical manufacturing licensing, including GMP inspections, actually exists for parallel traders is open to a large debate.
- *Supply chain security requirements.* Ensuring security of product sources and transparency of product flow. Given that products change hands several times via the PPT process, the costs of tracking products is likely to be high, assuming that parallel traders have systems to track product flow.
- *Continuous supply provisions.* The EC rules and provisions governing continuous pharmaceutical supply are also incumbent on parallel pharmaceutical traders.

A The product imported in parallel (ie. after a first marketing authorisation has been granted by the Member State of destination) does not have to be identical in all respects to the product already marketed by the manufacturer but it should have at least been manufactured according to the same formulation, using the same active ingredient, and should have the same therapeutic effects (Com 2003).

B 'The artificial partitioning of the market may not necessarily be directly attributed to and intended by the proprietor of the trademark but to such factors as the ones mentioned by the Court: a rule authorising packaging only of a certain size or a national practice to the same effect, sickness insurance rules making the reimbursement of medical expenses depend on the size of the packaging, or well-established medical prescription practices based, inter alia, on standard sizes recommended by professional groups and sickness insurance institutions.' (Com 2003).

C The Court has clarified the term 'effective access', ruling that there may exist on a market, or on a substantial part of it, such strong resistance from a significant proportion of consumers to relabelled medicinal products that there must be held to be a hindrance to effective market access. Therefore, in those circumstances, the proprietor of the trademark may not oppose repackaging. (Com 2003).

D Centrally authorised products: 'The Court has held that the detailed and specific requirements regarding the packaging, which are intended to prevent consumers from being misled and, thereby, to protect public health preclude the joining together and relabelling of packages of that medicinal product. The Court added, however, that the creation of new packaging may be possible if that repackaging is objectively necessary so that the imported product gains effective access to the market of a Member State.' (Com 2003).

E 'It is, nevertheless, not necessary to require that the further express statement be made on the packaging that the repackaging was carried out without the authorisation of the trademark owner, since such a statement could give the misleading impression that the repackaged product is not entirely legitimate.' (Com 2003).

F 'Can the Member State of destination stop or restrict parallel imports? Yes, if they can establish that any restrictive measure aims at the protection of human health and life or the protection of industrial and commercial property (ie, patents and trademarks). National authorities must also show that such measures are necessary and proportionate.' (Com 2003).

G 'If the authorisation for the 'reference product' is withdrawn, can Member States also remove the relevant parallel import from the market? When the authorisation for the reference product is withdrawn on grounds other than the protection of public health (for example, for reasons related to the marketing policy of the manufacturer), that should not automatically result in the withdrawal of the parallel import licence.' (Com 2003).

H 'The public is particularly demanding as to the quality and integrity of pharmaceutical products, and defective, poor quality or untidy packaging could damage the trademark's reputation. However, the requirements to be met by the presentation of a repackaged pharmaceutical product vary according to whether the product is sold to hospitals or, through pharmacies, to consumers. In the former case, the products are administered to patients by professionals, for whom the presentation of the product is of little importance. In the latter case, the presentation of the product is of greater importance for the consumer.' (Com 2003)

I Although no further authorisation is required, the Community (in practice the EMEA) and national authorities of the Member States in which the medicinal product will be distributed in parallel shall be informed that such parallel distribution will take place in order to enable the EMEA to check compliance with the terms of the Community marketing authorisation and the national authorities to monitor the market (batch identification, pharmacovigilance, etc) and to carry out post-marketing surveillance (Commission Communication on the Community marketing authorisation procedures for medicinal products, OJ C 229, 22/7/1998, p.4–17) [53]. The Commission is proposing to make

this system compulsory in the on-going review of the pharmaceutical legislation (articles 76(3) of Directive 2001/83/EC and 57(1)(n) of the proposed regulation replacing Regulation (EEC) No 2309/93).

J 'The proprietor of the trademark must be given advance notice of the repackaged product being put on sale. The proprietor may also require the importer to supply him with a specimen of the repackaged product before it goes on sale, to enable him to check that the repackaging is not carried out in such a way as directly or indirectly to affect the original condition of the product and that the presentation after repackaging is not likely to damage the reputation of the trademark. If the parallel importer does not satisfy that requirement, the trademark proprietor may oppose the marketing of the repackaged pharmaceutical product.' (Com 2003).

K Presentation of the repackaged product. The Court has acknowledged that even if the person who carried out the repackaging is indicated on the packaging of the product, there remains the possibility that the reputation of the trademark, and thus of its owner, may nevertheless suffer from an inappropriate presentation of the repackaged product. In such a case, the trademark owner has a legitimate interest, related to the specific subject-matter of the trademark right, in being able to oppose the marketing of the product. In assessing whether the presentation of the repackaged product is liable to damage the reputation of the trademark, account must be taken of the nature of the product and the market for which it is intended. (Com 2003).

L An analysis of fees for the licences in 2004 by Kanavos et al., revealed that they varied from as little as $224 in Greece to as much as $12,068 in Norway.

Circumventing European PPT: pharmaceutical research-based industry options (A Simplified Guide)

The complexity and opacity of the legal situation concerning PPT and the tension between PPT traders and the research-based industry have meant that the rules governing PPT have had to be frequently updated based on EU jurisprudence. There exist legal opportunities for research-based manufacturers to circumvent PPT, for example as illustrated by the 2004 landmark judgement on PPT in favour of the original manufacturer:

'The 2004 Bayer Adalat Case'

The legal framework supporting parallel trade in the EU has restricted the actions pharmaceutical companies can take to restrict parallel trade, but Bayer's legal victory on the Adalat case in 2004 has provided companies with an opportunity to take action that can effectively restrict parallel trade without infringing EU law.

There may be good reasons for research-based manufacturers to do so. According to a leading academic expert on social pharmacy, Professor David Taylor, London School of Pharmacy "… given legitimate concerns about 'exporting' individual Member State price controls across the Union's internal borders into other Member States where there are different national policies, an arguably more desirable approach for Europe would (as has recently been discussed in Spain) be to permit pharmaceutical manufacturers to charge wholesalers/traders the highest European price for medicines that it is believed will be parallel traded. If evidence is supplied that the order has in fact been used in the Member State it was initially supplied to, the research based manufacturer could discount back (with due interest) the relevant price difference".[24]

How can the research-based pharmaceutical industry circumvent PPT? In lieu of the weaknesses and gaps in the current regulatory guidelines pertaining to European PPT, several options are open to the research-based industry. Datamonitor has identified four main options open to research-based pharmaceutical manufacturers to legally circumvent European PPT:

- supply management – restricting the volume of drugs available for parallel trade
- price management – introducing a 'price corridor'* across the EEA, introduction of dual pricing schemes in a potential exporting country, manipulating profit-based pricing systems (eg. UK PPRS)**

* Where a company prices its products by establishing a minimum and maximum price across multiple national markets rather than setting a different price for each market.

** Some companies strategically used the UK Pharmaceutical Price Regulation Scheme (PPRS) to modulate the price cuts on particular drugs and particular packs that were subject to high levels of parallel importation.

- legal challenges – clarifying the application of EU law and an intellectual property owner's rights
- different packaging and brands – imposing the extra burden of repackaging on parallel distributors.

In addition, Datamonitor states there is also the 'do nothing' approach.

The fact that there are several options for manufacturers to circumvent and minimise PPT, implies that the PPT system is unsustainable. There is constant tension between manufacturers and healthcare payers. Clearly this situation is a symptom of a fundamental problem with the EU single pharmaceutical market that is not being solved by PPT.

European medicines safety: the situation and concepts

One of the major issues pertaining to PPT is concern over ultimate medicines safety, hence it is important to look at what ultimate medicines safety is (or should be) and how it is guaranteed with respect to legitimate authorised medicines, as well as the safety issues that surround the illegitimate supply of medicines.

Is there a medicines safety problem in the developed world (let alone in the developing world)? What is pharmacovigilance and what is medicines safety? At the same time we have to consider what evidence-based pharmacotherapy is and whether patients (healthcare consumers) have an informed choice with respect to the pharmacotherapy they receive.

The problems of ensuring safety for regulated medicines in the legitimate European supply chain

As the recent EC consultation document on the single European pharmaceutical market states, 'events such as the 'Vioxx' case (on September 30, 2004, Merck voluntarily withdrew Vioxx – rofecoxib – from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use. Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market)[47] or the failed clinical trial in the UK that resulted in significant trial volunteer morbidity due to unforeseen catastrophic immunological reaction to an innovative new product under test for the first time in humans[48] demonstrate that the safety of medicines remains a major EU internal market issue.'

Satchwell[38] summarises the situation concerning drug safety problems in the UK based on real evidence:

'Medication errors account for 11% of hospital admissions in the UK. There are about 850,000 adverse events every year, with an average of 7–8.4 bed days per adverse event. There is an extra annual expenditure of £1.1bn on drug-related adverse events, up to 70% of which are preventable. 95% of problems are due to 'processes', and only 5% to people. The research suggests that in 2002 in England, ADRs caused the hospital admission, followed by the death, of 5,700 patients. The true rate of death, taking into account all ADRs (those causing admission, and those occurring while patients are in hospital), may therefore turn out to be greater than 10,000 a year. Older drugs continue to be most commonly implicated in causing such admissions and deaths, and measures are urgently needed to reduce the burden on the NHS.

In terms of the need for the UK authorities to review their existing adverse reaction reporting systems to incorporate the eventuality that substandard or counterfeit medicines can enter the system, Satchwell states that there is a need to 'review again' the yellow card scheme (UK MHRA Adverse drug reaction reporting system) to ensure that healthcare professionals, the pharmaceutical industry and patients can report both adverse reactions and packaging and tampering concerns or errors in sufficient detail to enable meaningful analysis leading to identification of potential counterfeit products and enabling prioritisation of efforts. In 2004, a major review of the yellow card scheme was carried out and improvements were made, but the essential need was focused on gathering information on apparent adverse reactions to 'established' pharmaceutical products.'

There are clear inadequacies regarding the reporting of adverse drug reactions, related to weaknesses in the regulatory management of PPT within the UK healthcare system. The UK is considered to be one of the more rational and supervised pharmaceutical markets in Europe. So if this is the case in the UK, what is the case likely to be elsewhere in Europe?

There is evidence from the rest of the EU of ADR problems, but it is hard to compile it in the absence of an EU-wide pharmacoepidemiological reporting system. It is beyond the scope of this report to compile the EU-wide data on drug safety issues relating to legitimate medicines placed on the EU market, but certainly the topic demands attention such that the EC authorities gain a comprehensive understanding of drug safety within their borders.

The US also has a problem with drug safety. The US Institute of Medicine Committee (IOM) in 2006 published an Assessment of the US Drug Safety System, entitled *'The Future of Drug Safety: Promoting and Protecting the Health of the Public'*,[49] which is summarised in the following box:

The Future of Drug Safety: Promoting and Protecting the Health of the Public (22nd September 2006)

In response to growing public concern with health risks posed by approved drugs, the US Food and Drug Administration (FDA) and the Department of Health and Human Services announced a series of steps to address drug safety, including asking the IOM to convene a committee to assess the US drug safety system and to make recommendations to improve risk assessment, surveillance, and the safe use of drugs. The result is the production of a report entitled *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. The committee considered the drug safety system as the sum of all activities conducted by the FDA and other stakeholders to monitor, evaluate, improve, and ensure drug safety.

Although much of the committee's work was focused around the drug review, safety surveillance and related activities of the Center for Drug Evaluation and Research (CDER), the committee also reviewed some key aspects of the roles and considered the potential contributions of the pharmaceutical industry, the academic research enterprise, Congress, the healthcare delivery system, patients and the public. During its research, the committee found that there is a perception of a crisis which has compromised the credibility of the FDA and pharmaceutical industry.

Most stakeholders, the agency, the industry, consumer organisations, Congress, professional societies and healthcare entities appear to agree on the need for certain improvements in the system.

The drug safety system is impaired by the following factors: serious resource constraints that weaken the quality and quantity of the science that is brought to bear on drug safety; an organizational culture in CDER that is not optimally functional; and unclear and insufficient regulatory authorities particularly with respect to enforcement. The FDA and the pharmaceutical industry do not consistently demonstrate accountability and transparency to the public by communicating safety concerns in a timely and effective fashion.

Noting that resources and therefore efforts to monitor medications' risk-benefit profiles taper off after approval, the committee that wrote the report offered a broad set of recommendations to ensure that consideration of safety extends from before product approval through the entire time the product is marketed and used.

Recommendations include:

- labelling requirements and advertising limits for new medications
- clarified authority and additional enforcement tools for the agency
- clarification of the FDA's role in gathering and communicating additional information on marketed products' risks and benefits
- mandatory registration of clinical trial results to facilitate public access to drug safety information
- an increased role for FDA's drug safety staff
- a large boost in funding and staffing for the agency.

Thus, we have a drug safety problem with respect to legitimate medicines as well as illegitimate medicines. Furthermore, given the concerns and weaknesses that exist with current drug safety systems throughout

the developed and developing world, it is not unreasonable to suggest that the practice of PPT is likely to add to the existing difficulties of ensuring global drug safety.

The concept of drug safety

Drug safety, in theory, concerns the current regulatory practice of pharmacovigilance and other related concepts such as 'medicinal product defect', 'supply chain security' and 'evidence-based pharmacotherapy'.

Pharmacovigilance

Global medicines safety is governed principally by the system of pharmacovigilance which is the regulatory system geared towards regulatory professionals and prescribers concerning the reporting of ADRs. This, arguably, has been a major weakness of the EU's pharmaceutical regulatory system. ADR reporting has traditionally been weak in Europe for several reasons and, while it is also as (if not more) fragile elsewhere in the world, the EC has made major recent efforts to improve its pharmacovigilance. The recent EC pharmacovigilance review[50] has addressed the important 'system weaknesses' in particular which exist in European coordination, decision making, reporting and action in this field. However, there are now concerns that pharmacovigilance may be 'over regulated'. The following box summarises the purpose and conclusions of the review as provided by EC press announcements in February 2007:

Assessment of the community system of pharmacovigilance *(EC Announcement, 26 February 2007)*

'Based on the results of the public consultation of 2006, on 26 February 2007 Commission Vice-President Günter Verheugen announced a strengthening of the EU pharmacovigilance system. The announcement is based on the results of the 2006 public consultation and includes both better implementation of the current system and proposals to change the legal framework for pharmacovigilance in the EU. The change to the legal framework will involve an impact assessment during the course of 2007 with a view to a legal proposal in 2008.'

Strengthening medicines safety monitoring *(IP/07/240, Brussels, 26 February 2007)*

'A public consultation shows that the current EU system of medicines safety monitoring (pharmacovigilance) needs rationalisation and strengthening. There are unclear roles and responsibilities, complex reporting rules implemented differently by different Member States, a lack of robust safety studies and complex decision-making at EU level. Commission Vice-President Günter Verheugen announced today a strengthening of the EU pharmacovigilance system. By making clear the roles and responsibilities for pharmacovigilance, by simplifying reporting rules and by ensuring that robust safety studies are performed to support rapid EU decision-making, the planned reform will better protect public health and support the safe use of new and innovative medicines.'

However, in spite of the review, the EU pharmacovigilance system is arguably ill equipped to address safety concerns which may occur in the European distribution chain, and is not well coordinated with the business of regulating pharmaceutical trade. The issues of counterfeit medicines and medicines diversion are not explicitly included in any European pharmacovigilance or other European-level official reporting systems. The EC states in its recent single pharmaceutical market consultation document that, analysis has demonstrated the existence of multiple and sometimes inefficient requirements as regards pharmacovigilance in the EU. The challenge is thus to strengthen and rationalise drug safety monitoring, while avoiding unnecessary requirements that would impair patients' access to treatments'.[15]

Medicinal product defect

In the EC, there is no unified concept of what could be considered to be a 'medicinal product defect' in a way that a patient, as the ultimate consumer, can understand. In other consumer sectors, where consumer safety is of high concern, the concept of a product defect is more or less clear (eg. food safety, electrical

products). Ideally, the concept of a medicinal product defect should incorporate, *inter alia*, the following:

- Suspected Unexpected Serious Adverse Reaction (SUSAR) to an authorised medicinal product, ie. an adverse drug reaction not specified in the medicinal product's Summary of Product Characteristics (SPC)/Company Core Safety Information (CCSI)
- medicinal product ineffectiveness as ascertained against the product's SPC and in respect of appropriate prescribing and dispensing
- product manufacturing quality defects
- product or packaging tampering against the specification of the original manufacturer
- mislabelling/incorrect Patient Information Leaflet (PIL) against the specification of the original manufacturer and not in the language of the intended destination country
- a Counterfeit (product, labelling, or packaging).

Pharmaceutical supply chain security technology

The issue of developing and implementing pharmaceutical supply chain security technology is a topic gaining increasing importance. For example, the WHO IMPACT initiative has recently created a Technology Group with the task of addressing global pharmaceutical supply chain technology and identifying the best solutions that can be made in a coordinated and cost-effective fashion and in a way that addresses the obvious different resources between the developed and developing world.

The key technological concepts for pharmaceutical supply chain security are:[51]

- 'tracking' includes various methods to determine the location of a product at any time and to compare that with expectations of where it should be
- 'pedigree record of a product' complements or replaces tracking by establishing a certified record of the transactions through which the product has passed
- 'physical authentication' techniques that enable the product to be identified as genuine through examination of the product and/or its primary or secondary packaging.

Also these methods can be described as product traceability and verification. The exact terminology for pharmaceutical supply chain security technological measures needs to be defined more precisely.

Evidence-based pharmacotherapy

Evidence-based pharmacotherapy is the "systematic, explicit and judicious use of best evidence in making decisions about drug treatments for patients both at individual and population (policy) levels" *(A. Li Wan Po, 1999)*. Including economic evaluation of drugs in addition to risk-benefit considerations, evidence-based pharmacotherapy aims to ensure that patients receive the most cost-effective therapy using the best available evidence. EBP combines the concepts of medicines assessment, pharmacoeconomics and pharmacoepidemiology.

Ultimate patient safety and health consumer choice: parallel traded pharmaceutical products in the context of the 'European patient/consumer'

There is sometimes confusion in defining a patient and a healthcare consumer. Is there or should there be any difference? The differentiation between a patient and a healthcare consumer is becoming increasingly artificial in the age of information and trade globalisation. The concept of drug safety has to adapt to this situation. In the light of increasing global information and more informed healthcare consumers, the traditional model of prescriber (doctor), dispenser (pharmacist) and patient (healthcare consumer) is being challenged.

There is a need to update policy with respect to patient (healthcare consumer) medicines information and which addresses the reality of the rapidly changing and complex world in which we live. There has to be a globally acceptable standard of what is patient- (healthcare consumer) informed choice with respect to medicines consumption.

Do we have the right level of informed medicines consumption in Europe?

There is widespread, ongoing debate about the issue of patient information on medicines in the EU. How much should consumers be informed? What messages should they receive? It is beyond the scope of this report to examine this issue in great detail but some general comments can be made with particular reference to the subject of parallel traded pharmaceutical products and patient choice.

In order to understand the impact of PPT in the context of ultimate patient safety, first of all we need to understand the level of knowledge of European consumers about medicines and their consumer rights. The scenario is not positive.

The European pharmaceutical sector with respect to patient safety is getting out of control. In addition to serious concerns about pharmaceutical supply chain security in Europe, the sector is driven by uncoordinated and inconsistent health economic policies that often disregard ultimate patient safety and consumer rights to access good quality medicines. The average prescriber (doctor) and dispenser (pharmacist) interested in providing an effective public health service has limited understanding of the supply chain security concerns and health economic distortions placed upon the European system of medicines supply, and why should they?

What does the average European healthcare consumer/patient know about policies, for example, on generic and therapeutic medicine substitution and parallel-traded medicines? The situation is made worse when healthcare consumers are not informed on issues such as medicines counterfeiting and the risks of purchasing medicines from unregulated sources (ie. the internet and through mail order pharmacy), and confounded by different national policies on these topics in the various EU Member States – and which operate with varying levels of transparency.

Today, the average European patient or consumer of medicines has a limited concept of what is ‘drug safety’ or ‘evidence based pharmacotherapy’. Consumers are relatively well informed about their consumer rights with respect to food safety for example, but what about their rights with respect to medicines? The European consumer of medicines is generally a patient, that has to rely on the prescribing decision of doctors and the subsequent dispensing decision of pharmacists (both decisions being influenced by the pharmaceutical policies implemented by EU/EEA Member States and which diverge significantly across the EU/EEA).

At the same time, the EC operates restrictions on direct to consumer advertising of medicines in Europe, contrary to the situation in the US. Thus, European patients who want to be better informed about medicines have to rely on the internet; it is often difficult for busy primary healthcare doctors and pharmacists to provide European patients with the medicines information they require and/or desire.

The consumer of medicines in Europe has limited choice in what they are prescribed or dispensed. In the meantime, they have to trust the health payer, the prescriber and dispenser to make the right decisions on their behalf.

The potential for consumers to be confounded by parallel traded medicines

Consumers taking prescription medicines rely on receiving the same branded medical product for reasons of bioequivalence and treatment compliance, as differences in packaging, instructions, excipients and pack size etc. have considerable potential to blur the parameters of what should be precise therapy. Thus it is perhaps not surprising that evidence is now emerging that parallel traded medicines confound patient therapy and well being.

The following box lists a number of anecdotal cases that illustrate the potential of PPT to confound patients, as gathered by an informed healthcare consumer in the UK.

Examples of patient confoundation with parallel-traded medicines

1. Patient supplied with a medicine produced by a pharma company with one name for Italy and one for the rest of Europe. Italian version protected by licensing agreement with Italian pharma company. Medicine was dispensed in Essex. Phone call to PPT licence holder was met with an offer to exchange the pack, as long as the patient drove to PPT company's car park. No mention of a prescription being required.
2. Loose tablets (popped out of blisters) supplied in a vial. No patient information leaflet.
3. Blister-packed tablets supplied in pairs, again in a vial, with no patient information leaflet and with duplicate days on the blister.
4. Medicine for advanced Alzheimer's disease, supplied as blister packs to an NHS hospital, where the packs showed abbreviated days of the week marked for each tablet in Greek. The Greek patient information leaflet was present and so was an additional slip of paper translating the Greek abbreviations into English language abbreviation. Astonishingly, this medicine was for people hospitalised with Alzheimer's disease.

The examples given in numbers 2 and 3 above are significant because they show what happens when medicines packed for the German market find their way via parallel trade to the UK. Germany dispenses in packs of 30, while the UK dispenses in 28s. The enterprising parallel trader (or pharmacist) either snips the last two tablets from the pack into a vial, or pops the last two from the blister into a vial. Ergo, every 15th patient gets a bastardised pack of medicine. There is absolutely NO guarantee that all tablets are from the same batch – nor is there any way of checking.

Source: EAASM 2007

This situation alludes to a potentially very big patient safety problem in Europe; if an informed UK healthcare consumer has identified these anecdotal cases personally in the last few months, what is the situation likely to be in the broader UK and European context? The majority of normal healthy people in Europe have a limited concept of medicines safety and effectiveness and the importance of having a secure pharmaceutical supply chain, so it is unlikely that few European healthcare consumers are aware of the potential confounding nature of parallel traded medicines in medical therapy.

There is no such thing as an average consumer of medicines in Europe; pharmacoepidemiology varies considerably across the EU/EEA area in terms of diseases and therapeutic habits. Pack sizes and PILs often vary between countries for these reasons. In addition, very often for good medical reasons, patients may have obviously limited faculties to understand the medicines they are being given, eg. the elderly and psychiatric patients. Parallel-traded medicines have considerable potential to undermine patient safety not just in general, but particularly in the case of patients with compromised mental faculties.

Should patients have a choice in choosing between original and PPT medicines?

In principle, the average European consumer should be able to have an informed choice about what products they can buy. But of course in the medicines sector this is not possible because medicines are mainly prescribed and dispensed and publicly-funded. In addition, due to differences between national pharmaceutical policies, there are significant variations between EU/EEA Member State controls over consumer access to medicines (eg. variations between European states in the availability of both medicines classified as OTC and new prescription medicines that are publicly-funded).

For good reasons, the average consumer of medicines needs to rely on prescribing and dispensing decisions. However, where trade factors intervene between a patient obtaining a rational prescription with rational dispensation, then this is not a satisfactory situation. The following quote from a leading UK public health expert provided to the author anonymously illustrates the point: "I find it really interesting that health authorities are basically compelling prescribers/pharmacists into the position where they prescribe on price rather than medical opinion. There is good recent data to show that, certainly UK GPs are extremely concerned about generics and counterfeits".

Given that there is a major EU debate on the security of its pharmaceutical supply chain, a patient should have the right to a choice between a parallel traded medicine and the original nationally authorised product (as well as having the choice for good therapeutic reasons, eg. bioequivalence and treatment compliance considerations). There is enough evidence to show that the very often uninformed generic and biotherapeutic substitution of medicines for health economic reasons undermines ultimate patient benefit. There are good therapeutic reasons for a patient maintaining therapy with a single sourced product.

What are the arguments against giving health consumers a choice of an original nationally authorised medicine or a parallel traded so-called equivalent? Does the pharmacist say to the patient that if they buy the parallel traded medicine, the prescription fee is lower? Does the prescriber know that the patient often does not have a choice between an original nationally authorised medicine or one which is parallel traded? Doesn't the consumer have the right to make an informed choice between an original product and a parallel traded so-called equivalent? Patients, particularly those on long-term therapy, have good reasons to request that prescribed medicines are provided from a single source.

On which medicines dispensing topics should patients have an informed consumer choice as a matter of priority? Surely the choice of being dispensed an original nationally authorised or parallel traded medicine has to be an important area of consumer choice. Even the EC 2003 Communication states the importance of the need to indicate on who repackaged and manufactured the product and in a way that the consumer can understand.* How easy is it for a consumer to determine this? Are they actually given a choice by the dispensing pharmacist?

The following quote on this topic comes from a UK policy think tank:

Social Market Foundation (2006)[11]

'There is a need to encourage the Department of Health (UK) to issue a memorandum outlining patients' choice in the matter of imported (parallel traded) medicines to all pharmacists, stating that when dispensing an imported medicine the patient is to be informed and given the option of whether to accept or reject this medicine. This is in order to assist those patients whom may be confused, alarmed or at risk of non-compliance by the use of an imported medicine.'

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* EC Com 2003 statement concening packaging and manufactuer identification. "Since it is in the trade mark owner's interest that the consumer should not be led to believe that the owner is responsible for the repackaging, an indication must be clearly shown on the external packaging of who repackaged the product. That indication must be printed in such a way as to be understood by a person with normal eyesight, exercising a normal degree of attentiveness. Moreover, where the parallel importer has added to the packaging an extra article from a source other than the trade mark owner, he must ensure that the origin of the extra article is clearly indicated in such a way as to dispel any impression that the trade mark owner is responsible for it."

Stakeholder positions and the position of PPT on the policy agenda

Stakeholder positions

A number of key stakeholders have raised questions and formulated opinions on the topic of PPT. The table below summarises their positions on this topic:

Stakeholder views of PPT

Association of the British Pharmaceutical Industry (ABPI)

Causes sales revenue loss, consumers benefit relatively little, importers are interfering with the integrity of the product potentially affecting its safety and quality and patients are confused.

European Brands Association (AIM)

On the issue of exhaustion of trademark rights, recognises that it is a highly complex debate. Nevertheless, AIM believes that parallel trade is only good for parallel traders, not for consumers.

The European Association of Euro-Pharmaceutical Companies (EAEPC)

A number of benefits can be provided by PPT:

- reduced costs of pharmaceutical spending for consumers, health providers and governments
- providing an extra layer of security and value added in the form of: several product controls, relabelling/repackaging, creating and inserting information leaflets etc. – all in accordance with national requirements
- ensuring competition
- pharmaceutical companies make very high profits. With its market share of 2%, EU parallel trade can only redistribute small parts of these industry profits towards the consumers in the Member States
- as parallel trade only offers the original products of the industry itself, their total sales volumes are not affected.

European Commission (DG Enterprise)

Under Community law as it currently stands, the parallel trade of medicines is a lawful form of trade within the EU as confirmed by the European Court of Justice in several rulings. Following the decisions of the Court, a prohibition of parallel trade between Member States would represent a quantitative restriction on imports or exports or a measure having equivalent effect, which is prohibited by the EC Treaty unless justified on grounds related to the protection of health and life of humans or animals.

The Court has based its decisions on the fact that a relationship between parallel trade and a threat to public and animal health cannot be assumed as a general rule. However, the Commission has been presented with examples of quality defects related to parallel trade medicinal products in the past. To explore the public health impacts of this situation further, the Commission has launched a study on safe medicines in parallel trade.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

The fragmentation of the EU pharmaceutical market results in parallel trade which does not provide benefits for patients or social security systems, but its lucrative profits accrue mostly to the traders themselves, depriving the research-based pharmaceutical industry from valuable resources to fund the research and development of new products. Parallel trade was estimated to exceed €5bn (value at ex-factory prices) in 2003, which means a net loss of about €2bn for research-based companies.

Furthermore, the nature of PPT is such that it greatly complicates the traditional route of supply where quality control is effectively checked at all stages.

The EFPIA will continue to call on Community authorities to remedy trade and competition distortions caused by differences among Member State governments' pharmaceutical pricing laws. The fragmentation of the EU pharmaceutical market results in a lucrative parallel trade, which benefits neither social security systems nor patients, but just a few intermediaries. One EFPIA member states that 'When there is a repackaging process through the trade of products cross-border, any overt or covert technologies that we invest in are compromised or even removed. We believe this creates inherent danger to patients.'

European Association of Pharmaceutical Full-Line Wholesalers/Groupement International de la Repartition Pharmaceutique (GIRP)

The financing of healthcare and reimbursement of healthcare costs is a national competence in the EU. Therefore, there are 25 different healthcare systems throughout the region, each regulated and operated according to different frameworks. Parallel trade is a consequence, on one hand, of different ex-manufacturers' prices throughout the EU Member States while, on the other hand, of quite different legislative situations in the 25 Member States. Price differences between the Member States give rise to this activity and the existence of PPT is proof of the non-existence of a single market for medicines in the EU.

The European Consumers' Organisation/Bureau Européen des Unions de Consommateurs (BEUC)

When looking at the coding and distribution systems, it is important to ensure that whatever is done is single market neutral, that it preserves the rules of the single market and that it is pro-competition. Small companies may not have the resources to check supplies. However, large ethical companies do have the means to check what they are buying, in order to identify any counterfeits.

Academic/independent expert opinion

UK Pharmaceutical Security Expert (Graham Satchwell)[38]
A rise in parallel trade does not necessarily mean a corresponding rise in the incidence of substandard pharmaceuticals. What is clear, however, is that the greater the number of parallel imports the greater the chance that substandard pharmaceuticals, counterfeit or otherwise, will be imported.

UK Social Pharmacy Academic Expert (Professor David Taylor)
In Europe, patients rarely have to pay in full for their medicines, except as tax payers and insurance purchasers. They are thus likely to experience directly only the adverse effects of parallel importing, rather than its financial advantages. 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.

US (ex-FDA) Pharmaceutical Regulatory Expert (Peter Pitts, personal communication, September 2007)
Parallel trade in prescription medicines is the weak link in the pharmaceutical chain of custody, causing safety problems – and providing counterfeiters with a back door they can exploit for huge profits, causing immense danger to the public health of both the EU and the US. It is time to stop accusing the drug industry of crying wolf about counterfeit drugs. Policymakers must confront the serious business of ensuring that drugs entering our markets are legitimate and safe. It is an area where mistakes are dangerous to everyone's health.

Canada Health Policy Expert (Mike Tremblay)
The lack of a single European market in medicines encourages specific forms of EU cross-border trade, but the state-based regulation means that repackaging, and other requirements to meet national market features, creates vulnerabilities in the supply chain, which can be exploited for criminal gain. In addition, the approach taken by current EU legislation assigns priority to the intellectual property rights of trademark holders, and views this as providing appropriate protection against counterfeits. The patient safety issue thereby falls to Member State authorities. It is the differences between Member States' approaches that create a patchwork of regulation and, thus, the weaknesses that organised criminal groups can exploit. Patient safety is an EU and cross-border priority. The freedom of movement of medicines within the EU may create incentives that make it difficult to track and identify counterfeit products and rogue traders of counterfeit medicines.

Norway Pharmacy Expert (anonymous, personal communication, September 2007)
I wish we had no PPT, but as long as it is permitted by the EU and the national regulatory authorities, I wish big pharma would not compound the problem and hurt patients. Norway used to have a well-regulated market with a few generic equivalents – enough to get competition. Now we have parallel traded products, which are not identical to those directly imported, and we have many generics. The PPT products are not much cheaper (the price difference is not so great to justify the PPT practice). In addition, in our country, the medicines have to be repackaged. This is, of course, an additional source for error. The information in package inserts differs, indications differ and the additives differ. I am not sure about the net benefit. Also, Norwegian doctors tend to change to a new patented product as soon as one gets off patent (eg. from Cipramil to Cipralex).

Add to this the confusion created by so many new products (both new substances and new generics) and PPT products being registered every week. I am for generic competition and I do not think the new patented medicines are any better, but now we have created so much confusion that I think the patients suffer. We see that from the ADR reports we receive.

I would have liked proof that there are no links between parallel pharmaceutical traders and big pharma and innovators. I think there might be some deals going on to make both parties 'happy'. Big pharma has restricted stocks in the lower-priced country to prevent PPT and has also created problems (eg. Norwegian pool procurement hospital tender) by not making stock available once tender was awarded.

Netherlands Pharmacy Expert (anonymous, personal communication, September 2007)
The whole parallel import business is very nice for countries where medicines are expensive. However, in the Netherlands we currently seem to be among the cheapest countries for medicine costs.

This means that some of my colleagues export medicines which they buy from local wholesalers. As a result, pharmaceutical companies have limited the amounts made available on the Dutch market, which means that we have very regular shortages of important medicines and so need to order them separately and directly from the companies in order to be able to dispense to our clients. This is becoming highly annoying. On the other hand, I am glad that parallel import seems to help other countries to keep their medicine costs down.

Policy debate: PPT is now high up on the European pharmaceutical and health policy debate agenda

Due to the inherent conflict between creating a single European pharmaceutical market and healthcare subsidiarity, we are witnessing increasing tension between the European research-based pharmaceutical industry and European authorities with respect to 'artificial partitioning of the market' not least of which is due to diverging national pharmaceutical pricing and reimbursement policy. PPT was conceived and set up to be a significant measure to achieve pharmaceutical price convergence in the EEA/EU area.

Is PPT working in terms of being a force for achieving European pharmaceutical price convergence? What is the definitive case for legitimising the practice of European PPT? Recent years have seen an escalating number of opinions from various stakeholders and academic reports appearing on the topic. The debate surrounding the benefits, or otherwise, of PPT is intensifying. The debate to date has largely focused on health economic issues, but increasing concerns over European pharmaceutical supply chain security (particularly concerning the increasing threat of counterfeit and adulterated medicines) has led to the practice of PPT now receiving serious scrutiny by European policy makers, irrespective of the heavily debated health economic arguments that are either in favour or against PPT.

Thus in view of the above issues and tensions, there is now recognition on the sides of both the European Parliament and the European Commission (EC) that the whole subject of PPT needs a thorough review in order to make informed policy in a way that ultimately benefits the European patient/healthcare consumer. The European Parliament has, therefore, raised a parliamentary debate on the subject and the EC has commissioned a full report on PPT (in addition to commissioning related reports on: (i) counterfeit medicines, (ii) pharmaceutical pricing & reimbursement system and (iii) European health policy).

The current situation concerning European PPT (in view of the unresolved understanding of the complicated issues involved and escalating tensions between certain stakeholders) is not sustainable and it is time for the benefit or otherwise of PPT to be settled through an informed public health policy debate.

Several conclusions can be drawn from the information and analysis presented in this report. It is clear that the issues surrounding PPT are diverse, involving a complex interplay of health economic, trade, regulatory and patient safety factors. This conclusion section is, therefore, divided into three main parts: (1) general conclusions concerning problems in the European single pharmaceutical market relating to patient safety and which provide background context for PPT; (2) specific conclusions on PPT; (3) the PPT cost/benefit calculus based on the existing evidence.

General conclusions concerning the European pharmaceutical market in the context of patient safety

Europe's pharmaceutical market suffers from the 'Potential Public Health Disaster' syndrome of 'invisibility, biohazard and system failure'

'Invisibility, biohazard and system failure' is a concept coined by the author of this report with respect to the situation of counterfeit medicines in Europe[52] – yet is one which equally may be extended to the way in which the European pharmaceutical market (the distribution system in particular) and financing system operates and is regulated currently. The existence of – and problems associated with – PPT are symptoms of deeper, more complex underlying faults in the European pharmaceutical sector which effectively result in a 'market failure'.

EU expansion has added to 'system stress'

The recent rounds of EU expansion, in 2004 and 2007, with the addition of a further 12 Member States which were in just recent times operating under socialist and impoverished conditions (and some of whom argueably still are), has put a huge amount of stress on the Union. The priority of achieving political union has come at the price of major internal EU economic distortions, which also impact on the functioning of the EU internal pharmaceutical market.

Achievements have been made, though Europe is far from attaining a single pharmaceutical market

The EC achieved a lot in developing the EU pharmaceutical regulatory framework through a thorough consultative and codification process *(Pharma Review 2001)*, however, it is still a long way from attaining the objective of creating a single European pharmaceutical market. The EC has concluded rightly that there is a real need to consult on and review the actions needed to achieve this objective in the light of both lack of progress to date and new emerging challenges resulting from: (i) globalisation of the sector and the increasing internationalisation of the value chain; (ii) the smooth functioning of the internal market in a widening Europe; (iii) advances in science and technology.

In this respect, the recent launch by the EC of initiatives to examine, diagnose and provide recommendations on the single market, pricing and reimbursement system, counterfeit medicines, PPT and an EU public health policy is positive. The EU faces a major challenge in creating a globally competitive research-based pharmaceutical industry. In this regard, progress towards solving the single European market problems, in

such a way that benefits both the patient and European research-based pharmaceutical companies, can provide major impetus in attaining this objective.

Europe's pharmaceutical pricing and reimbursement system suffers major divergence and inefficiencies

There is considerable tension between the single European market and the derogation of national healthcare provision that results from subsidiarity. Member States operate widely diverging and often inefficient pharmaceutical pricing and reimbursement systems with a plethora of ad hoc and dynamically changing measures and incentives regarding the employment of PPT. In spite of the EC Transparency Directive on pharmaceutical pricing and reimbursement, there is frequently a lack of transparency in the operation of national pricing and reimbursement schemes.

There is also very often a complete absence of pricing and reimbursement policy coordination between Member States – though there is no incentive or basis for them to do so – as well as confusion about comparative pharmaceutical prices. As Tremblay[16] notes, "given evidence from other jurisdictions, a review of the drug reimbursement policies of Member States is needed to determine whether Member State control of medicines pricing and the resulting price divergence create an incentive for counterfeiters and their trading partners to exploit price differentials through the parallel trade in medicines within the EU."

This situation is a major reason for the lack of effective EU pharmaceutical market functioning, diverting attention from important EC health issues and development of the European research-based pharmaceutical industry.

Europe's pharmaceutical distribution system is extremely complex and potentially puts patient safety at risk

How easy is it to compile a map of the European pharmaceutical distribution system? Theoretically this should be possible based on a compilation of registered distributors and import licences issued by the various EU Member State regulatory authorities. Yet, there is no such system for doing so. Even the European researched-based pharmaceutical manufacturers association (EFPIA) has difficulties putting together a map of European pharmaceutical distribution.

Given that medicinal products should be highly regulated for public health reasons and it should be possible to know where any particular medicinal product is at any particular time, the not inconsiderable difficulty in composing a map of pharmaceutical distribution in Europe in surprising. In fact, because the pharmaceutical trading situation in Europe is so confusing and unregulated there may be a need to compile a lexicon of the types of businesses that enter into pharmaceutical trade. This should be a minimal requirement for the authorities responsible for regulating the pharmaceutical supply chain; access to a geographic information system of European pharmaceutical distribution is vital to patient safety.

Multiple and parallel layers of distribution complicate the supply chain and it can be argued that a simplification of the system is in the best interest of the patient (as well as the regulator). The recent experience in the US, as highlighted in the book *Dangerous Doses*, illustrates the high patient risk attached to a complicated and convoluted pharmaceutical distribution system. The fact that the EU now has 27 Member States (and 12 new members since 2004) raises serious concerns for the current and future state of European pharmaceutical distribution security.

European pharmaceutical distribution regulation and supply chain security

In light of, *inter alia*, the increasing threat posed by counterfeit medicines (and medicines diversion) to the European population, and the rise of internet pharmacy, authority attention is being focused increasingly on the issue of supply chain security. Pharmaceutical regulation should address the entire supply chain from R&D to consumption. However, it is plainly apparent that in the EU we have a major weakness in pharmaceutical regulation with respect to the distribution system. Distribution chain regulation is governed currently and principally by 'soft law' (ie. guidelines on good distribution practice), which is out of date in view of the intensifying threats to the pharmaceutical supply chain. As a result, we see major divergence between the EU Member States in the implementation of 'good regulatory practice' pertaining to regulation of the distribution chain.

Some EU national DRAs are placed much more in the public eye then others and this puts pressure on the former to provide tougher regulatory oversight of their national distribution system. For example, the UK MHRA has to be regarded as one of the most proactive DRAs in Europe with respect to overseeing its pharmaceutical supply chain. The largest number of counterfeit medicine reports and batch recalls in Europe seem to originate from the MHRA. Is this because the UK is the main target of medicines counterfeiting or because the MHRA has put in place a strong intelligence and enforcement system? The MHRA often receives a lot of criticism, but you would rarely see this criticism and debate in most other EU Member States because the level of stakeholder knowledge on the topic of pharmaceutical supply chain security in the latter is comparatively not well developed.

Supply chain security – human versus technological solutions

The debate concerning pharmaceutical supply chain security has focused so far on potential technological solutions (RFID etc.) to improve security. We should not ignore the human factor. We need better human management systems to provide satisfactory oversight and management of a complicated European pharmaceutical distribution system.

European stakeholder coordination on the subject of drug safety

There is large-scale incoordination between stakeholders. Incoordination occurs not only between the various relevant authorities in a given country but also between countries. At the same time there is incoordination between the different types of stakeholders (ie. manufacturers, patients, doctors, pharmacists and authorities). There are many stakeholders on the issue of drug safety, not least of which is the patient. Given the large number of stakeholders, there should be a system that allows for better coordination on patient safety issues related to medicinal products (and medical devices). Among other patient safety issues related to the European pharmaceutical market, the level of understanding of the PPT issue within and between stakeholders is very low and there is a lack of informed debate. The European Alliance for Access to Safe Medicines is attempting to achieve greater stakeholder communication, coordination and cooperation.

Clarification and institutionalisation of meaningful concepts and definitions – what is drug safety, what is a medicinal product defect?

The concept of 'drug safety' is not well conceived or currently understood at any level in the EU system; from EC level down to the individual patient. To date, there has been a reluctance to understand or ignorance of the fact that supply chain security is very much connected with the pharmacovigilance issue. There is a lack of coordination and communication between authorities and manufacturing and distributing company professionals who work in the fields of pharmaceutical trade and pharmacovigilance. Particularly

in light of the increasing threat from counterfeit and diverted medicines, there is a real need in the EU to couch in more precise terminology what is drug safety.

Theoretically the concept of drug safety should encompass and be amalgamated to include: (i) the regulatory requirement of pharmacovigilance; (ii) supply chain security; (iii) informed prescribing and dispensing; (iv) patient informed choice. There is a need in the EU to adopt this concept and ensure it is communicated clearly.

The EC needs to clarify and institutionalise a number of meaningful concepts and definitions covering drug safety issues that all stakeholders can understand and interpret (eg. medicinal 'product defect'). This would help inter-authority and inter-stakeholder communication considerably across a diverse Europe. The functioning of the European pharmaceutical market should not be an academic/philosophical/political entity, but should be something that all stakeholders can understand and benefit from. Employing clear concepts and definitions would help all stakeholders in terms of understanding the important issues.

Drug safety reporting systems

There is no functioning centralised European database and reporting system for product concerns relating to what can be described as medicinal 'product defects'. We have a European reporting system for pharmacovigilance but this does not encompass the broader area of drug safety and the concept of product defects. It would be most helpful, for example, to include the reporting of suspected counterfeit medicines, tampering and packaging errors within the existing pharmacovigilance system.

In comparison, the US FDA's MedWatch scheme[53] is more comprehensive on drug safety than is the European pharmacovigilance system. In addition to covering serious adverse events, MedWatch also explicitly covers the issues of product use error (eg. incorrect prescribing, dispensing or consumption) and product quality problems (FDA states that problems with product quality may occur during manufacturing, shipping, or storage, including suspect counterfeit products, product contamination, defective components, poor packaging or product mix-up, questionable stability, device malfunctions and labelling concerns).

Who should report product safety issues and to whom should they report? In the MedWatch scheme, this is made very clear and encompasses all stakeholders. Ideally an effective reporting system in Europe needs to allow the participation of all stakeholders, including manufacturers, distributors, pharmacists and, of course, patients. Such a system needs to be well managed centrally and in a way that informs and drives coordinated policy action across the EU Member States. The EC has taken a long time to set up a functioning pharmacovigilance database and reporting system. This should be developed further to incorporate overall drug safety issues. European patients, doctors, pharmacists, manufacturers and the pharmaceutical supply chain business need a single point of control (SPOC) for reporting medicine 'product defects'.

Specific conclusions on European PPT

EU/EEA internal market parallel trade, which by its nature occurs outside of the original manufacturer's authorised distribution channels, is based on the principle that the practice contributes to price arbitrage across the EU/EEA so as to help achieve the objective of a single EU 'consumer price friendly' market. To what extent parallel trade in consumer goods in general has contributed towards price harmonisation between the EU/EEA member states in the market sectors the practice operates is open to question.

The typical European consumer has limited knowledge of the parallel trade practice. Parallel trade in animal food or DVDs, for example, does not have an impact on public health and does not need to be heavily regulated. Parallel trade in consumer healthcare products, children's toys and electrical products should be heavily regulated for good and obvious reasons. There is concern that regulation of parallel trade for consumer goods that have a health safety impact is not well achieved in the EU. It is very difficult to obtain any statistics on parallel traded consumer goods that require regulation for health and safety reasons.

The arguments posited in favour of European PPT are that PPT provides real health consumer savings, provides a mechanism for EU/EEA state pharmaceutical price arbitrage and that the recent accessing Member States have the right to participate in this pharmaceutical trading system. However a number of well considered counter arguments can be made and which are summarised as follows:

PPT provides marginal health economic benefit at best

Is PPT a driver of both pharmaceutical cost reduction and single European pharmaceutical market price convergence? At best, the health economic arguments in favour of PPT are marginal. A large amount of the PPT 'value added' accrues to the PPT traders themselves. This is clear from the PPT economic studies carried out to date that attempt to analyse the economic issues of PPT in their entirety. Irrespective of the many other non-economic arguments that can be weighed against PPT, the pure economic case in favour of PPT is slight.

Defacto, why then do we have a debate between leading economic research institutions on the topic? If the health economic academic argument is borderline, what is the point in discussing it? Is it necessary to start undertaking a sensitivity analysis of health economic studies on PPT? There are more important arguments than health economics that should be discussed concerning PPT, such as ultimate patient safety and wellbeing.

Limitations of the PPT debate so far – what is the real PPT cost/benefit calculus?

Effective healthcare should ultimately hold strong regard of patient safety and quality of care over cost minimisation. The debate to date concerning the benefits or otherwise of PPT have focused largely on pure economic considerations, tending to neglect the important pharmaceutical regulatory, supply chain security and patient safety issues. These latter issues need to be factored into the debate.

PPT exploits inefficiencies, divergence and rigidity within the EU pricing and reimbursement system

European parallel trade is, arguably, a beneficial trading practice in consumer goods sectors that are driven by the principles of free market competition and which do not require heavy regulation. For many reasons, however, the pharmaceutical market is not a free market and requires regulating heavily.

PPT is able to exploit the inefficiencies, divergence and rigidity of EU Member State pharmaceutical pricing and reimbursement systems. The business of PPT is also driven by specific targeted economic incentives

for the practice in some Member States. The existing EU pricing and reimbursement systems distort free market pricing. It is unclear how PPT can achieve better price arbitrage between the pharmaceutical markets of the EU Member States and indeed it can be argued that the sole achievement of PPT is the import of cost-control systems from other countries.

Not only is the practice an inefficient method of pharmaceutical price arbitration within the EC, it is an exploitation of the inability to arbitrage by other means innovative medicine drug prices between Member States. The existence of PPT, and the way in which it is conducted, is a symptom of a more fundamental problem. PPT is a poor surrogate measure for compensating for deficiencies in national health system cost effectiveness. PPT is not the most efficient economic tool for achieving pharmaceutical price convergence between the EU Member States.

Clarity and rationalisation of PPT legislation and regulation: divergent regulatory implementation and 'over/under regulation'

There is considerable scope for improving the legal clarity and regulatory rationalisation of PPT. Implementation of existing EC rules on PPT diverges widely at the national level. To the extent that PPT is a welcome activity, there is scope for providing more clear guidance to national regulatory authorities on the regulation of PPT that goes beyond the 2003 EC Communication. Unfortunately the 2003 EC Communication is clouded by vague interpretations of not well defined concepts based on imprecise EC case law. The EMEA[3] has produced an extensive guidance document with coverage of 40 key regulatory issues on 'parallel distribution' which is not well coordinated with the 2003 EC Communication on parallel pharmaceutical trade. It is no surprise therefore, that national regulatory authorities have problems interpeting and implementing effective regulation of PPT resulting in large inconsistencies of regulatory approach between Member States.

The need by the central European drug regulatory authority, the EMEA, to present extensive regulatory guidance on PPT for medicinal products that come under its mandate (i.e. the Centralised Procedure for medicinal product authorisation and which covers a small fraction of medicines authorised in the EU), on what is considered by the pharmaceutical parallel trading business itself to be a marginal pharmaceutical trading issue (i.e. the EAEPC states that PPT accounts for only 3% of pharmaceutical trade in Europe) is a symptom of wider pharmaceutical regulatory and pharmaceutical financing problems within the EU/EEA.

It is time that European regulatory control of PPT went beyond case law. It is hoped that the current EC review of PPT looks at the legal and regulatory issues surrounding PPT so as to provide more concise, rational and firm regulatory guidance and also which provides some real obligations for regulatory supervision and enforcement.

The cost and burden of regulating and supervising PPT

In terms of a cost/benefit analysis, the regulatory cost and burden of PPT has so far been largely ignored in the health economic (and management) equation, but is likely to be considerable. The current European pharmaceutical regulatory system is unable to satisfactorily cope with the regulation of PPT. Parallel trade complicates the already existing difficult situation of regulating the 'normal' pharmaceutical distribution system (not least of which is the fact that the practice combines manufacturing with distribution). Original manufacturers now have the additional burden of ensuring regulatory compliance of their products that are traded through PPT and DRAs have the added burden of ensuring regulatory compliance of parallel traded medicinal products.

'Pseudo pharmaceutical manufacturing' – PPT complicates the pharmaceutical supply chain, undermines supply chain security and could potentially facilitate the entry of counterfeit, adulterated and diverted medicines into the European market

PPT complicates the European supply chain in myriad ways. Given the increasing concerns related to pharmaceutical supply chain security and in particular the threat of counterfeit, adulerated and diverted medicines, there are good grounds for reviewing the entire operation of European PPT.

Ostensibly PPT can be considered to be a combined pharmaceutical manufacturing and distribution business, given that PPT, in addition to distribution, is founded on repackaging and relabelling original products. Under the best international pharmaceutical regulatory conditions, a pharmaceutical manufacturing licence is required for packaging and labelling of medicinal products, as these activities are considered to be part of the pharmaceutical manufacturing process. The PPT business engages in both pharmaceutical manufacturing and distribution activities simultaneously and which should require separate distribution and manufacturing licences in order to conduct legitimate business. To what extent that the PPT business receives licensing supervision for its combined manufacturing and distribution operations is open to question. However, the PPT business is somehow exempt from the requirement of obtaining a manufacturing licence in addition to a distribution licence. This situation can best be described as 'pseudo pharmaceutical manufacturing' which surely circumvents strict internationally agreed pharmaceutical manufacturing regulations. How many parallel pharmaceutical trading companies exist in Europe? No one knows. The best information available indicates that the figure could be in the region of 500.

Due to system weaknesses it is difficult to estimate the exact scale of counterfeit, adulterated and diverted medicines in the European supply chain (through legitimate supply channels or otherwise). EU drug regulatory authorities, such as the UK MHRA, that have a market intelligence and surveillance capability, are now detecting cases of counterfeit medicines in the PPT supply chain. It is not clear what the real situation with counterfeit medicines entering the PPT supply chain is likely to be in other Member States due to *inter alia* weak intelligence.

There can be no question that PPT undermines packaging measures to both secure supply chain security and ensure legal dispensing. The practice of repackaging, relabelling and resizing packs by parallel pharmaceutical traders not only seriously undermines supply chain security but also increases the risk of dispensing error. For reasons relating to both 'artificial partitioning of the market' and varying pharmacoepidemiology, there are often different pack sizes and different information contained in the patient information leaflets that are authorised in the EU/EEA States.

The ability of original manufacturers (that actually have a manufacturing licence, as opposed to parallel traders), to use 'tamper proof' packaging, blistering and labelling is a vital measure against the threat of medicines counterfeiting and diversion as well as a measure that ensures that the patient recieves the correct prescription size package and indications for use in his country.

PPT compromises the ability implement a product batch recall. For example, the copying of batch numbers from the original manufacturers' packaging to parallel traders' packaging inevitably affords the opportunity for errors and thus weakens the vital product recall system.

It has been argued by the EAEPC, the European association that represents parallel pharmaceutical traders, that 'PPT adds an extra layer of security', but this has to be an absurd argument, particularly as repackaging and relabelling by parallel traders is poorly regulated throughout Europe. It has been advocated by some that parallel pharmaceutical traders should "over box" and not "underbox/debox" as

a measure to safeguard product security. To the extent that 'overboxing' contributes to pharmaceutical supply chain security, although it is hard to see how 'overboxing does not confound the patient (never mind the dispensing pharmacist), then a manufacturing licence should be required. Of course, the introduction of a manufacturing licence for (and Good Manufacturing Practice supervision of) parallel pharmaceutical traders and the extra packaging of 'overboxing' adds cost to the product and these factors needs to be taken into consideration for future health economic debates concening the benefit or otherwise of PPT.

PPT and internet/mail order pharmacy

In view of the increasing role of internet and mail order pharmacy in pharmaceutical trade it is highly likely that we will see increasing PPT at the individual rather than commercial level. The introduction of personalised medicines trading through the increasing trend of mail order and internet pharmacy is likely to have a complex interaction with the business of PPT which will make distribution chain regulation and supply chain security much harder.

PPT in active pharmaceutical ingredients, excipients and Bulk Intermediate Products

If there are concerns about the safety of PPT in finished medicinal products, then we should be truly concerned about PPT in active pharmaceutical ingredients, excipients and Bulk Intermediate Products (BIPs) which are utilised to produce a finished medicinal product. The global system for regulation of API, excipient Bulk Intermediate Products manufacturing trade is a major international regulatory loophole. Chemical brokers and intermediate product traders lie outside of any international regulatory control system. How is it possible to ensure that the medicines we receive are safe when the ingredients are manufactured and traded uncontrolled around the world? The Council of Europe 2006 Report raised the issue, on which has also been recently raised by a New York Times investigation.

PPT undermines the guarantee of continuous pharmaceutical supply

Due to the conflict and tension between the European 'normal' and parallel pharmaceutical trading systems, 'exporting' countries suffer in terms of medicine shortages caused by the diversion of regular supplies for sale in other Member States. This situation impacts negatively on the quality of patient care and safety in PPT exporting countries. At the same time, small-scale traders can take advantage of this situation, further complicating the supply chain.

PPT and derogation closure with the new Member States

A system of derogation from PPT by the new Member States, due to the need to harmonise medicinal product IPR issues in the EU, has meant that to date PPT has been restricted to the old Member States. However, as this derogation is shortly to come to an end, this situation is likely to place further complexity on the already complicated European pharmaceutical distribution system against a background of European pharmaceutical supply chain insecurity. Derogation closure will also likely raise the tensions between the European research-based industry on the one side and national healthcare purchasers and PPT traders on the other side.

PPT complicates existing weaknesses in the global drug safety system

Global drug safety may be considered to be weak for multiple reasons. Recent cases in the EU and US, concerning legitimate medicines supplied through main distribution channels, illustrate the problem in regulating new medicines placed on the market at all stages of product development. PPT complicates the current need for global authorities to define better systems of securing drug safety.

The original manufacturer can circumvent PPT legally

The fact that the European research-based pharmaceutical industry can legally obviate PPT using various supply strategies implies that PPT is an unsustainable business.

Does the management of PPT in Europe indicate that it is a legitimate business?

Irrespective of the arguments made for and against PPT based on economic, regulatory and patient safety grounds, the question remains as to why we have two separate European-level pharmaceutical wholesaler associations, one representing full-line wholesalers and the other representing parallel pharmaceutical traders. The name of the association that represents European parallel pharmaceutical traders is cryptic: The European Association of Euro-Pharmaceutical Companies (EAEPC). Most trade associations have names that provide a clear understanding of what and who they represent. Why is it not possible for a European level pharmaceutical parallel trade association to call itself, for example 'the European Pharmaceutical Parallel Traders Association'?

Is there such a thing as a short-line pharmaceutical wholesalers association? Why not? There are strong regulatory reasons concerning the guarantee of supply of medicines and supply chain security to make full-line wholesaling a legal pharmaceutical distribution requirement.

Ultimate patient safety and health consumer rights

It is extremely difficult to see how the practice of PPT provides any patient benefit. There is good evidence to suggest that the PPT practice undermines patient safety in terms of inaccurate dispensing, patient confoundation and the risk of counterfeit and adulterated medicines entering the supply chain.

Currently in Europe, patient safety and choice appear to be secondary to pure health economic objectives. Today the typical European patient has a limited concept of drug safety and effectiveness. They have little, if any choice in what medicinal product is given to them in the pharmacy. Patients should have a right to know and to choose. Patients need to be informed of the issues, as not only do they have consumer rights, but ultimately they can play an important role in reporting product defects, packaging and tampering concerns or errors. This issue relates not just to the choice of receiving an original nationally authorised or a PPT product, but also a patient choice of whether they want to receive therapeutic or generic substitutes that may be dispensed by pharmacists.

Criticisms of the European research-based pharmaceutical industry with respect to PPT

The reasons for the continued existence of PPT in Europe also lie with the research-based pharmaceutical industry. Rather than just accepting the status quo of the problems of the single European pharmaceutical market, companies have to be proactive in achieving single European pharmaceutical pricing, rationalisation of the distribution chain and achieving pharmacoepidemiological convergence. The European research-based manufacturing industry is criticised by the EC for creating 'artificial partitioning of the market'. It is in the interest of the industry to avoid both the 'do nothing' approach and to accept the status quo; it needs to be seen to make efforts to achieve single European pharmaceutical pricing. Once such a situation is achieved, the industry can better focus on doing its job of pharmaceutical research and development. European patients need new and better products, not pharmaceutical pricing wars in Europe between 'big pharma' and 'big bureaucracy'.

Summary of the evidence for and against European PPT – the cost/benefit calculus

The topic of European PPT is highly complex. There are arguments both in favour and against PPT that involve many complex elements. A summary of the arguments and overview of the evidence for or against the practice of European PPT is provided in the following table. The level of evidence assessment is based on a combination of both objective evidence and the author's analysis. At the same time, it is recognised that there may be a need in some areas (as noted below also) to obtain further information to inform the debate.

TABLE 4. THE ARGUMENTS FOR OR AGAINST PPT	LEVEL OF EVIDENCE
For PPT:	
1. Provides savings to payers	Debatable (1)
2. Provides a mechanism for price comparisons between Member States	Possible (2)
3. The right of the new Member States to participate in PPT following derogation closure	Confirmed (3)
Against PPT:	
1. Value added largely goes to intermediary traders	Confirmed
2. Exploits inefficiencies, divergence and rigidity in the European pricing and reimbursement system	Confirmed
3. Not a driver of European pharmaceutical price convergence (PPT is partly driven by targeted incentives). PPT results in the import of cost control systems from other countries.	Probable (4)
4. Imprecise PPT legal and regulatory framework which is implemented highly divergently at a national level	Confirmed
5. Creates additional regulatory costs and burden	Confirmed
6. Complicates pharmaceutical manufacturing with distribution	Confirmed (5)
7. The PPT distribution network complicates the pharmaceutical supply chain	Confirmed
8. The practice of repackaging and relabelling undermines supply chain security. Evidence exists of PPT being an entry point of counterfeit medicines into the legitimate supply chain	Confirmed
9. Leads to product shortages in the exporting national market	Confirmed
10. Forthcoming derogation closure will likely have European distribution complication and security implications	Debatable (6)
11. PPT can be legally circumvented by the original manufacturer which implies that PPT is an unsustainable business	Confirmed
12. Global drug safety is weak. PPT complicates the existing weaknesses	Confirmed (7)
13. In the absence of enforced GDP, PPT is managed as a non transparent business activity	Debatable (8)
14. Ultimately undermines patient safety (e.g. confoundation, safe dispensing and therapy), patients have little knowledge of the PPT practice	Confirmed (9)

(1) The health economic debate in favour of PPT appears to be marginal at best
[2] Given the confusion that surrounds pharmaceutical purchasing power parity and prices between the old and new EU member states in particular, PPT may provide a mechanism facilitating price comparisons
[3] The new Member States have the right to participate in a previously existing EU trade system once derogation is closed
[4] More evidence is required (e.g. study of European Pharmaceutical Purchasing Power Parity)
[5] A parallel trading licence permits the trader to engage in manufacturing activities (i.e. repackaging and relabelling)
[6] The impact of deorgation closure on the functioning of the European distribution system and on supply chain security remains to be seen
[7] To ensure better drug safety, the developed country authorities need to provide better oversight and regulation of legitimate medicinal products in a more coordinated way before PPT can be considered to be a viable option of pharmaceutical trading
[8] This is not to say that all PPT is managed non transparently, but there is good evidence to suggest that this could be the case in light of weak Europe-wide implementation of PPT regulation
[9] Although the evidence so far is largely anecdotal (except for the recent batch recalls on PPT counterfeits in the UK), there are indications of a serious problem that needs further study to provide thorough evidence

Missing evidence

This report has attempted to provide an evidence-based analysis of the situation of European PPT based on the best information available. However, there are some information gaps in terms of being able to provide a full analytical evidence-based review. The following information would be helpful to inform the debate fully based on well-designed, pan-European surveys:

- Full analysis of pharmaceutical pricing and purchasing power parity between the EU/EAA Member States
- Full market data on European and country-level PPT trends (current statistics are imprecise and can be misleading)
- A comparison of PPT with parallel trade in other consumer goods sectors (which consumer goods sectors are big in parallel trade and why?)
- Professional stakeholder survey (ie. involving European drug regulatory authorities, original manufacturers, wholesalers, pharmacists) – their experience of PPT; the benefits or otherwise
- Review of consistency of national drug regulatory authority practice with regard to the regulatory supervision of PPT
- Further economic studies – these should include an analysis of the actual costs of regulating and supervising PPT and the concept of 'indirect economic benefits' of PPT
- European patient/healthcare consumer survey – their understanding/satisfaction with PPT including provision of case studies where patients may have been confounded.

From the analysis and conclusions of this report a number of recommendations can be made for consideration and discussion. These are presented in two sections: (i) general recommendations that impact on European PPT; (ii) specific recommendations concerning European PPT and 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 (which supports the development of a rational global pharmaceutical market)**

   The EC recently actioned a single pharmaceutical market consultation process that addresses several areas including PPT and the related issues of counterfeit medicines and pharmaceutical pricing and reimbursement. The EC has to put in place a clear action plan with convergence measures for achieving a real single European pharmaceutical market which incorporates realistic milestones. The plan should cover, *inter alia*, the issues of PPT, counterfeit medicines and supply chain security, rationalisation of national pricing and reimbursement policy (particularly transparency and coordination of policy), areas of 'under' or 'over' pharmaceutical regulation, rational centralisation and decentralisation of the European pharmaceutical regulatory system, and measures to eliminate the artificial barriers to achieving European pharmacoepidemiological convergence.

   The EC must make greater efforts to tackle the deficiencies in pharmaceutical regulation in the less developed countries of the world, particularly as medicinal products placed in Europe are often manufactured through a complex global supply chain and as Europe acts as a conduit for supply of medicines worldwide. The action plan needs to focus on not just achieving ultimate European patient pharmaceutical safety, but also the safety of patients in the rest of the world (comparable pharmaceutical manufacturing standards should be applied in the EU to products destined for sale outside the EU as for products intended for the EU authority market).

2. **Defining and implementing good pharmaceutical regulatory practice in Europe**

   Effective pharmaceutical regulation necessitates the appropriate allocation of both public authority overseer and private sector provider regulatory resources to the pharmaceutical sector activities that provide ultimate benefits to patients. In Europe, there is often a strong tendency to go overboard with introducing regulatory 'quality management systems' which support pre-existing irrational pharmaceutical market activities.

   There is considerable divergence in drug regulatory practice between the various Member States. At the same time, several regulatory activities are perhaps duplicated unnecessarily at a national level and which may be performed better and more rationally at a centralised level. Arguably, models of drug regulatory practice are better in some Member States than in others (which can vary considerably according to any particular section of pharmaceutical regulation). There is great scope to learn from best practice in one particular Member State pertaining to any particular regulatory area. It would help considerably to have a model of best EU Member State drug regulatory practice.

In this context, Tremblay states, "the different practices of the EU Member States need to be 'mapped' to identify where mismatches in regulatory practices may contribute to problems at EU level or between Member States; this 'cross-border regulatory map' should identify how enforcement practices differ, and consider inconsistencies in terms of definitions of counterfeiting and data collection practices. The benchmarking of regulatory performance should also be undertaken as part of this to provide the basis for consistent and high standards going forward."

3. **Further conceptualise, define and address 'artificial partitioning of the market'**

   With respect to the European pharmaceutical market, the concept of artificial partitioning (as defined originally by the EC) requires defining more clearly in such a way as to recognise that the market can be partitioned artificially by any stakeholder – manufacturers, national authorities, healthcare professionals, pharmacists – and even patients – in terms of how products are placed (marketed), financed, prescribed, dispensed and consumed.

   In reducing or eliminating artificial partitioning, there are, *inter alia*, several areas that need attention: (i) further rationalising the EU marketing authorisation system (achieving convergence between the centralised, mutual recognition and national procedures); (ii) achieving convergence and transparency in European national pricing and reimbursement (see 4, below); (iii) achieving common product indications irrespective of national market; (iv) introducing common packaging and patient information leaflets (PILs). A vital step in minimising artificial partitioning, with respect to PPT's ability to exploit in a way which undermines supply chain security, is to introduce 'all European packs and PILs' (irrespective of marketing authorisation procedure and printed language) to serve the needs of the intended market; they should also be printed in common European languages. As Tremblay[16] says, "this would, in practice, prevent the need for parallel traders to 'repack' the vast majority of products".

4. **Achieve European national pricing and reimbursement system convergence and transparency**

   Efforts need to be made to achieve convergence and transparency of the national pricing and reimbursement systems and in a way that takes account of national purchasing power parity and per capita healthcare expenditure. The EC Transparency Directive[10] requires revising and updating. Measures need to be put in place to monitor national authority efforts in achieving EU pharmaceutical pricing and reimbursement system convergence. The research-based pharmaceutical industry needs to be more proactive in achieving system convergence with the final objective of achieving single market pricing. Ultimately it is in its interest to support this objective, so that it can then better focus on doing its job of research and development.

5. **Rationalise and coordinate national demand and supply incentives employed to achieve cost-effectiveness of pharmaceutical consumption**

   A full review is required of the measures employed by national authorities, particularly those used to encourage PPT, in order to provide recommendations for rationalisation and coordination of such measures in a way that addresses ultimate patient safety, rather than pure health economic objectives.

6. **Create a centralised European drug safety reporting system including a database of 'product defects'**

   On the basis that there is a strong connection between pharmacovigilance, supply chain quality control, counterfeit medicines and diversion, there is a need for a unified European reporting and database

system which acts as a Single Point of European Contact (SPOC). The FDA MedWatch scheme achieves this for the US market. The EC Pharmacovigilance database system needs to be expanded to incorporate all drug safety issues and in a way that allows reporting from manufacturers, wholesalers, prescribers, dispensers and patients. There should be the capacity at EC level to coordinate, manage, assess, analyse and use data in order to inform policy at EU and member state levels.

As Tremblay[16] states, "good data collection, analysis and monitoring are needed to inform policy makers, regulators, industry and the public to ensure a high level of understanding of safety across the EU supply chain".

7. **Adopt technological solutions to supply chain security issues**

   Although addressing the human factors and administrative systems concerning pharmaceutical regulation are key, it is vital also to adopt technological solutions to ensure traceability, verification and authentication of pharmaceutical products through the supply chain, thus enhancing the ability for reporting of suspected medicinal product defects and batch recall. While product verification (authentication) measures should be the prerogative of the original manufacturer, there is a need for Europe to adopt common standards on product traceability measures. The ultimate RFID standard does not yet seem to be a practical solution for product traceability anywhere in the world, so it is necessary to look at less expensive, but also coordinated solutions across Europe. In the light of the various pharmaceutical traceability 'projects' being employed in the various EU Member States, they need to be assessed and coordinated thoroughly.

8. **Define and institute the concepts of 'drug safety', medicinal 'product defect', 'pharmaceutical crime', 'counterfeit medicine' and 'supply chain security'**

   There is a real need now to define some important concepts and how they interact in a way that all stakeholders understand and which have meaning for, and assist in, securing ultimate patient safety.

Specific recommendations concerning European PPT and pharmaceutical supply chain security

1. **Formal European consultation process on PPT**

   The EC needs to institute a formal consultation process on PPT, as it did successfully with pharmacovigilance, for example.

2. **Rationalise and simplify the European pharmaceutical distribution system – the right of original manufacturers to secure their product supply chain**

   The extent to which free market forces are rationalising the complex European pharmaceutical distribution is questionable and open to debate. The right of research-based manufacturers to simplify the distribution of their products, for example via sole/selected distributorship agreements, should be considered in the light of both current supply chain security concerns and also because of arguably 'market failure' in terms of achieving a single European pharmaceutical market.

3. **Full audit of the European pharmaceutical supply chain**

   Given the high level of concern with the current complexity and security of the European pharmaceutical supply chain, there is a real need to conduct an immediate and full audit of the system. Particular

attention needs to be paid not just to PPT but also the trading of APIs and bulk intermediate products.

4. **Create a centralised European database and geographic information system of pharmaceutical distributors (and API/bulk intermediate product traders) which all stakeholders can access**

   Tremblay states, "to improve sharing of information between regulators, the EU should have a central clearing house of information on all companies and organisations involved in the movement of medicines within, across, into and out of the EU, and which provides access to member-state regulatory documents and licences from any of the member-state jurisdictions; standard formats and information should prevail to meet the diverse needs of users in other member states."

   It is vital that European regulators have immediate knowledge of all legitimate (and potentially illegitimate) companies involved in pharmaceutical distribution and trading (not just for finished products, but also for APIs and Bulk Intermediate Products [BIPs]). Such a database also benefits all stakeholders interested in ultimate patient safety. For finished products, this should be possible to achieve based on national distributor, and product licenses, issued; but for APIs and bulk intermediate products, creation of such a database is likely to be much more problematical as intermediate traders and brokers lie outside of the pharmaceutical regulatory system.

5. **Implement measures to achieve 'real' pharmaceutical Good Distribution Practice (GDP) in Europe**

   In light of increasing complexity in the supply chain, and threats to its security, the EC guidelines on pharmaceutical GDP are out of date and require urgent revising (see 7 below). A number of measures have been proposed to improve pharmaceutical GDP by various stakeholders interested in patient safety; those proposed by Celesio AG (member of GIRP), and described above under the report section 'Global supply chain security' have much merit.

6. **Review and codify EC case law on PPT**

   European PPT case law is highly complex and requires thorough review and codification in such a way that all stakeholders can understand and interpret.

7. **Strengthen regulation of the European pharmaceutical supply chain (with particular regard to PPT) at EC and national levels**

   There seems to be a requirement to update and coordinate several rules that relate to the governance of the European pharmaceutical supply chain and in a way that addresses supply chain security issues, particularly concerning the minimisation of the risk of counterfeit and adulterated medicines as well as diversion. The rules that require attention in this respect are listed in the following box:

- Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)
- Commission Communication COM/2003/0839 on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted
- EMEA Post-Authorisation Guidance on Parallel Distribution (EMEA/Ho/2368/Rev 4)
- Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use
- Regulation EC 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.

The updating process must pay attention to coordination between the various regulatory documents in a way that provides clarity for ease of implementation at a national level. The current EC pharmaceutical GDP guidelines need not only updating, but also converting into harder European regulation. Although the regulation of PPT requires strengthening, this will likely add additional cost to the management and regulatory supervision of the European PPT system.

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**

   This requires adopting a standard European model for 'good regulatory practice' with respect to obviating counterfeit, adulterated and diverted medicines. It also requires the resources to carry out the necessary regulatory oversight of PPT. The UK MHRA, with its recently introduced market intelligence, investigation and enforcement with respect to counterfeit medicines and product diversion, can potentially provide a good model for other Member State DRAs.

9. **Prohibit 'de-boxing' – PPT undermines technological measures to secure supply chain security**

   While some research-based manufacturers now take all necessary precautions to limit adulterated contamination of products by implementing authentication measures, including technologies such as tamper-proof packaging, the product authentication system is undermined by the PPT process. The practice of 'de-boxing' should be prohibited. The value added of 'overboxing' is highly questionable in terms of both pure economics and patient safety.

10. **For public safety purposes, restrictions can be potentially imposed on the freedom of movement of pharmaceuticals within the EU/EEA territory**

    It has been suggested that restrictions should be imposed on the freedom of movement for certain goods, such as medicines, for public safety reasons.[24] In view of public safety concerns related to the European pharmaceutical distribution system, not just in terms of the internal market but also the control of import and export of medicinal products from the EU territory (the situation with API and bulk intermediate product trading controls is frightening), there are arguably good reasons for introducing Draconian pharmaeutical trade restrictions particularly in respect of parallel-traded pharmaceutical products. To the extent that restrictions are deemed to be required, the following recommendations can be made:

    - repackaging and relabelling of medicinal products destined for parallel trade should be conducted under the supervision of the original trademark holder. The original trademark holder has a legitimate manufacturing licence, while a parallel trader does not. To whatever extent that EU/EEA national DRAs are unable to supervise the process of repackaging and relabelling of PPT products, then the original manufacturer should have the obvious right to supervise the process so as to guarantee both the integrity of its products and ensurance of its obligation to achieving pharmaceutical supply chain security

    - transit licensing for parallel traded medicines between the states of the EU/EEA should be introduced. This measure should not just apply to finished products but also to APIs and bulk intermediate products. This measure, while Draconian, may need to be introduced as a short term measure until confidence is gained with the EU/EEA supply chain (confidence not just on the part of EU/EEA healthcare consumers but also for consumers worldwide given that a significant amount of global pharmaceutical trade passes through the EU/EEA)

- PPT should be suspended temporarily – while being the toughest Draconian measure that can be proposed short of eliminating PPT, this option should be considered seriously as a public safety measure until such a time as there is deemed to be sufficient supply chain security, regulatory supervision and general public confidence in the medicines supply chain. This option also needs to be considered expediently in light of the forthcoming expiry of new Member State derogation from PPT which is likely to complicate further the already complicated situation of PPT and pharmaceutical distribution in general in Europe.

11. Patient involvement and empowerment measures with respect to PPT and related drug safety issues

Measures need to be taken whereby patients are: (i) informed of the debate surrounding parallel traded medicines and pharmaceutical supply chain security; (ii) informed of, and have the right to request a choice, upon presenting a pharmacy prescription, between an original nationally-authorised or a parallel traded medicine. At the same time, patients should be informed of where they should report "product defects" and unsatisfactory dispensing.

12. Further studies to obtain more evidence to inform policy

While this report has attempted to be comprehensive in identifying and reviewing relevant available data so as to provide a thorough informed review of European PPT, there are several areas where it may be considered that more primary data is required to inform the debate. The section entitled 'Missing Evidence' highlights some issues (there may be others) where further study is required in order to provide a final evidence-based assessment on the subject of European PPT.

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