Title:
Falsified Medicines Directive 2011/62/EU
IA No: 4024

Lead department or agency:
Medicines and Healthcare Products Regulatory Agency
Other departments or agencies:

Impact Assessment (IA)

Date: 20/03/2013

Stage: Final

Source of intervention: EU

Type of measure: Secondary legislation

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Summary: Intervention and Options

RPC Opinion: GREEN

Cost of Preferred (or more likely) Option				
Total Net Present Value	**Business Net Present Value**	**Net cost to business per year** (EANCB on 2009 prices)	**In scope of One-In, One-Out?**	**Measure qualifies as**
£16.274m	£16.274m	£1.891m	No	NA

What is the problem under consideration? Why is government intervention necessary?

The problems that this IA analyses are the human and other economic costs caused by:

A. The infiltration of falsified medicines into the regulated EU medicines supply chain.

B. The introduction of substandard active substances and excipients into legitimate medicines.

Both problems arise because of patients and medical professionals are usually unable to distinguish between genuinely beneficial medicines and medicines that could harm them of fail to treat their conditions. The EU believes that current regulatory controls have not removed this information asymmetry market failure and that further action is necessary to control counterfeit infiltration in EU supply chains.

What are the policy objectives and the intended effects?

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

What policy options have been considered, including any alternatives to regulation? Please justify preferred option (further details in Evidence Base)

Option 0: Do nothing

This option is used as a comparator to act as a baseline for current costs of Option 1. The UK is legally obliged to implement the Directive. Option is therefore not feasible as an alternative to Option 1

Option 1: Implement the Directive

The Directive contains several discrete interventions, affecting different business sectors in the UK, the EU and the rest of the world. These proposals have been incorporated into one option for the sake of simplicity and because there is, with one exception, no scope for designing the UK implementation of the Directive so that impacts on business are minimised consistent with achieving the aims of the Directive. The exception concerns how MHRA intends to minimise the need for inspection in lower risk settings.

Will the policy be reviewed? It will be reviewed. **If applicable, set review date:** 01/2017

Does implementation go beyond minimum EU requirements?			No		
Are any of these organisations in scope? If Micros not exempted set out reason in Evidence Base.	**Micro** Yes	**< 20** Yes	**Small** Yes	**Medium** Yes	**Large** Yes
What is the CO_2 equivalent change in greenhouse gas emissions? (Million tonnes CO_2 equivalent)			**Traded:** 0	**Non-traded:** 0	

I have read the Impact Assessment and I am satisfied that (a) it represents a fair and reasonable view of the expected costs, benefits and impact of the policy, and (b) that the benefits justify the costs.

Signed by the responsible Minister: *Earl Howe* Date: *8th July 2013*

Summary: Analysis & Evidence

Policy Option 1

Description:

FULL ECONOMIC ASSESSMENT

Price Base Year 2011	PV Base Year 2013	Time Period Years 10	Net Benefit (Present Value (PV)) (£m)		
			Low: -4.276	High: -28.272	Best Estimate: 16.274

COSTS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Cost (Present Value)
Low	0.800	1	0.416	**4.384**
High	4.922		2.725	**28.380**
Best Estimate	2.861		1.571	**16.382**

Description and scale of key monetised costs by 'main affected groups'

Compliance with good distribution practices is expected to cost between £0.353 million and £2.683 million per year. These costs are mainly borne by manufacturers of medicinal products, active substances and excipients.

Other key non-monetised costs by 'main affected groups'

We have been unable to estimate the costs to active ingredient manufacturers in non-EU countries. It is unclear to what extent these costs might be passed on to buyers in the UK.

BENEFITS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Benefit (Present Value)
Low	Optional		Optional	**Optional**
High	Optional		Optional	**Optional**
Best Estimate	0		0.013	**0.108**

Description and scale of key monetised benefits by 'main affected groups'

The estimated benefits are enjoyed by medicines wholesalers who will no longer have to pay for notarised translations of the registration documents of non-EU suppliers. The new measures include an EU central database of suppliers and will remove the need to get notarised translations.

Other key non-monetised benefits by 'main affected groups'

We have been unable to estimate the impact the Directive will have on reducing the costs imposed on legitimate business and the harm caused to human health that falsified medicines create. However, we have provided an estimate of the total cost that falsified medicines imposes on UK patients, the NHS and UK business interests. The midpoint estimate is £0.845 million.

Key assumptions/sensitivities/risks **Discount rate (%)** 3.5

The assumptions that have the greatest impact on estimates relate to the costs of complying with good practice. We have calculated a range (annualised at between £0.353 million and £2.683 million) to account for our uncertainty.

BUSINESS ASSESSMENT (Option 1)

Direct impact on business (Equivalent Annual) £m:			In scope of OIOO?	Measure qualifies as
Costs: 1.904	**Benefits:** 0.013	**Net:** 1.891	No	NA

Evidence Base (for summary sheets)

Problems under consideration

1. The problems that this IA analyses are the human and other economic costs caused by:

   A. The infiltration of falsified medicines into the regulated UK medicines supply chain.

   B. The introduction of substandard active substances and excipients into legitimate medicines.

2. Both problems arise because suppliers, patients, and the health professionals who advise them, are usually unable to distinguish between genuinely beneficial medicines and those products that could harm them or fail to treat the patients' conditions. This problem of information asymmetry is used as a justification for government intervention to decrease the probability that falsified or substandard genuine medicines are supplied to patients.

3. The issue that is addressed in this IA is whether current EU safeguards are sufficiently robust. In effect the EU believes that the social marginal costs are currently lower than the social marginal benefits and hence further action is justified.

The Problem of Falsified Medicine Infiltration

4. By "falsified medicines" we mean those that are deliberately and fraudulently misrepresented with respect to identity, origin or provenance. In this IA, the terms "counterfeit" and "falsified" are used interchangeably. Counterfeiting can apply to both branded and generic products, and counterfeit products may include products:

- with the correct ingredients,
- with the wrong ingredients,
- without active substances,
- with insufficient active substances,
- with falsified packaging, or
- falsified accompanying documentation.

5. By "the regulated UK medicines supply chain" we mean:

- The manufacturers, importers, exporters, brokers, wholesalers, and pharmacies involved in supplying medicines within the UK and to other EU Member States
- The transactions between these players
- The physical movement and storage of medicines

6. Note that in this IA we are not addressing the problem of counterfeit medicines made available directly to patients through unregulated sources such as illegal internet sites.

7. The rest of this section is structured as follows:

- First we discuss the size of the problem
- Second, the costs it imposes on the UK
- Third, how infiltration of counterfeits has occurred
- Finally, why further intervention is justified

<u>The size of the counterfeit infiltration problem</u>

8. For counterfeit medicine to enter the regulated supply chain it has to appear identical to the genuine product. It is usually capable of deceiving a pharmacist or other healthcare professional. It is often not until a suspicious product is submitted to a laboratory for forensic analysis that its true counterfeit nature is established. This results in these types of cases being very difficult to detect.

8. A list of known incidents appears below. Note that this list is not necessarily comprehensive. Also note that we can not be sure that the size of the seizures reflects the entirety of the counterfeit batch that was circulating. When a case comes to light and an investigation follows, it is rare to establish that it is the first incident and that a number of previous transactions have not already occurred. When the UK Border Agency make seizures of counterfeit medicine entering the UK again it is rare that this is the first importation and sometimes uncovers a long history of previous similar importations.

9. The table below gives summary data for medicines detected in the supply chain from 2004 to the present.

Table 1. Known cases of counterfeit medicine infiltration

Year	Product	Manufacturer	Nos of known counterfeits (packs)	BNF Price	Levels of Active Substance in Counterfeit	Total Retail price of Counterfeits
Aug-04	Cialis 20mg	Lilly	30,000	£19.34	Batch 1: 25-95% Batch 2: 85-90% Trace of other actives in both batches	£580,200.00
Sep-04	Reductil 15mg	Abbott	1,000	£39.31	85-100%	£39,310.00
Jul-05	Lipitor 20mg	Pfizer	2,500	£24.64	Wrong active – 90-100%	£61,600.00
Feb-06	Viagra 100mg	Pfizer	Not available	£23.50	Not known	Not available
2005	Lipitor	Pfizer	300	£24.64	50-105%	£7,392.00
2005	Celebrex	Pfizer	250	£21.55	25%	£5,387.50
2005	Cialis and Viagra	Lilly and Pfizer	Not available	£23.40/23.50	Cialis: 85-95% (trace of other actives) Viagra not known	Not available
Jul-06	Lipitor 40mg	Pfizer		£28.21	Wrong active – 90-100%	
Aug-06	Lipitor 20mg	Pfizer	1900	£24.64	85-90%	£53,599.00
Jul-06	Propecia 1mg	MSD	450	£26.99	90%	£12,145.50
May-07	Zyprexa 10mg	Lilly	13900	£79.45	Batch 1: 55-60% Batch 2: 65-85% Batch 3: 60-70%	£1,104,355.00
May-07	Plavix 75mg	Sanofi Aventis	41400	£35.31	Batch 1: 70-75% Batch 2: 80-85% Batch 3: 80-85%	£1,461,834.00
Jun-07	Casodex 50mg	Astera Zeneca	15000	£128.00	70-80%	£1,920,000.00
Jan-07	Plavix 75mg	Sanofi Aventis	26500	£35.31	Batch 1: trace amounts of active Batch 2: 35-45%	£935,715.00
May-09	Seretide 250 Evohaler 8 ml pressurised inhalers	GSK	800	£62.29	Active 1: 84% Active 2: 88%	£49,832.00
Nov 11	Truvada and Viread[1]	Gilead Pharmaceuticals	335 200[2]	£418.50 £255.00	98-100%	£191,197.50
Total			**134,535**			**£6,422,567.50**

10. In the eight years since the beginning of 2004, the average annual value of counterfeit medicines known to have infiltrated the supply chain (measured at the retail price of the genuine products) was approximately £917,000[3]. This is approximately 0.06% of the total annual value of the NHS drugs bill.

11. We have no clear evidence that the size of the problem is increasing or decreasing.

The costs imposed on UK society by the counterfeit medicines problem

12. We have identified five types of potential cost that could be avoided through earlier detection of counterfeit medicines in the regulated supply chain.

- The health loss suffered by patients receiving counterfeit medicines that do not treat the patients' conditions, or in a worst case scenario, actively harm patients
- The additional costs of treatment for these patients
- The lost profit for legitimate companies whose products are counterfeited and consumed by patients
- The costs to legitimate companies of product recalls at the pharmacy and patient level.
- Loss of public confidence in UK medicines regulation.

13. Note that we have not included the lost sales costs to legitimate pharmaceutical companies as a result of negative publicity surrounding counterfeits reaching patients. Although there is no evidence that this has occurred as a result of counterfeit products reaching patients in the UK, it nevertheless remains a possibility, given a significant enough counterfeit case. However, although this is an issue for individual companies, it is arguably not a problem for the UK as a whole. Where reasonably close substitute treatments exist, one firm's loss is likely to be another firm's gain. Where close substitutes do not exist, there could be an aggregate loss to pharmaceutical firms. However, the loss remains a hypothetical one, on which we have no evidence.

14. There is also a category of cost that could be avoided if counterfeits never reached the UK. The principle category is the cost to UK government agencies of investigating and prosecuting cases of counterfeit infiltration. The likelihood of avoiding these costs depends on the deterrent effect of any new measures introduced in the UK. We have estimated these costs separately.

Health loss

15. Note from Table 1 that all but one of the known instances of UK supply chain infiltration have involved counterfeits that contain some level of active substance (usually the correct one). This level of sophistication indicates the counterfeiters' desire to avoid detection. Nevertheless, it is not clear whether the levels of active substance inclusion would deliver therapeutic doses to the patients that took the counterfeit medicines. There is also the problem that counterfeiters' manufacturing processes may not formulate the medicine in the correct way that allows the active substances to be released properly and give therapeutic effect.

16. All of the counterfeits discovered in the UK have included a range of impurities. It is not known whether they were harmful. Although the introduction of harmful ingredients through poor manufacturing processes continues to pose a health risk, we do not know the size of this risk and hence have not included estimates of the harm that harmful ingredients could generate. Nevertheless, a reasonable worst case scenario could involve UK patients taking counterfeit medicines that are actively harmful (as opposed to just not treating their underlying medical condition). Although it appears that such a scenario has not happened to any detectable degree since 2004, it remains a threat for the future. Not accounting for such a scenario remains a potential weakness of our analysis.

17. Our estimate is based on the assumption (assumption A) that manufacturers of patented medicines (the target of all known counterfeit activities in the UK) receive a price in the UK that equals the National Institute of Health and Clinical Excellence (NICE) threshold of £25,000 per QALY (figures expressed in £s per QALY measure the incremental medicine health gains that are over and above the gains from the next best alternative). Although the originator firms are free to price their patented drugs at whatever price they choose, they also know that the cost-effectiveness guidance produced by the NICE is unlikely to recommend that the NHS buys the drugs if their prices exceed the cost-effectiveness

threshold. The firms therefore attempt to price their drugs at the cost-effectiveness threshold to maximise the returns they earn on their investments.

18. Assumption A means that for every £25,000 that is received by originator firms for patented drugs consumed in the UK, patients, and therefore society, benefit by one QALY.

19. If we make the further assumption (assumption B) that none of the counterfeit drugs that have been taken by UK patients delivered any therapeutic benefit, then for every £25,000 spent on counterfeit drugs (that would otherwise have gone to the genuine manufacturer), patients and therefore society lose 1 QALY.

20. The standard Department of Health figure for the maximum that society is willing to pay to prevent the loss of one QALY is £60,000. We have used this figure in valuing the loss of QALYs that patients experience when taking counterfeit drugs.

21. The price that is reimbursed by the NHS to the pharmacists who dispense medicines to patients includes the value of the services provided by the pharmacists themselves and the wholesalers that store and distribute the drugs throughout the UK. By convention, manufacturers give a 12.5% discount on the NHS reimbursement price to wholesalers[4]. We assume (Assumption C) that this margin represents normal competitive returns to pharmacists and wholesalers, and that the residual amount is what society is willing to pay for the health gains that the genuine drugs would deliver.

22. Putting assumptions A, B and C together yields an average annual estimate of £427,000 for the health loss from the cases of counterfeit medicines that we know reached patients, and that we assume were consumed by those patients.

23. There are several reasons why this estimate of the foregone health value may not be accurate.

24. First, there are three reasons why our estimate might under-represent the real picture.

- We do not know whether we have detected all counterfeit medicines that have reached patients
- Our methodology does not count the total health gain from taking a medicine, but merely the incremental gain from taking a medicine compared with the next best alternative.
- There may be important threshold effects that mean that declines in health from taking counterfeit drugs are no longer marginal in nature (as implied using our methodology) and become dramatic – for instance, involving death.

25. Second, there is one reason why our estimate might over-represent the real picture:

- Assumption B may be wrong. As already noted, most of the counterfeit medicines that we know have reached patients have contained a proportion of the correct active substance. It is possible that at least some of the counterfeit drugs had a therapeutic effect on the patients who took them.

26. Given these uncertainties, we offer our estimate as an approximation that indicates the rough, possibly lower bound order of magnitude of harm.

Additional costs of treatment

27. A consequence of our Assumption B is that it is reasonable further to assume that some of the patients who take counterfeit medicines will need additional medical attention because their conditions worsen. Again, we have no patient level data that helps us to estimate these additional costs. On what we believe is a conservative basis, we have assumed that in 10% of the cases where patients have received counterfeit medicines, the patients need to see their GP once.

28. Our estimate of the additional costs of treatment is based on the average cost of a GP consultation of £53[5]. Our total estimated annual cost is £26,000.

Lost returns for UK shareholders in legitimate pharmaceutical companies

29. Firms who own the rights to drugs that are counterfeited and consumed lose the profit that they would otherwise have earned by selling the genuine drug. Note that we assume that companies do not lose profit in cases where counterfeit medicines are detected before they reach patients. Our assumption is that the genuine products replace the counterfeit ones in time for there to be no lost sales.

30. This gross profit should be adjusted for three reasons:

- First, we are only concerned here with losses to UK interests. RPC and DH economists have yet to agree an acceptable methodology for apportioning costs to the UK in circumstances where policies change the costs of multinational firms. As a holding position, we have assumed that the effects will be felt in proportion to UK shareholding in the global pharmaceutical industry. A rationale for this assumption appears in Annex A. We have assumed a 20% Net Profit Margin[6] in the originator pharmaceutical industry as a proxy for shareholder returns. Further, we assume that UK shareholding in the affected firms is 6%[7].
- Second, some of the profit earned by originator firms is spent on promotional activities designed to persuade prescribers to choose their products in preference to others'. This expenditure is unlikely to increase the amount of useful information available to society. We have assumed that 15% of profits is spent on these socially unproductive activities[8], and have discounted the profits by the same proportion.
- Third, financial gains to UK shareholders should be adjusted to reflect the social opportunity cost of those gains. If on average the beneficiaries are wealthier than the UK national average, then distributional weighting of less than one should be used to convert financial losses to economic (societal) losses (Annex 5 of Treasury Green Book 2003). We have applied a weighting of 0.682 to account for this effect. The evidence for this weighting is given in Annex A.

31. Combining our assumptions for annual lost returns to UK shareholders yields an estimate of £6,000.

Product recall cost

32. The pharmaceutical company Lilly has provided us with estimates of the costs of recalling its product Zyprexa in 2007:

- The sales value of the 6242 cartons of Zyprexa (£434,000) returned in the recall. However, we have assumed that there is no lost profit on drugs that are intercepted before they reach patients (see above). Some of the cartons received under recall would be genuine, and therefore we should count the manufacturing costs that Lilly did not recoup because the genuine products were destroyed. However, we do not know what proportion of the cartons was genuine and furthermore, the manufacturing costs are a small proportion (assumed to be 2%) of the price that Lilly receives for its product. We have therefore not included any estimate of the costs.
- The estimated costs to customers in the pharmacy trade (£20,120) for their time in returning counterfeit Zyprexa.
- The cost to Lilly in taking staff away from their normal duties to field customer enquiries, coordinate returns and receive products relating to the recall in the UK - estimated total to conduct this operation was £80,231.

33. The Lilly estimates also included lost profit from the counterfeit products that patients consumed. Note that this loss is estimated in the previous section.

34. Assuming that the Lilly estimates are typical for a product recall, and applying the adjustments to gross profit that we discussed in the lost profit section above, our estimated cost to the UK for a recall is £24,000 in 2007 prices. Uprated to 2011 prices (using the HMT GDP deflator) the estimate is £25,000.

35. From Jan 2005 to June 2010, there were 50 recalls in the EU as a result of counterfeit medicines detected in the EU supply chain. If this number is representative of the need for future recalls, we can expect on average 7.1 recalls per year. The annual cost of recalls to the UK is estimated at £224,000.

Loss of public confidence in medicines regulation

36. There is no evidence that the public has lost any confidence in UK medicines regulation as a result of the counterfeit medicines cases that have arisen since 2004. We have therefore not included any estimate of this effect. However, a reasonable worst case future scenario that involved significant harm to patients could have a negative impact on public perceptions, particularly if the victims are regarded as being vulnerable (for instance, children, the elderly and the severely ill). The costs associated with a loss of public confidence would be the health losses associated with patients refusing to take medicines in the belief that they could be counterfeit and harmful. There would also be costs to the government in restoring and maintaining public confidence. We currently have no evidence on the likelihood of such a reasonable worst case scenario occurring, and therefore have been unable to analyse the expected harm. This represents a potential weakness in our analysis.

Investigation and prosecution costs

37. As noted above, prosecution and investigation costs would be avoided if counterfeit medicines never reached the UK.

38. We have included MHRA's costs associated with the laboratory costs of analysing counterfeit medicines, and the legal costs of prosecuting cases. We have been unable to estimate the MHRA staff costs of investigating counterfeit cases and providing evidence for prosecutions.

39. MHRA estimates that it has spent £0.62 million on testing counterfeit medicines since 2000. The average annual cost was therefore £0.06 million.

40. The prosecution costs can be estimated from the costs awarded against convicted defendants by the courts. Since 2008/09 the average cost awarded to MHRA has been £0.22 million. However, the standard deviation is £0.36 million and the median is £0.02 million. To overcome this problem of a highly skewed distribution, we took natural logs of the costs, calculated the mean and then anti-logged. This yielded an average of £0.04 million. We adopted £0.04 million as the average cost of prosecution per case. The number of cases brought to court each year is difficult to predict. Over the last four years, the number of cases each year has ranged from 1 to 5. We have adopted these figures as the lower and upper bound estimate.

41. The total investigation and prosecution cost estimate ranges from £0.09 million to £0.23 million.

Total costs to the UK from counterfeit medicines

	£ million
Harm to patients	0.427
Additional treatment costs	0.026
Lost return for UK shareholders	0.006
Recall costs	0.224
Sub-total	***0.684***
Investigation and prosecution	
Lower	0.091
Upper	0.231
TOTAL	
Lower	**0.775**
Upper	**0.915**

Critique and analysis of the European Commission's estimate of harm to health from counterfeit medicines

42. In its opinion on the consultation stage IA, the RPC asked that a comparison be made between our estimates of harm and those produced by the EC for its IA. We have reservations about doing this

because, as summarised below, we believe that the EC's estimates are poorly supported by evidence. However, for the sake of transparency, we have produced the following critique and analysis.

43. The EC estimates are based upon several assumptions that lack a credible empirical evidence base. For instance, the IA claims that the problem of counterfeit infiltration is becoming substantially worse year on year. This conclusion is based on comparing just two consecutive years and does not account for the likelihood of random variation between years and potential differences in enforcement activities within the EU across years (seizures of counterfeit medicines are sufficiently rare that one big case can make a dramatic difference to a particular year's figures). Our own evidence, collected in the UK over 8 years and presented in the table on page 4, indicates no clear evidence of any change in infiltration.

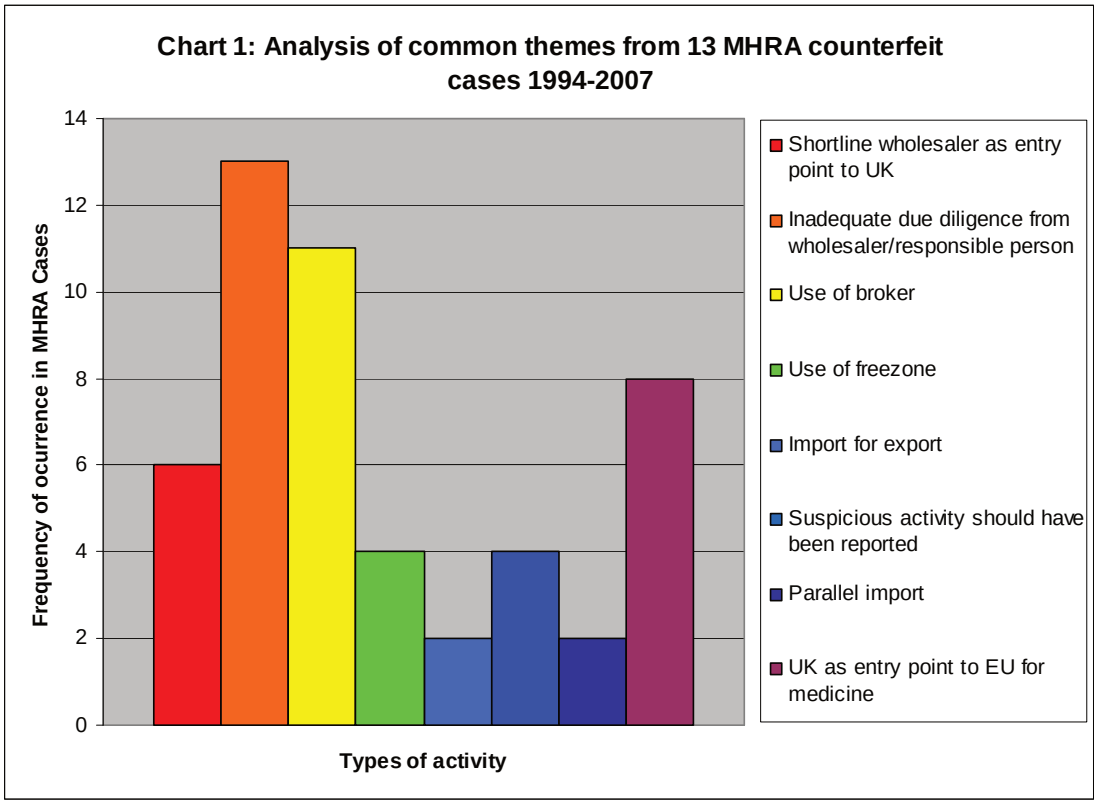
44. The EU IA also makes claims about the reasonableness of some of its other assumptions but provides little or no evidence for why they should be considered so. For instance, there is an assumption that 5% of counterfeit packs that enter the regulated EU supply chains cause harm to patients that is equivalent per patient of living two months in a health state that is equivalent to being dead (or to put it equivalently, spending a full year with a constant 17% health loss, which is approximately the same as having measles for a full year). The 5% figure was apparently chosen on the basis that it was "conservative" but the EU IA provides no justification for this belief or exploration of alternative assumptions. Furthermore, if the EU's assumptions about the large scale of the health loss per patient are correct, it would seem curious that there have been few if any reports of such health losses from clinicians and patients across EU.

45. The EU IA estimated that the annual EU-wide harm to health is Euros 765 million. Converting an EU-wide estimate to a UK estimate is not straightforward. The EU IA assumes that in any year 1.5 million packs of counterfeited medicines infiltrate EU regulated supply chains. The basis for this estimate is not entirely clear but it seems to have been based on seizures of counterfeit medicines in 2007, which, according to UK records, saw by far the greatest number of seizures over the last 8 years. If the same was true across the whole EU, then the choice of 2007 would introduce a very substantial upward bias into the EU estimate. The number of seized packs in 2007 in the UK was approximately 97,000 (over two thirds of the total seizures between 2004 and 2011). This suggests that an EU to UK conversion factor of 6.5% might be appropriate.

46. As noted above, the EU IA assumes that 5% of these packs cause a health loss of 0.17 Quality Adjusted Life Years (QALY). Valuing the loss of a QALY year at the Department of Health's standard value of £60,000, and using the EU's assumptions about QALY losses from counterfeit medicines, suggests that the annual harm to UK health is £49 million. Our own estimate of the harm is two orders of magnitude lower at £0.4 million. For the reasons given above, and because our figures are based on data that stretches over an eight year period rather than the EU's one year period, we believe that our estimate is more justifiable.

<u>How infiltration of counterfeit medicines into the regulated UK supply chain has occurred</u>

47. The graph below shows some of the areas that have been common factors in the cases detected in the UK since 1994.



48. Description of key themes

Short-line wholesaler as entry point to UK: Most wholesale dealers in the UK are 'short-line', meaning that they do not stock the full 20,000 medicines required by the NHS. Only about 10 wholesale dealers are full-line, and they make up for 90% of all trade in medicines in the UK. Conversely, short-line wholesalers typically only trade about 10% of the medicines in the UK. The significance of short-line wholesales as entry points to the UK market helps to illustrate how a proliferation of wholesale dealing companies compared to other member states has led to greater opportunities for counterfeiters to introduce their counterfeits in the UK.

Inadequate due diligence from wholesale dealer/responsible person: In nearly every case of counterfeiting, the medicines could have been identified as counterfeit had the wholesale dealer or responsible person conducted the checks that are required of them.

Use of a broker: Medicines are sometimes traded between wholesale dealers through the use of a broker, who arranges that the two parties make the trade, but never actually takes possession of the goods. Brokers have been a key feature of UK medicines counterfeiting cases, and are outside of the current regulatory regime.

Use of free zones: A Free Zone is a designated area in which non-Community goods are treated as being outside the Customs territory of the Community for the purpose of import duties. Currently there are five Free Zones in the UK. Medicines that have been imported can be held in a Free Zone for further trade in export from the UK. Whilst in a Free Zone they can be subject to alteration or repackaging.

Import for export: Medicinal products may also be introduced into the UK while not being intended to be imported, i.e. not intended to be released for free circulation. If those medicinal products are falsified they present a risk to public health within the UK. In addition, those falsified medicinal products may reach patients in EEA and third countries..

Suspicious activity should have been reported: In some of the cases brought by the MHRA, a check on seized records has shown that the counterfeit medicines that eventually made their way into the supply chain were first offered to wholesale dealers, or failed the scrutiny of Responsible Person, who rejected them due to concerns about their authenticity. However, these concerns were not then notified to the MHRA.

Parallel import: The UK Parallel Import Licensing Scheme allows medicinal products authorised in other EU Member States to be marketed in the UK, provided the imported products have no therapeutic difference from the equivalent UK products. Such medicines are subject to repackaging in the UK language by authorised manufacturers. If falsifed medicines are sold to the authorised manufacturers any legitimate repackaging can disguise their authenticity.

UK as entry point to EU for counterfeit medicine: In a large number of the medicines cases examined, the UK is the point at which the counterfeit has entered the EU. This could suggest weaknesses in our importing controls (although without full European analysis, this could not be proven), but also shows that the majority of counterfeits are coming to the UK from outside of Europe.

Why new intervention is theoretically justified

49. As already noted, the justification for government intervention is to overcome the information asymmetries that exist between suppliers of medicines and patients. The EU's view is that the level of protection against counterfeits reaching patients is not currently optimal – in effect the EU seems to believe that the social marginal costs are lower than the social marginal benefits and that further protection is justified.

The Problem of Sub-Standard Active Substances and Excipients

50. Active substances are those substances which give a medicinal product its therapeutic effect. Excipients are those substances (excluding packaging elements) present in a medicinal product which are not active substances. Excipients are used as a carrier for the active substance in a medicinal product. For example excipients may be used to bulk up formulations that contain small amounts of very potent active substances to aid in the handling of the medicine, or modify the release of the active substance once the medicine has been consumed.

The size of the sub-standard problem

51. Over the last few years there have been a small number of overseas incidents caused by sub-standard active substances and excipients used in medicinal products.

52. In 2008 the contamination of Heparin active substance sourced from China is considered to have been associated with a sudden increase in adverse events (including a significant number of deaths) reported in the United States of America. The Heparin had been contaminated with a substance called OSCS, which mimicked the effects of Heparin but was associated with an increased risk of serious allergic reactions. Baxter International recalled all stocks of the product in the US (some 23 batches at a reported cost of $19 million), and at the time of the recall it was estimated that Baxter supplied around half of the million plus multi-dose vials of Heparin product supplied to the US market each month (reported sales of $30 million in 2007). Three other companies also recalled batches from the US market, and the issue also affected medical devices used in cardiac bypass operations. As a result of the US FDA investigation ten other countries which had received contaminated Heparin active substance were identified, including Denmark, France, Germany, Italy and the Netherlands. Although a number of adverse events were reported in Germany, no problems were reported in the UK. The event led to a significant revision of the US and European pharmaceutical quality standards for Heparin. Costs associated with litigation against Baxter in the US (an estimated 770 filed lawsuits) were reported to be $62 million in 2010-2011. The first of the class action cases to be resolved in 2011 resulted in a reported award of $625,000 in compensatory damages to the plaintiffs.

53. The 2008 Heparin contamination incident particularly highlighted weaknesses in the transparency of the complete active substance supply chain, and adequate supply chain oversight by manufacturers.

54. Manufacture of active substances, excipients and finished medicinal product has become an increasingly global industry over the last 25 years. It is currently estimated that around 60% of UK authorised medicinal products use active substances sourced from outside the European Union, with China and India supplying the vast majority of those substances.

55. Issues relating to active substance quality have to date had no reported impact on UK markets and patients.

Why new intervention is theoretically justified

56. As already noted, the justification for government intervention is to overcome the information asymmetries that exist between patients and manufacturers of active substances. The EU's contention is that the level of protection against sub-standard medicines reaching patients is not currently optimal – in effect the EU believes that the social marginal costs are lower than the social marginal benefits and that further protection is justified.

Policy objectives of the Falsified Medicines Directive

57. We have reproduced below the objectives as stated in the EU impact assessment on the Falsified Medicines Directive.

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

Specific objectives

- *Ensuring that the medicinal product itself, as made available, is sufficiently protected against counterfeiting ("Specific objective n°1 – Strengthening product protection measures"): EU legislation regulates the characteristics of a medicinal product placed on the EU market. Specific objective n°1 aims to ensure that these products are sufficiently distinguishable from fake copies.*
- *Ensuring that the legal distribution channels of the medicinal product in the EU cannot be infiltrated by counterfeit products ("Specific objective n°2 –Ensuring reliability in the wholesale distribution"): … it is crucial to ensure that the distribution chain is not "infiltrated" by counterfeit products. These aspects of wholesale distribution are regulated at EU level.*
- *Adopting efficient and proportionate rules for transit of counterfeit medicinal products through the EU ("Specific objective n°3 – Defining clear obligations for import for export"): Clarification of the legal requirements for products imported for export is needed. Depending on the content of the clarification the substantial impact can differ.*
- *Ensuring that the* active substance *contained in the product is not counterfeit ("Specific objective n°4 – Stepping up scrutiny of* active substance *actors").*

Description of options considered (including do nothing)

Option 0. Status quo (or 'do nothing')

58. This option is to maintain the law as it stands, with no incremental costs or benefits incurred. For the sake of demonstrating the effects of the adoption of the Directive, we have chosen the current regulatory framework as the baseline against which we measure the costs and benefits of intervention.

59. The do-nothing option is not a realistic option because of the UK's obligation to adopt EU Directives into national law[9].

Option 1. Implement the Directive

60. The Directive contains several discrete interventions, affecting different parts of different sectors, as well as activities currently undertaken by the MHRA. For the sake of convenience, we have incorporated all these proposals into one option.

61. So, in effect, our single option contains several sub-options where the UK has the chance to maximise the net benefits of implementing the Directive. We have included summary cost and benefit information for each discrete intervention, so that each can be judged and justified on its own merits.

62. The following bullet points summarise the Directive's interventions.

- Increasing the controls relating to active substances and excipients, by requiring their importers and distributors to become registered and audited for their compliance with specific GDP. This is designed to prevent falsified active substances entering the manufacturing process.
- Increasing the controls on active substance manufacturers in the EU by requiring that all manufacturers are registered and compliant with specific GMP. This is designed to reduce the risk that poor quality active substances will be used in manufacturing processes.
- Requiring finished dosage form manufacturers to ensure that active substance standards have been met by active substance manufacturers, both in Europe and from active substances imported to Europe from the rest of the world. This measure is designed to reduce further the possibility that poor quality active substances enter manufacturing processes.
- Inclusion of safety features on certain medicines to ensure that the packs can be traced individually, and to ensure that they have not been tampered with. This will speed product recalls and aid the detection of counterfeit medicines. It will also give patients reassurance that their medicines are genuine. Note that this part of the Directive will be subject to further consultation on the safety features which will be around 2013/2014 once the safety feature has been decided. Consequently these measures have been excluded from this IA and will be the subject of a separate IA.
- Requiring brokers of medicinal products (those who find sellers and buyers of medicines, usually for a commission, but never take title to the goods) to register their activities with the MHRA, and be prepared to be audited on the systems for quality assurance and GDP that they have put in place. This will deter unscrupulous brokers from infiltrating the medicines supply chain with counterfeit medicines.
- Requiring holders of wholesale dealers licences to ensure that those they trade with hold the appropriate authorisations, and requiring by law that they report suspicious activity without delay to the national regulator. This intervention makes use of the honesty of the vast majority wholesalers to spot suspicious transactions and products, making it more likely that counterfeits will be detected earlier.
- Setting up European databases to record compliance to ease checking and compliance processes. This will facilitate the role of wholesalers and others in the supply chain in checking the authenticity of trading partners.
- Enhancing cooperation between the medicines regulators and customs authorities. This will extend the regulators' jurisdiction into free customs areas, to enhance governments' ability to intercept counterfeits that pass through the EU but do not necessarily enter it.
- Harmonising logos for online pharmacies in order to ensure that their authenticity can be verified. This will enable potential patients to check the credentials of online suppliers.

63. The deadline for implementation of this Directive is 2 January 2013. The RPC asked to justify that the proposed route of implementation of the Directive is the least costly one. We have copied out the Directive's words as closely as possible, and only made minor changes where incompatibility with existing UK legislation was evident, or where the use of the Directive wording might lead to confusion. We have sought the least burdensome options in transposing the Directive and have not gold-plated. No additional requirements beyond those required by the Directive are being introduced.

64. The RPC asked why the overall negative net impact of the proposal was not raised in the negotiation phase of the Directive. We initially worked on the basis of the Commission's Impact

Assessment. As discussed in the IA, an accurate assessment of the costs and, in particular, the benefits of this legislation to the UK is not straightforward and it was not until the final shape of the Directive was clearer and we started drafting our own IA that we gained a fuller understanding of the impact on UK businesses. The responses to the recent consultation on the transposition of the Directive and pro-active stakeholder engagement following this consultation have led to a more accurate assessment of the impact and significant amendment of this IA.

65. Regarding the new safety features, we are still at an early stage in the discussions with the Commission. A delegated act establishing the detailed rules for the safety features will not come into force until 2014. Until we know what the safety features will look like, we are unable to look at the impact on businesses. Safety features are therefore outside of the scope of this IA.

Monetised and non-monetised costs and benefits of each option

Common assumptions used in the analysis

66. We have used the standard ten year appraisal period and the HMT social discount rate of 3.5%.

67. MHRA Good Distribution Practice (GDP) and Good Manufacturing Practice (GMP) Inspectors have provided information on staff costs. For staff who (will) have direct responsible for ensuring good distribution practice firms that trade medicines, we have assumed that the annual salary cost is £30,000. Assuming further that non-salary costs add another 30%, that the working year is 215 days and that the working day is 7.5 hours, we estimate the staff cost per hour is approximately £24. A majority of public consultation respondents agreed with these assumptions and estimates.

Changes made in response to the RPC opinions, consultation responses and pro-active engagement with stakeholders by phone and email

68. We have amended large parts of this Impact Assessment as a result of consultation responses, pro-active stakeholder engagement and the RPC opinions. The changes are described in the text in the places where they have been made.

69. In its opinion on the final stage IA, the RPC wrote “The IA needs to provide evidence to support the costs and benefits or a clearer explanation as to how, despite the consultation, it has been unable to provide any evidence to assist in assessment”. In all the specific cases where the RPC opinion identified an apparent lack of rigour in our evidence gathering, we believe that our fault lay in not explaining sufficiently clearly the steps we had taken in gathering additional information and why we believe that extra effort would not have yielded a worthwhile improvement in the accuracy of our estimates. The rest of this section explains, in significantly more detail than appeared in the previous version of this IA, the steps we took to secure additional information.

70. In addition to the public consultation, the Agency contacted 51 firms directly by phone and/or by email to narrow estimates and strengthen the evidence base. Agency staff conducted in-depth research in the following sectors:

o **Exporters to third countries:** The responses to the public consultation did not provide sufficient extra detail on this sector. We therefore targeted specific companies to gain more information. In total we contacted 15 firms. This represents a quarter of the total number of firms that we subsequently discovered undertake this exporting activity. We conducted semi-structured telephone interviews with five of these firms, three of whom followed up with email correspondence. Of the remaining ten firms, seven did not reply to either email or phone, while three provided email responses. The information that we gained from these firms triangulated well and hence we felt that making additional efforts to gain more information would have been unproductive.

o **Life raft service stations:** A respondent to the public consultation identified that we had not taken into account the impacts on life raft service stations. In response, we sought expert advice and conducted a structured telephone interview with an MHRA GDP inspector who deals with life raft service stations. Furthermore, we contacted an experienced life raft service station operator and conducted a

telephone interview with its General Manager. Finally, we contacted a sales director at a medical supplies distributor by telephone to get estimates of the volume of medicines business conducted by life raft service stations. This allowed us to estimate the value of the fee concessions that firms operating below a certain level of medicines related turnover are eligible for. Given the absence of any previous experience of complying with Good Distribution Practice (GDP) in this sector, we concluded that asking firms for more information on likely compliance costs would prove unproductive. We have therefore relied on the knowledge of MHRA's GDP inspectors to gauge what individual firms will have to do in order to comply with GDP, and from this we estimated a plausible range of costs.

o **Medicines Brokers:** This sector has not been the subject of regulation before and hence MHRA has historically known very little about it, particularly regarding the number of brokers that operate in the UK. Unfortunately, the public consultation yielded only one broker-related response, which did not provide information on the number of firms. MHRA staff contacted medicines wholesalers to obtain estimates of the number of brokers that wholesalers deal with before and after consultation but had received responses that demonstrated no knowledge of the broker sector both times. As with life raft service stations, there has been no previous experience of complying with Good Distribution Practice (GDP) in the Medicines Broker sector. We have therefore relied on the knowledge of MHRA's GDP inspectors to gauge what firms will have to do in order to comply with GDP, and from this we estimated a plausible range of costs. Since we submitted the previous version of this final IA to the RPC, new evidence has emerged in the shape of applications from broker firms to hold licences. To date only five such applications have been received.

o **Number of active substance distributors:** Although the RPC opinion on the previous version of this final IA did not identify any specific problems with the section of the IA that dealt with active substance distributors, we followed the RPC Secretariat's advice and checked the entire IA for the robustness of our evidence and justification of our assumptions. In doing so, we decided to review the evidence supporting our assumption about the number of active substance distributors. Our investigations led us to revise the number down from 65 to 51. Our review process was as follows. We obtained more information about the sector and number of firms by initially contacting the two Active Substance Distributors that had replied to the public consultation. One of our industry contacts provided a list of 39 firms thought to distribute active substances. We sought confirmation of this list by conducting internet searches of all 39 companies. For 14 firms, information on their website confirmed that they were involved in active substance distribution. The remaining 25 firms either did not have a website or the information provided was insufficient to confirm their status and we thus contacted them by telephone. Out of the 25 contacted, 5 of them stated that they are not distributing active substances and were subsequently discarded from the list. Out of the other 20 firms, 14 confirmed that they distribute active substances and 6 did not answer repeated calls or promised to call back but failed to do so. MHRA staff also provided a list of 27 active substance distributors that have already applied for licenses. We cross-checked the two lists and eliminated the double-counted firms and were left with a total of 51 active substance distributors. The information gained from our evidence gathering gave what we considered to be a justifiable estimate and we felt that further pro-active stakeholder engagement would have been unproductive.

o **Responsibilities of active substance distributors:** While we were reviewing the section on active substance distributors, additional expert input highlighted that our previous assumption that the Directive requires these firms to employ a Responsible Person was incorrect. There is no requirement to employ anybody in this capacity. Removing these costs substantially decreased our estimated annualised costs for this sector from a midpoint of £2.1 million to £0.1 million.

Impacts on exporters to third countries

Current provisions

71. Currently exporters of medicinal products for human use, who export from the UK direct to companies in third countries, are exempt from the requirement to hold a wholesale dealer's licence.

72. In addition, persons who import medicines from a third country for re-export to a third country are also exempt from the requirement to hold a wholesale dealer's licence.

73. This means that procedures and premises are not subject any regulatory oversight or compliance with the EU guidelines on Good Distribution Practice.

What's wrong with the current approach?

74. The EU believes that the loose controls on exporters to third countries has contributed to the vulnerability of the EU medicines supply chain to counterfeit infiltration. Falsified medicines may find their way into exporters premises and have the potential to be diverted into the licensed supply chain either deliberately or due to the lack of due diligence The following are examples the cases where counterfeit medicines have passed through the UK supply chain from 3rd countries:

- **Lipitor 20mg - 2005.** Counterfeit Lipitor product, packaging and PIL intercepted for inspection by Dutch customs on route from Dubai to Canada. Action led to MHRA contacting UK wholesalers. Counterfeit packs discovered in UK supply chain and led to recall in the UK. The counterfeits reached UK patients.
- **Lipitor 40 mg 2005** - counterfeit Lipitor product, pack and PIL discovered at UK wholesaler during the course of an unannounced inspection. Counterfeits imported from Middle East, claimed to have arrived having not been ordered. Counterfeits did not reach patients.
- **Plavix, Jan 2007** - Counterfeit products, packs and PILS imported by German wholesaler from British Virgin Islands and Mauritius under Clinical trial exemption that allows 3rd country imports with no requirement for a licence. German company sold on to UK company and made ready for Clinical trial use but identified before used. Counterfeits did not reach patients.
- **Plavix, Zyprexa and Casodex, May 2007** - counterfeit product, packs and PILs were imported into Belgium before being sold on to the UK leading to reccalls. Counterfeits reached patients in the UK.
- **Enbrel - 2008**. Genuine Enbrel purchased from Turkey was sold via the UK and on to Germany in counterfeit packaging with a counterfeit PIL. The UK company imported from Turkey. The counterfeits reached patients in Germany.
- **Seretide 2009.** Genuine Seretide with counterfeit dispenser, packaging and PIL was purchased by a UK wholesaler from Pakistan via Belgium. The UK company imported from Pakistan via Belgium. The counterfeits are believed to have reached UK patients and were recalled by the MHRA.
- **Norvir - 2010.** Genuine Norvir in counterfeit packaging and with counterfeit PIL sold from SA to Germany via Switzerland to Antwerp to UK. The counterfeits reached patients in Germany.
- **Tarceva - 2010.** Genuine Tarceva purchased from India was sold into Germany via UK first and then Bulgaria in counterfeit packaging and PIL. The counterfeits reached patients in Germany.
- **Truvada/Viread - 2011**. Genuine Truvada and Viread purchased from Turkey was sold in counterfeit packaging and PIL via the UK to Denmark and the Cayman Islands. The counterfeits reached patients in Denmark and the Cayman islands.
- **Avastin 2011**. Counterfeit Avastin product in counterfeit packaging and PIL sold via UK to US. The counterfeit reached patients in the US. UK company purchased from Danish company that purchased from a Swiss company that purchased from Turkey via Egypt.

Changes brought in by the Directive

75. The existing wholesale dealing licensing regime is to be extended to this currently unregulated area. It will be applied to exporters of medicines regardless of whether the medicine is introduced from or simply exported to a third country. This regime fulfils current Directive requirements prior to the adoption of the Falsified Medicines Directive and includes existing and established national provisions to operate the licensing system.

76. The requirement to hold a Wholesale Dealer's Licence will affect three types of distributors which are currently unlicensed. Those that:

- do not see any goods at all who only respond to third country government tenders covering a year's supply of medicines for the particular country concerned. These are usually large tenders so the tendering company try to get the best deal for the supply of proprietary or patent drugs. If successful the winning supplier will arrange for delivery of the medicinal products to a bonded warehouse;
- actually receive the medicinal products and then repack the pallets for shipping in order to cut costs and

- import medicinal products from a third country for export back to a third country. There is no third country government contract. The supplier may arrange for the medicinal product to be made in a third country and will supply the art work which may imply that the medicinal product is sourced in the UK/EU giving the impression that it is made in the UK/EU. There is often a real, if unquantifiable, commercial advantage to products being presented as coming from the UK and EU, as it is assumed that such products have been assessed and approved by robust regulatory regimes.

77. Companies that operate in free zones in this way will also be subject to the need for an appropriate licence and compliance with good practices that go considerably beyond the parts of good practice that are designed to prevent falsified medicine infiltration (for instance – firms will be required to monitor the temperature of storage facilities).

78. These measures are intended to increase the due diligence among exporters to third countries and reduce the possibility that counterfeit medicines will enter free zones and regulated EU supply domestic chains. The inspection regimes that come with the measures should ensure compliance is maintained at a high level.

Who will be affected by the changes brought in by the Directive?

79. Any person that exports a medicine for human use to a non-EEA country, by way of wholesale dealing.

80. Any person that imports a medicine for human use from a non-EEA country to re-export it back to a non-EEA country by way of wholesale distribution (introduced medicines).

Costs

81. In our previous IA we assumed that 793 firms are exporting to third countries without a wholesale dealing license (WDL) and they would thus be affected by the new measures. This figure was based on a comparison of UK Borders Agency and MHRA databases but the methodology used was prone to substantial error. We were aware of the following deficiencies

- The data in the HMRC database were old and thus not particularly representative of the current position
- The database did not differentiate between individuals and businesses. This may have led to double-counting
- Companies selected themselves into their respective category which made the database vulnerable to coding errors.

82. The Agency therefore decided to engage with some of the affected firms directly to gain a better understanding of the market. As described in paragraph 70, we contacted fifteen firms, which is approximately a quarter of the companies in the sector. Out of the eight firms that provided a response, two were able to provide an estimate of the number of relevant exporters and the proportion that already holds wholesaler dealer licences. Both respondents have many years of experience in this sector and agreed that the number of firms in this sector is approximately 60. Furthermore, they confirmed each others' views that nearly all of these firms already possess a WDL (98% was suggested as the correct proportion). They cited the following reasons to support this opinion:

- exporting to 3rd countries only makes up part of these companies' activities and most of them engage in other trading activities that already requires wholesale dealer licences
- companies that export to third countries encounter fewer problems procuring pharmaceuticals from the supply chain inside the UK if they hold a WDL

83. Furthermore, in an email communication with MHRA, a Canadian medicines importer reported that all the UK medicines exporters it deals with already have wholesale dealer licences.

84. Since all companies holding WDLs already incur costs such as inspection fees, license variations fees and GDP related expenditures, the new measures brought in by the directive will not affect them.

Impact on wholesale dealers

Current legislation

85. Persons wholesale dealing medicines for use in the UK and to other EEA Member States must hold a wholesale dealer's licence. Holders of such a licence must comply with Good Distribution Practice guidance, keep certain records, notify specific authorisation holders and authorities of their intention to import products from the EEA and to only purchase medicines from and supply medicines to the regulated supply chain and exporters.

What's wrong with current approach?

86. As noted in the section on the "Problem of Counterfeits in the UK Supply Chain", shortline wholesalers were the UK entry points for all the known counterfeit cases in the last eight years. In six of these cases, lack of due diligence on the part of wholesalers was considered to have contributed to the problem. This suggests that some wholesalers are not complying with their current obligations.

Changes brought in by the Directive

87. Licensed wholesale dealer will now have to verify that the medicinal products received are not falsified. They must do this by checking a new safety feature which will appear on the outer packaging of the medicinal product. Those products with a safety feature will be:

- medicinal products that are subject to prescription and unless they are excluded or
- medicinal products which are not subject to prescription but are included because they are at risk of being falsified.

88. The verification will be in accordance with new requirements laid down in new EU delegated acts which have still to be adopted by the Commission. This is to be introduced because the characteristics and technical specifications of the unique identifier of the safety features will enable the authenticity of medicinal products to be verified and individual packs to be identified. Depending on the details of the delegated act, these requirements could generate considerable incremental costs for wholesalers. However, because the safety features options are still being discussed within the Commission, we feel unable to speculate what the costs might be. We have therefore decided to conduct a separate IA on this aspect of the Falsified Medicines Directive when more is known about the "safety features" delegated act.

89. The holder of a wholesale dealer's licence will also be required to comply with extended or new obligations to:

- keep certain records if they broker medicines. In practice, MHRA inspectors believe that UK wholesalers already do this in the vast majority of cases.
- maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities. MHRA inspectors believe that UK wholesalers already do this in the vase majority of cases.
- inform the MHRA, and where applicable the Marketing Authorisation holder, of medicinal products if they receive or are offered medicines which they identify as falsified or suspect to be falsified. This was identified as a weakness in several cases of falsified medicine infiltration into UK supply chains.
- check that their suppliers hold the appropriate licence or registration and comply with the appropriate Good Practice guidelines for their activities to supply medicines. MHRA inspectors believe that UK wholesalers already do this. However, the existence of the central register of suppliers should reduce costs to UK wholesalers.
- enclose a document that makes it possible to ascertain batch number of the medicinal products at least for products bearing the safety features when they supply the medicinal products to a person authorized or entitled to supply medicinal products to the public. This is a part of the "safety features" delegated act and hence will be assessed as part of the separate "safety features" IA.

Costs and benefits

90. *Informing MHRA of suspicious transactions and products*. A UK wholesaler provided us with an estimate of £15 to £20 for the cost of informing MHRA. Given that these events are, we believe from available evidence, extremely rare we estimate that the incremental cost of this provision is insignificant.

91. *Checking bona fides of suppliers*. As noted, we believe that the vast majority of UK wholesalers already diligently check the bona fides of suppliers. Currently wholesalers check the bona fides of their suppliers by securing a copy of their WDL. If the supplier is based in another Member State, a notarised translation of documents is obtained. The introduction of the EU central database of suppliers will remove the need to secure notarised translations of documents. Each notarised translation costs approximately £125. MHRA GDP inspectors believe that there are 100 UK firms that currently import from EEA suppliers, that each supplier has on average 20 suppliers and that the annual turnover of suppliers is 5%. Our assumptions yield annual cost savings of £12,500 (present value of £107,596).

92. Given that UK wholesalers are expected to experience no other changes to their activities as a result of the parts of the FMD that we are analysing in this IA, we do not expect there to be any incremental health benefits.

Life raft service stations

Current legislation

93. All commercial vessels and pleasure vessels over 13.7 metres under the UK flag, and International vessels operating under SOLAS ('Safety Of Life At Sea'), must have inflatable life-saving appliances serviced at an approved service station. In the UK life raft service stations such as the SOLAS stations replace SOLAS first aid kits as part of the servicing arrangement.

94. The first aid kits contain medicines for human use. They are supplied to the ships owner for use in the course of their shipping business. Under such circumstances the supply of the medicine by the SOLAS station to the ships owner is a wholesale supply activity. Under existing UK medicines legislation any person who supplies medicines by way of wholesale requires a wholesale dealer's licence unless an exemption exists.

What's wrong with current approach?

95. Currently SOLAS stations have been relying on UK medicines legislation which exempts persons exporting medicines for use outside the EEA by way of wholesale from the need to hold a wholesale dealer's licence. SOLAS stations contend that medicine in the first aid kits they supply will be used at sea and thus consider these medicines to have been exported. This is why they have not applied for WDLs before and why they have been unregulated in this respect. The MHRA, until the introduction of the Falsified Medicines Directive, was not sighted on this group of companies.

Changes brought in by the Directive

96. The Falsified Medicines Directive has brought to our attention and clarified the legal issues surrounding SOLAS stations. The directive eliminates all exemptions and requires that all firms engaging in medicines wholesaling to obtain a wholesale dealing license (WDL) and to follow Good Distribution Practice (GDP). This means that SOLAS stations will now need to obtain a WDL, comply with GDP guidance, keep certain records and only deal with persons in the regulated supply chain. Although it was not the Falsified Medicines Directive that introduced these requirements, the Directive did bring the issue to our attention and we have therefore included the impact on the SOLAS stations in this IA.

Costs and benefits

97. MHRA staff and consultation respondents have identified **24** 'Safety of Life at Sea' (SOLAS) stations which are expected to be impacted by the directive.

98. The affected SOLAS stations will now have to apply for a wholesale dealing licence (WDL). We have assumed that in the first instance that all new applicants will have to be inspected. The stakeholder

engagement described in paragraph 70 as indicated that approximately 80% of the SOLAS stations (i.e. 19 operators) are expected to be eligible for a license and inspection fee concession of 50%. The combined cost per eligible firm will then be £1,818 (£877 application fee plus £941 inspection fee). The 50% concession on a WDL is available to any company that generates less than £35,000 in revenue through the wholesale of medicines per year. The remaining 20% of the SOLAS stations will be charged the full application and inspection fee, totalling £3,636 per firm. We have assumed that the internal costs to each company of applying for a WDL is £48 (2 hours at the £24 per hour for a Responsible Person – see assumptions section) and £242 for hosting an inspection (10 hours at £24 per hour). Assuming that there is an annual 10% turnover of firms in this sector (and that the total number as well as the ratio of firms eligible for concessions remains constant), we estimate that the first year cost for applying for WDLs is £0.060 million and that the subsequent annual cost is £0.005 million (present value of £0.045 million)

99. The SOLAS stations will then be inspected regularly on a 3 to 4 year cycle. Using the same inspection cost assumptions above, we estimate that the annualised cost to UK firms will be £0.009 million (present value of £0.080 million).

100. Firms will also be charged for making certain mandatory changes to their licences. The fee for these "variations" is £250 if there is no need for an inspector to verify the changes, and £473 if there is such a need. MHRA GDP inspectors expect that only 10% of variations will need inspector time. From experience with existing wholesalers we expect that 5% to 10% of firms will need one variation a year. These cost estimates are of a very low magnitude and have therefore been excluded from the analysis.

101. The biggest incremental costs will come from the requirement to comply with and maintain GDP compliance. Estimating these costs is not straightforward, as compliance with GDP involves a number of diverse factors including:

- Developing and maintaining a quality system, including systems of internal audit;
- Ensuring that facilities are appropriate, controlled and secure;
- Staff are appropriately trained and have defined responsibilities;
- Written records are made, and maintained for minimum periods;
- Medicines are transported in appropriate and monitored conditions

102. GDP compliance costs. In the process of complying with GDP, each firm will need the services of a "Responsible Person" (RP). In the Consultation IA we have assumed that companies have the option to either contract an RP or assign the RP role to an existing member of staff. Following the pro-active stakeholder engagement described in paragraph 70, we discovered that SOLAS stations will generally assign the RP role to an existing staff member.

103. Stakeholder engagement with GDP inspectors and managers at life raft service stations has also shown that the newly designated RPs are expected to devote two hours to initial training in order to familiarise themselves with their duties. The cost estimates for these one off costs are of a very low magnitude and have therefore been excluded from the analysis.

104. GDP inspectors and the SOLAS managers consulted as part of our pro-active engagement efforts estimated the total time devoted to GDP compliance to be between 52 hours and 72 hours per year. Using these two estimates and the assumptions made above, this yields annual costs between £0.030 million and £0.042 million. Moreover, stakeholders contended that no costs would be incurred for the training of non-RP staff. This yields present value of staff costs between £0.260 million and £0.360 million.

105. The pro-active engagement with stakeholders described in paragraph 70 has also helped us estimate more accurately the time and effort spent on the setting up of a quality system and SOPs. GDP inspectors estimate that half of the SOLAS stations already have satisfactory SOPs and quality systems in place and that no additional costs are therefore incurred. For the remaining 12 stations, the RP is expected to spend between one and five working days on the initial setting up of the quality systems. Using the assumptions above this yields one-off costs between £0.002 million and £0.011 million.

106. Firms will also need to monitor the temperature of their facilities. This involves a one off cost for purchasing monitoring equipment of between £100 and £3,000 depending on the size of the facility (total

cost of between £0.002 million and £0.072 million) and periodic temperature mapping cost of between £200 and £3,000 every two years (annualised cost of between £0.002 million and £0.037 million).

Summary of cost

	PV	Annualised
Application for WDL	£ million	£ million
First year	0.060	0.007
Annual churn	0.045	0.005
Subsequent inspections	0.080	0.009
Variations		
Lower	0.003	0.000
Upper	0.006	0.001
Annual staff costs for complying with GDP		
Lower	0.260	0.030
Upper	0.360	0.042
Cost of establishing quality system / SOP		
Lower	0.002	0.000
Upper	0.011	0.001
Temperature control costs		
Transition cost		
Lower	0.002	0.000
Upper	0.072	0.008
Recurring costs		
Lower	0.021	0.002
Upper	0.315	0.037
TOTAL		
Lower	0.473	0.055
Upper	0.948	0.110

Benefits

107. Estimating the benefits of these measures is difficult. We have insufficient evidence to allow us to link the measures to a reduction in harm to the UK from counterfeit medicine infiltration. Unsurprisingly, given the complicated nature of the causality involved, the public consultation yielded no new information. However we can put the costs into context by estimating how much of our estimated total UK harm from counterfeits would have to be reduced before the benefits of these measures would justify their costs.

108. The new measures would have to reduce total UK annual harm from falsified medicines (harm estimate: £0.845 million) by approximately 10% to justify the costs for the 24 SOLAS stations (midpoint £0.083 million).

109. However we may have substantially underestimated the future societal harm from counterfeit medicines, especially if we have failed to take account of rare events that cause significant harm (such as large numbers of deaths). We have no information on the likelihood or severity of such events – there have been none in the UK in the past.

110. **Note that <u>none of the potential benefits counts towards the Expected Annual Net Cost to Business</u>**. This is because the benefits would be to patients in terms of reduced ill-health, to the government in terms of reduced investigation and prosecution costs, and to the private sector but only in terms of indirect benefits to pharmaceutical firms, mostly from having to deal with fewer product recalls.

<u>Active Substance Distribution</u>

Current approach

111. The distribution of active substances is currently indirectly regulated through obligations placed on authorized manufacturers of medicinal products. Such manufacturers are expected to have assessed their suppliers for compliance with the relevant GDP.

What is wrong with the current approach?

112. The EU believes that the risk of adulteration of active substances in the supply chain is unacceptably high.

113. Some of the evidence on active substance falsification is purely anecdotal. There does not seem to have been a careful examination of the problem. An October 2009 article in "Securing Pharma" (which appears to be pharma industry sponsored) claimed that 20 to 30% of active substances used in generic medicines are falsified, and attributed this figure to EU inspectors.

114. Between 2006 and 2007 Diethylene Glycol ("DEG") contamination of toothpaste and cough syrup led to hundreds of deaths in Panama. In July 2007 around 150 packs of counterfeit toothpaste containing DEG was found on sale at a car boot sale in Derbyshire. DEG has been identified both as a contaminant of Glycerine and as a falsified substance, where DEG has been mis-represented as Glycerine.

Changes brought in by the Directive

115. EU active substance importers and distributors will have to be registered with the Competent Authority of the Member State in which they are established (in the UK this would be the MHRA).

116. There will be a new formal requirement for compliance with Good Distribution Practice (GDP) particular to active substances

Costs

117. As outlined in paragraph 70, we have reviewed the evidence base for our estimates in this section and strengthened it further as a result. We therefore updated the previous estimate of 65 firms to 51 firms following internet research and pro-active engagement in the form of telephone conversations with roughly half of the firms in the sector. We also discovered that very few new firms enter and exit the sector and hence we abandoned our previous assumption of an annual churn of 10% and adopted 2%.(approximately one firm per year)

118. Each active substance distributor will have to register with the MHRA. The fee for registration will be £1,754 and we assume that each distributor will spend 2 hours at an average staff cost of £24 per hour (see assumptions section) in making the application. These assumptions yield a first year cost of £0.092 million and subsequent annual costs of £0.002 million. Active substance distributors will also be charged a fee for assessing the application. The fee will be £1,317 and if an inspection is needed (assumed to be 10% of assessments), an extra charge of £565 will be made. We have assumed that active substance distributors spend 10 hours hosting inspectors. These assumptions yield assessment costs in the first year of £0.071 million and subsequent annual costs of £0.007 million.

119. MHRA will assess on-going compliance with GDP by requiring active substance distributors to submit an annual compliance report. The fee for assessing the report will be £250. From information provided by MHRA inspectors, we have assumed that 10% of reports will trigger the need for inspection at an additional cost of £1,632 and that each of the relevant active substance distributors will spend 10 hours hosting the inspection. These assumptions yield annual costs of £0.025 million.

120. Firms will also be charged for making certain mandatory changes to their licences. The fee for these "variations" is £250 without the need for an inspector to verify the changes, and £473 with an inspector. MHRA GDP inspectors expect that only 10% of variations will need inspector time. We expect that 10% of firms will need one variation a year. These assumptions yield annual cost estimates of £0.014 million.

121. In the previous version of this final IA, we had included costs of employing Responsible Persons based on the assumption that this would be required. However, as part of our evidence base review that we undertook in response to the RPC's opinion, we realised that the text of the Directive does not require API distributors to employ an RP which was confirmed through further discussion with experts at MHRA. We have therefore removed these costs from our estimates.

122. Firms will also need to monitor the temperature of their facilities. This involves a one off cost for purchasing monitoring equipment of between £100 and £3,000 depending on the size of the facility (total cost of between £0.005 million and £0.153 million) and a periodic temperature mapping cost of between £200 and £3,000 every two years (annualised cost of between £0.005 million and £0.078 million).

Summary of cost

	PV £ million	Annualised £ million
Registration costs		
First year	0.092	0.011
Subsequent years	0.014	0.002
Assessment costs		
First year	0.071	0.008
Subsequent years	0.054	0.006
Variation costs	0.120	0.014
Complance reporting costs	0.213	0.025
Annual staff costs for complying with GDP		
Lower	0.000	0.000
Upper	0.000	0.000
Temperature control costs		
Transition cost		
Lower	0.005	0.001
Upper	0.153	0.018
Recurring costs		
Lower	0.045	0.005
Upper	0.670	0.078
TOTAL		
Lower	0.614	0.071
Upper	1.387	0.161

Benefits

123. Estimating the benefits of these measures is difficult. We have insufficient evidence to allow us to link the measures to a reduction in harm to the UK from counterfeit medicine infiltration. Unsurprisingly, given the complicated nature of the causality involved, the public consultation yielded no new information. However we can put the costs into context by estimating how much of our estimated total UK harm from counterfeits would have to be reduced before the benefits of these measures would justify their costs.

124. The new measures would have to reduce total UK annual harm from falsified medicines (harm estimate: £0.845 million) by approximately 14% to justify the costs to API distributors (midpoint £0.116 million).

125. However we may have substantially underestimated the future societal harm from counterfeit medicines, especially if we have failed to take account of rare events that cause significant harm (such as large numbers of deaths). We have no information on the likelihood or severity of such events – there have been none in the UK in the past.

126. **Note that <u>none of the potential benefits counts towards the Expected Annual Net Cost to Business</u>**. This is because the benefits would be to patients in terms of reduced ill-health, to the government in terms of reduced investigation and prosecution costs, and to the private sector but only in terms of indirect benefits to pharmaceutical firms, mostly from having to deal with fewer product recalls.

Brokers

Current approach.

127. Currently there are no legal obligations at all on brokers of medicinal products in UK medicines legislation.

What's wrong with the current approach?

128. As noted in the section on the "Problem of Counterfeits in the UK Supply Chain", brokers were involved inappropriately in 11 of the 13 of the known UK counterfeit cases. Regulatory oversight of this sector arguably could have prevented these cases.

Changes brought in by the Directive

129. Brokers who are involved in the sale or purchase of medicinal products without selling or purchasing those products themselves, and without owning and physically handling the medicinal products, will be brought into scope of EU regulations.

130. A broker who is resident in the UK will have to register with the MHRA. This registration will be recognised by other Member States. This will allow the broker to broker across the EEA. UK medicines legislation will also recognise registered brokers in other EEA Member States in the same way.

131. Brokers will only be able to broker medicines that are subject to authorisation in the UK and EEA. Brokering introduced products in the EEA will be prohibited. However, as far as we aware, no products are brokered in this way.

132. The MHRA will have an obligation to enter the minimum information on a publically accessible UK register following the determination of successful application for registration.

133. This publicly available UK register is needed to enable National Competent Authorities in other EEA Member States to establish the bona fides and compliance of brokers established in the UK where they are involved in the sale or purchase of medicines on their territories and the UK will investigate complaints of non-compliance. Reciprocal arrangements will apply for brokers established in other Member States involved in the sale or purchase of medicines to and from the UK.

134. UK brokers will be subject to inspection at their registered premises by the MHRA. This will be under a risk based inspection programme using a compliance report system requiring applicants for registration and registered brokers to provide information to the MHRA on or before a specified date.

135. The person responsible for management of the brokering activities will be required without delay to notify the MHRA of any changes to their compliance report that might affect compliance with the requirements of the legislation in respect of brokering.

136. Once registered, a broker will have to notify the MHRA of any changes to the details for registration without unnecessary delay. This notification will be subject to a variation procedure so that the broker can change the original details provided.

137. Brokers will also have to comply with certain good distribution requirements applicable to holders of a Wholesale Dealer's Licence as set out in the European frame work. Brokers will have to:

- have an emergency recall plan for the product that they have brokered.
- keep certain records of products brokered
- Make such records available for inspection, for a period of five years;
- comply with the principles and guidelines of good distribution practice for medicinal products as laid down in EU guidance.

- maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities;
- immediately inform the competent authority and, the authorisation holder, of medicinal products they are offered which they identify as falsified or suspect to be falsified.

138. In, addition to the provisions of the Directive, the MHRA will introduce national provisions that allow the new registration regime to be appropriately operated. A registered broker will therefore be subject to a procedure for:

- consideration of applications for registration
- de-registering a broker.
- compulsory variation of their registration, (Sites and Personnel)
- suspension of their registration and
- revocation of their registration
- an appeals procedure.
- submission of a compliance report as part of the risk based inspection programme

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139. These procedures will be similar in principle to those which exist for holders of wholesale Dealer's licences

Costs

140. As explained in greater detail in paragraph 70, exact information on the total number of UK medicines brokers is not available. Brokers have not been regulated before and the MHRA has very little information on this sector, particularly with regard to the number of firms. The public consultation yielded one broker-response and did not provide an estimate of the number of firms. After the consultation, we therefore made new attempts to estimate this number. MHRA staff had previously contacted medicines wholesalers to obtain estimates of the number of brokers wholesalers deal with but had received responses that demonstrated no knowledge of the broker sector. MHRA repeated this exercise post-consultation and again received the same respons e. Since we submitted the previous version of this final IA, MHRA has received licence applications from five medicines brokers in the UK. It seems unlikely that this is the total number of brokers in the UK but nevertheless indicates that the true number is low.

141. The consensus opinion within the Agency is that the overall number of brokers in the UK is likely to be in the low double digits. We have assumed that between 10 and 20 brokers are active in the UK.

142. We have no information with regard to the annual churn of broker companies. As noted in paragraph 70, we have made considerable efforts to discover more about the medicines broker sector but have consistently drawn a blank. We have assumed that there is a 10% churn each year and that the total number of firms stays the same. Given the small number of brokers that we believe operate in the UK, any assumption made on the rate of churn would not have a substantial effect on overall cost estimates.

143. Each UK broker will have to register with the MHRA. The fee for registration will be £1,754 and we assume that each broker will spend 2 hours at an average staff cost of £24 per hour (see assumptions section) in making the application. These assumptions yield a first year cost between £0.018 million and £0.036 million and subsequent annual costs between £0.002 million and £0.004 million. Brokers will also be charged a fee for assessing the application. The fee will be £1,317 and if an inspection is needed (assumed to be 10% of assessments), an extra charge of £565 will be made. We have assumed that brokers spend 10 hours hosting inspectors. These assumptions yield first year costs of between £0.014 million and £0.028 million and subsequent annual costs of between £0.001 million and £0.002 million.

144. MHRA will assess on-going compliance with GDP by requiring brokers to submit an annual compliance report. The fee for assessing the report will be £250. We have assumed that 10% of reports will trigger the need for inspection at an additional cost of £1,632 and that each of the relevant brokers will spend 10 hours hosting the inspection. These assumptions yield annual costs of between £0.004 and £0.008 million.

145. Firms will also be charged for making certain mandatory changes to their licences. The fee for these "variations" is £250 without the need for an inspector to verify the changes, and £473 with an inspector. MHRA GDP inspectors expect that only 10% of variations will need inspector time. We expect that 10% of firms will need one variation a year. These assumptions yield cost estimates of between of £0.002 and £0.005 million.

146. Brokers will also need to spend time throughout the year complying with good practice. However, because brokering does not involve physical handling of products, compliance will be a paper exercise. In the Consultation we have assumed that each broker will spend 80 hours a year complying with good practice, at an hourly cost of £24 (see assumptions section). Our assumptions yield annual costs between £0.019 million and £0.039 million.

Summary of costs

	PV	Annualised
Registration costs – First year	£ million	£ million
Lower	0.018	0.002
Upper	0.036	0.004
Registration costs – Subsequent years		
Lower	0.014	0.002
Upper	0.027	0.003
Assessment costs – First year		
Lower	0.014	0.002
Upper	0.028	0.003
Assessment costs – Subsequent years		
Lower	0.011	0.001
Upper	0.021	0.002
Compliance reporting costs		
Variation costs		
Lower	0.002	0.000
Upper	0.005	0.001
Lower	0.167	0.019
Upper	0.333	0.039
TOTAL		
Lower	0.259	0.030
Upper	0.517	0.060
Lower	0.033	0.004
Upper	0.067	0.008
Compliance costs		

Benefits

147. Estimating the benefits of these measures is difficult. We have insufficient evidence to allow us to link the measures to a reduction in harm to the UK from counterfeit medicine infiltration. Unsurprisingly, given the complicated nature of the causality involved, the public consultation yielded no new information. However we can put the costs into context by estimating how much of our estimated total UK harm from counterfeits would have to be reduced before the benefits of these measures would justify their costs.

148. The measures of the directive would have to reduce annual harm from falsified medicines (our best estimate £0.845 million) by approximately 5% in order benefits to justify their annual costs of £0.045 million (midpoint). We do not feel able to offer a view as to whether this level of reduction is plausible.

149. We may have substantially underestimated the future societal harm from counterfeit medicines, especially if we have failed to take account of rare events that cause significant harm (such as large numbers of deaths). We have no information on the likelihood or severity of such events – there have been none in the UK in the past.

150. **Note that none of the potential benefits counts towards the Expected Annual Net Cost to Business.** This is because the benefits would be to patients in terms of reduced ill-health, to the government in terms of reduced investigation and prosecution costs, and to the private sector but only in terms of indirect benefits to pharmaceutical firms, mostly from having to deal with fewer product recalls.

Distance selling

The current approach

151. All retail pharmacies operating in the UK must be registered with the General Pharmaceutical Council (GPhC). The GPhC operates a voluntary internet pharmacy logo scheme to identify legitimate online pharmacies so that the public can be sure they are purchasing safe and genuine medicines online.

152. The logo not only provides a visual means to help patients identify whether a website is connected to a registered pharmacy, but it also provides a direct link to the GPhC website. By clicking on the logo, visitors can verify the registration details of both the pharmacy and the pharmacist(s) behind the website.

153. General sales list medicines can be sold online without any specific medicines regulatory controls.

What's wrong with the current approach?

154. The GPhC registration and logo is common to the UK. It does not apply to registered pharmacies in other parts of the EU.

Changes brought in by the Directive

155. All persons offering medicinal products at distance should be registered and display a common logo recognised throughout the UK and EEA.

156. The common logo will be recognisable throughout the Union not just the UK, and allow for the identification of the Member State where the person offering medicinal products for sale at a distance is established. This logo will have to be clearly displayed on the websites of persons in the UK who can legally offer medicinal products for sale at a distance to the public.

157. New measures will require that any person offering a medicinal product to the public at a distance will not only have to be entitled to supply medicinal product but will also be required to notify to register their premises with appropriate authority.

158. The medicines that are supplied by way of distance selling will be restricted to those that are authorised under the current regulatory framework for medicines, it will not be possible for a registered premises to offer unlicensed medicines online.

159. The measures for the common logo for the internet are to be implemented 1 year after the date of publication of the implementing acts.

160. In, addition to the provisions of the Directive, national provisions will be introduced that allow the new registration regime to be appropriately operated. A registered person selling at a distance will therefore be subject to a procedure for:

- consideration of applications for registration
- de-registration.
- compulsory variation of their registration
- suspension of their registration
- revocation of their registration
- an appeals procedure

These procedures will reflect similar principles as to those which exist within an established licensing regime for medicines for human use.

161. The person selling medicines at a distance will be required, if they suspect that they are handling a counterfeit medicine, to notify the authorisation holder of the products and the MHRA.

162. The notified authority will also be required to set up a website providing at least the following:

- information on the national legislation applicable to the offering of medicinal products for sale at a distance to the public by means of information society services, including information on the fact that there may be differences between Member States regarding classification of medicinal products and the conditions for their supply;
- information on the purpose of the common logo;
- the list of persons offering the medicinal products for sale at a distance to the public by means of information society services as well as their website addresses;
- background information on the risks related to medicinal products supplied illegally to the public by means of information society services.

163. Under these new requirements the European Medicines Agency (EMA) is to coordinate the information and will be required to set up a website providing information on the purpose of the common logo background information on the risks related to medicinal products supplied illegally to the public by means of information society services, information on the Union legislation applicable to falsified medicinal products as well as hyperlinks to the authority's' websites. The EMA's website will explicitly mention that the authority's websites contain information on persons authorised or entitled to supply medicinal products at a distance to the public by means of information society services in the Member State concerned. The authority's website will contain a hyperlink to the EMA's website.

Costs and benefits

164. In the public consultation three respondents commented on the expected cost of changing the logo. The costs were estimated to be one-off and to range between £100 and £500 per website. As a result of the relatively small and one-off cost estimates we concluded that seeking further information would have been disproportionate.

165. In order to assess the UK-wide impact however, we require the number of pharmacies that would be affected by the Directive, i.e. the ones that offer distance selling over the internet. The number of participants in the voluntary internet pharmacy logo scheme run by the GPhC provides a rough estimate of the amount of distance-selling pharmacies. However, since pharmacies are not required to participate in the scheme, it is possible that we have missed out some firms in our calculations.

166. According to the GPhC, there are currently 326 pharmacies that operate 347 pharmacy websites displaying the GPhC internet pharmacy logo. We therefore assume that 347 pharmacy website will need to adapt their websites in response to the directive, amounting to one-off costs per website between £100 and £500. This yields costs between £0.035 million and £0.174 million.

167. The aim of the scheme is to promote and improve public awareness of the risks associated with purchasing medicines online, in a coherent manner across all Member States. Since the UK already has

a comparable voluntary scheme in place for pharmacy practice, so we do not expect there to be significant economic benefits to UK consumers.

Manufacturers of medicinal products, Active Substances and Excipients

Current approach

168. In the EU the responsibility for assuring the quality of active substances and excipients rests with the authorised product manufacturer. These manufacturers must comply with the EU GMP guidelines which provide the minimum standards to which an authorised manufacturer is expected to operate. Manufacturers have certain obligations under EU GMP in setting appropriate specifications for the materials they use, and assessing their suppliers for compliance with the relevant standards.

169. In addition, applications for Marketing Authorisation and variations to change the source of the active substances used as starting materials have had to be supported by a declaration of GMP Compliance of the active substance manufacturer by a Qualified Person (QP) of the dosage form manufacturer.

170. It is already an offence for anyone to supply an active substance which has not been manufactured in accordance with EU GMP, where that substance is intended for use in the manufacture of an authorised medicine for human use.

What's wrong with the current approach?

171. The EU asserts that the current provisions do not provide adequate assurance that substandard active substances and excipients will not enter the manufacturing processes of finished medicinal products. An example of this was the case of Heparin contamination that occurred in the US and Europe in 2008 (see the section on "The problem of sub-standard active substances and excipients")

Changes brought in by the Directive

Manufacturers of finished medicinal products

172. Current arrangements will be formalised for manufacturers of the finished medicinal products to audit their suppliers of active substances for compliance with the relevant GMP, and to provide a solid legal basis for the written confirmation of audit (the "QP Declaration", currently required as part of the Marketing Authorisation application).

173. Manufacturers of finished medicinal products will have to verify that their suppliers of active substances are registered in accordance with the new requirement for manufacturers, importers and distributors of active substances. Registrations will be entered onto a database operated by the European Medicines Agency.

174. Manufacturers of finished medicinal products will be required to assess the risk to product quality presented by any excipients they use, by way of a formalised documented risk assessment, and ascertain the appropriate good manufacturing practices necessary to assure the safety and quality of the excipients used. This will not place an explicit obligation on the medicinal product manufacturer to audit their suppliers of excipients, but it will require the manufacturer to assure themselves that the appropriate good manufacturing practices are being applied.

Manufacturers of active substances and excipients

175. EU active substance manufacturers will have to be registered with the Competent Authority of the Member State in which they are established (in the UK this would be the MHRA). An applicant for registration may be inspected on a risk-assessed basis.

176. Registered businesses will be required to submit an annual statement of changes to the MHRA, unless those changes could present a risk to active substance quality or safety in which case they

should be notified immediately. It is likely that factors considered to be high risk will be covered in guidance rather than legislation.

177. In addition to the provisions of the Directive, national provisions will be introduced that allow the new registration regime to be appropriately operated. A registered regime will therefore be subject to a procedure for:

- consideration of applications for registration
- de-registration.
- compulsory variation of their registration
- suspension of their registration
- revocation of their registration
- an appeals procedure.

These procedures will reflect similar principles as to those which exist within an established licensing regime for medicines for human use.

178. Countries exporting an active substance to the EEA can apply to the European Commission for an assessment of their regulatory controls for active substance manufacture, and if successful in the assessment procedure the country will be named on a list held by the Commission. Active substances from a country on this list are not required to be accompanied by a written confirmation that such substances have been manufactured to the relevant European standards of good manufacturing practice.

179. The Commission is consulting on the Implementing Act to ensure a consistent EU-wide approach, and has published a concept paper for public comment.

Costs

180. We do not expect manufacturers of finished medicinal products to incur greater costs as a result of the new measures. Firms already audit their active substance suppliers, and MHRA inspectors find that these audits are generally adequate.

181. Manufacturers of active substances will incur incremental costs. The markets for active substances are international and are split into two types – those supplying active substances to originator pharmaceutical firms that hold patents for their drugs, and those supplying generic drug manufacturers. The latter are highly competitive and we would expect that regulatory cost increases would to some extent be passed on to the generic manufacturers, who also operate in highly competitive markets and would therefore pass at least some of the costs on to buyers, depending on the elasticity of demand for the finished generic product. Active substance suppliers to patented medicine manufacturers may or may not be able to pass on their costs depending on the terms of their contracts with their buyers. The manufacturers of patented products are not able to pass on their costs to the NHS because pricing of their products is determined exclusively by the health value that the drugs deliver (through the guidance of the National Institute for Health and Clinical Excellence) rather than through firms' costs.

182. In the Consultation IA, we assumed that there are 1550 active substance manufacturers in the EU of which 450 are in the UK[10]. More recent MHRA figures show that there were 1416 active substance manufacturers in the EU and of which 411 are UK-based. We have therefore updated our estimates and adopted the newer, slightly lower figures.

183. We have adopted two extreme sets of assumptions to generate a range of incremental costs that the UK will bear.

184. At one extreme we have assumed (Assumption X) that these manufacturers are not able to pass their incremental costs onto their buyers. We also assume that the 411 active substance manufacturers in the UK are 100% UK owned[11]. These assumptions mean that the impact of incremental costs in the UK remains in the UK. It also means that incremental costs incurred by foreign located and owned firms are not borne by buyers in the UK.

185. At the other extreme, we have assumed (Assumption Y) that all costs incurred by UK and other EU active substance manufacturers are ultimately passed on in full to buyers of finished medicinal products. We have further assumed that the UK will bear costs in proportion to its share of OECD total expenditure on pharmaceuticals. This is consistent with firms seeking to recover their incremental costs by spreading them across all their affluent country buyers. In recent years the UK's proportion of OECD expenditure has been about 3.4%[12].

186. The turnover of firms in this sector is very small and so we have assumed a zero annual rate. We have also assumed that that all EU active substance manufacturers bear the same costs, which we have assumed are equivalent to the incremental costs imposed in the UK.

187. Each UK active substance manufacturer will have to register with the MHRA. The fee for registration will be £3,057 and we assume that each firm will spend 10 hours at an average staff cost of £24 per hour (see assumptions section) in making the application. Active substance manufacturers will also be charged a fee for assessing the application. The fee will be £1,812 and we have assumed that 70% of firms will need to be inspected. The length of inspection is expected to be on average three days. The fee for the first day will be £771 and subsequent days will cost £2,583. We have assumed that each active substance manufacturer spends 60 hours hosting inspectors. Under Assumption X, our estimated UK first year cost is £4.226 million. Under Assumption Y, the first year UK cost is £0.501 million.

188. MHRA will assess on-going compliance with GMP by requiring manufacturers to submit an annual compliance report. The fee for assessing the report will be £250. We have assumed that 70% of reports will trigger the need for inspection at an additional cost of £2.333 for the first day and £2,583 for two subsequent days. Each relevant manufacturer is expected to spend 60 hours hosting the inspection. Under Assumption X, the UK bears annual costs of £2.454 million. Under Assumption Y, the UK bears annual costs of £0.291 million.

189. Firms will also be charged for making certain mandatory changes to their licences. However, we expect such changes to be very rare and we have not estimated the cost.

Summary of cost

	PV	Annualised
Application for registration	£ million	£ million
Lower (Assumption Y)	0.501	0.058
Upper (Assumption X)	4.226	0.491
Assessment of annual compliance		
Lower (Assumption Y)	2.503	0.291
Upper (Assumption X)	21.127	2.454
TOTAL		
Lower (Assumption Y)	3.003	0.349
Upper (Assumption X)	25.354	2.945

Benefits

190. We have no evidence that sub-standard active substances have created harm in the UK in recent years. Benefits from these measures could theoretically be derived from possibility that active substance GMP is improved throughout the world by the measures introduced by the Directive. This could prevent future incidents of sub-standard active substance being used to manufacture drugs that enter the UK supply chain and possibly reach patients. We feel unable to speculate on how likely this is or how harmful such events could be.

191. **Note that <u>none of the potential benefits would count towards the Expected Annual Net Cost to Business</u>**. This is because the benefits would be to patients in terms of reduced ill-health, to

the government in terms of reduced investigation and legal costs, and to the private sector but only in terms of indirect benefits to pharmaceutical firms, mostly from having to deal with fewer product recalls.

Summary of Costs and Benefits

	PV	Annualised
Wholesaler		
Cost saving - notarised translation	0.108	0.013
Wholesale Maritime Business		
Application for WDL		
First year	-0.060	-0.007
Annual churn	-0.045	-0.005
Subsequent inspections	-0.080	-0.009
Variations		
Lower	-0.003	0.000
Upper	-0.006	-0.001
Annual staff costs for complying with GDP		
Lower	-0.260	-0.030
Upper	-0.360	-0.042
Cost of establishing quality system / SOP		
Lower	-0.002	0.000
Upper	-0.011	-0.001
Temperature control costs		
Transition cost		
Lower	-0.002	0.000
Upper	-0.072	-0.008
Recurring costs		
Lower	-0.021	-0.002
Upper	-0.315	-0.037
Sub-total		
Lower	*-0.473*	*-0.055*
Upper	*-0.948*	*-0.110*
Distance Selling		
Lower	-0.035	-0.004
Upper	-0.174	-0.020
API distribution		
Registration costs		
First year	-0.092	-0.011
Subsequent years	-0.014	-0.002
Assessment costs		
First year	-0.071	-0.008
Subsequent years	-0.054	-0.006
Variation costs	-0.120	-0.014
Compliance reporting costs	-0.213	-0.025
Annual staff costs for complying with GDP		
Lower	0.000	0.000
Upper	0.000	0.000
Temperature control costs		
Transition cost		
Lower	-0.005	-0.001
Upper	-0.153	-0.018
Recurring costs		
Lower	-0.045	-0.005
Upper	-0.670	-0.078
Sub total		
Lower	*-0.614*	*-0.071*
Upper	*-1.387*	*-0.161*
Brokers		
Registration costs		
First year		
Lower	-0.018	-0.002
Upper	-0.036	-0.004
Subsequent years		
Lower	-0.014	-0.002
Upper	-0.027	-0.003
Assessment costs		
First year		
Lower	-0.014	-0.002
Upper	-0.028	-0.003
Subsequent years		
Lower	-0.011	-0.001
Upper	-0.021	-0.002
Compliance reporting costs		
Lower	-0.033	-0.004
Upper	-0.067	-0.008
Variation costs		

Lower	-0.002	0.000
Upper	-0.005	-0.001
Compliance costs		
Lower	-0.167	-0.019
Upper	-0.333	-0.039
Sub-total		
Lower	*-0.259*	*-0.030*
Upper	*-0.517*	*-0.060*
API GMP		
Application for registration		
Lower	-0.501	-0.058
Upper	-4.226	-0.491
Assessment of annual compliance		
Lower	-2.503	-0.291
Upper	-21.127	-2.454
Sub total		
Lower	*-3.003*	*-0.349*
Upper	*-25.354*	*-2.945*
NET TOTAL	PV	Annualised
One-off cost		
Lower	-0.800	-0.093
Upper	-4.922	-0.572
Recurring cost		
Lower	-3.476	-0.404
Upper	-23.350	-2.713
TOTAL		
Lower	-4.276	-0.497
Upper	-28.272	-3.284

192. The table above does not include the benefits that the Directive might have on reducing the UK harm done by counterfeits that pass through the regulated EU supply chain. Our best estimate of annual UK harm done by counterfeits is £0.845 million. This may be an under-estimate, especially if we have failed to take account of rare events that cause significant harm (such as large numbers of deaths). However, we have no information on the likelihood or severity of such events.

193. There is an apparent gap between our estimate of the Directive's total annualised costs to the UK (£0.497 million to £3.284 million, midpoint £1.891 million) and our estimate of the maximum annual benefit that the UK could gain (£0.845 million). To put this gap into context, we can estimate the number of UK deaths that the Directive would have to prevent in order for the benefits to justify the costs. A reasonable estimate of the value of preventing a death is £1.8 million[13]. Assuming that the Directive will prevent all of our estimated UK harm, then, on top of that, the Directive would also have to prevent less than one additional death every year in order for the Directive's UK benefits to justify its UK costs. We do not feel able to offer any opinion on the likelihood of this happening.

Proportionality, risks and assumptions

194. There remain several gaps in our knowledge of the Directive's costs and benefits. Although we have made an estimate of the total annual UK harm that counterfeit medicines do, this estimate may not cover the full harm, especially if it is reasonable to expect rare but high impact events of the type that the UK has not seen to date. In the summary of costs and benefits section, we have exemplified how serious such events would have to be in order for the UK benefits of the Directive to justify its UK costs.

195. We do not know how effective the Directive will be at preventing the harm that is done by counterfeits. We are unable to fill this gap in our knowledge.

196. Uncertainty in our cost estimates is catered for by presenting ranges. Despite our pro-active stakeholder engagement and consultation replies, we do not have enough information to estimate costs for third country manufacturers of active substances. It remains unclear to what extent these costs might be passed on to buyers in the UK.

197. The assumptions that have the greatest impact on estimates relate to the costs of complying with good practice. We have calculated a range (annualised at between £0.353 million and £2.683 million) to account for our uncertainty.

Direct costs and benefits to business calculations (following OIOO methodology)

198. The expected annual benefit to private UK interests is £0.013 million. The expected net annual cost to private UK interests is estimated at between £0.497 million and £3.284 million (midpoint £1.891 million).

Alternatives to regulation

199. In transposing this Directive we have kept in mind the need to consider alternatives to regulation. In this highly regulated area many of the benefits for industry derive from consistency of rules across the EU and much effort is made by Member States to ensure harmonisation in implementation. In these debates the UK always promotes adoption of the least burdensome approach. Where we have some flexibility and it will not disadvantage UK industry we make strenuous efforts to find alternatives to a regulatory solution.

Wider impacts

Small firms impact test

We believe that between 500 and 650 small firms will bear increment costs as a result of the changes that we have analysed in this IA. Less than 100 small medicines wholesaling firms will enjoy small cost savings from no longer having to procure notarised translations of foreign wholesale dealers licenses. The estimated annual cost saving per firm is £125.

200. We believe that *all of the 24 affected life-raft service stations* are small or micro businesses. The ones that generate below £35,000 from medicines sales will be eligible for a Wholesale Dealer License concession and face combined one-off costs of £1,818 for obtaining a WDL and hosting the first inspection of their premises. Each of these firms is also expected to incur labour costs from filling out the application form (2 hours) and hosting inspections (10 hours) at £24 per hour. Furthermore, firms are expected to host follow-up inspections every 3-4 years, incurring a (reduced) fee of £941 per inspection and labour costs for hosting it (10 hours at £24). Some life raft service stations are also expected to spend time on establishing a quality system in accordance with GDP which is expected to incur between £181 and £907 in one-off costs. Each firm is also expected to incur costs from compliance with good distribution practice between £1,258 and £1,741 per year. The stations will also incur one-off costs between £100 and £3,000 (depending on the size of the facility) to monitor the temperature of their facilities. They will also have to spend between £200 and £3,000 on temperature mapping every two

years. Finally, firms may also have to amend their licenses which would incur a 'license variation fee' between £250 and £473.
We have **estimated the range of first year costs for a life raft service station to be between £7,757 and £3,466**.
We have also **estimated the range of annual costs for a life raft service station to be between £6,397 and £1,258.**

201. *Active Substance Distributors* are also impacted by the Directive and during our pro-active stakeholder engagement, four distributors offered estimates of the proportion of small and micro firms in their sector. The estimates ranged between 60% and 84% and we thus expect between 31 and 43 out of the total 51 firms to be small or micro in size. Every firm will have to pay a one-off registration and assessment of application fee totalling £3,071 and some will also face an inspection of their premises costing £565. Each firm is also expected to incur labour costs from filling out the registration form (2 hours) and hosting inspections (10 hours) at £24 per hour. Every distributor will also be required to submit an annual compliance report which comes with a £250 assessment fee. This compliance report may also trigger an inspection of the distributors premises which would cost £1,632. Every Active Substance Distributor will also incur one-off costs between £100 and £3,000 depending on the size of the facility to monitor the temperature of their facilities. They will also have to spend between £200 and £3,000 on temperature mapping every two years. Finally, firms may also have to amend their licenses which would incur a 'license variation fee' between £250 and £473.
We have **estimated the range of first year costs for a small Active substance distributor to be between £6,926 and £3,219.**
Furthermore, we have **estimated the range of annual costs for a small Active substance distributor to be between £5,645 and £498.**

202. *We also expect that all medicines brokers* are small and micro businesses. Each broker will face a one-off registration and application assessment fee with the MHRA, totalling £3,071. Some brokers may also be required to host an inspection of their premises which incurs fees of £565. Each firm is also expected to incur labour costs from filling out the registration form (2 hours) and hosting inspections (10 hours) at £24 per hour. Each broker will also be required to submit an annual compliance report which comes with a £250 assessment fee and may trigger an inspection of the broker's premises. This inspection would incur £1,632 in fees and 10 hours of staff time (at £24 per hour) hosting the inspection. Every broker will also need to comply with GDP and is expected to devote 80 hours (at £24 per hour) annually to this activity. Finally, firms may also have to amend their registration which would incur a 'registration variation fee' between £250 and £473.
We have **estimated the range of first year costs for a Broker to be between £5,861 and £5,054.**
We have also **estimated the range of annual costs for a Broker to be between £4,532 and £2,185.**

203. *Pharmacies selling at a distance* are also impacted by the directive. We have received data from the National Pharmacy Association (NPA) which helped us in our estimates of the number of affected small firms. The NPA provided information on the size of all their members' firms based on the number of pharmacy outlets they run and data shows that 78% of their members only have one pharmacy outlet. Although no specific reference is made by the NPA to distance selling pharmacies supplying medicines online, we adopted this proportion as the upper limit for our purpose and of small and micro-sized distance selling pharmacies. We thus estimate there to be at most 254 small and micro pharmacies (78% of the 326). As mentioned we believe that this is the upper estimate because since we would expect small firms to be under-represented in the distance-selling market due to greater resource constraints than their larger competitors. We felt that it would have been disproportionate, given the overall low costs, to investigate the number further. Every pharmacy supplying medicines will incur one-off costs between £100 and £500 to change the logo on their website.

204. We expect approximately *315 manufacturers of active substances* to be small and micro enterprises. As this sector had not been previously regulated, the MHRA has very little knowledge about the composition of it. MHRA inspectors and other expert staff were consulted but have been unable to provide estimates of the proportion of small and micro businesses in the sector. Subsequently we contacted 9 manufacturers of active substances but no company was able to offer an estimate of the proportion. We subsequently consulted the *BIS SME Statistics for the UK and Regions 2009* dataset and used the proportions in category 244 (*Manufacture of pharmaceuticals, medicinal chemicals and*

botanical products). According to the dataset, 76.6% of all companies in that category are classified as small and micro sized. Applying this proportion to our estimate of UK-based active substance manufacturers yields 315 small or micro enterprises. Each manufacturer will need to register with the MHRA which incurs one-off fee costs of £3,057. The firm also faces one-off costs for the assessment of their initial application (£1,812) and may be required to host an inspection which incurs a £771 fee for the first day of inspection and £2,583 for any further day. Each firm is also expected to incur labour costs from filling out the registration form (10 hours) and hosting inspections (60 hours) at £24 per hour. Moreover, each active substance manufacturer will need to file an annual GMP compliance report with a fee of £250. Some reports may trigger an inspection for which the company will have to pay a fee of £2,333 for the first day and £2,583 for any subsequent day. If the company were to host an inspection, we estimated that ca 60 hours of staff time would need to be devoted, incurring staff costs of £1,440. We have **estimated the range of first year costs for a small manufacturer of active substances to be between £12,499 and £5,111.**
We have also **estimated the range of annual costs for a small manufacturer of active substances to be between £9,442 and £492.**

It is reasonable to expect that some small firms may leave their sectors.

Competition assessments

Wholesale sector.

205. Medicines wholesaling provides distribution services that fill the gap between pharmaceutical manufacturers and pharmacies. Efficient distribution services are necessary to ensure that patients receive medicines with minimal delay.

206. Medicines wholesalers compete for business on the basis of scope of medicines, price and delivery terms. There are approximately 1,750 wholesalers operating in the UK[14]. Of these, only 11 supply close to the full scope of licensed medicines (approximately 12,000 lines). Three of these so-called "full-line" wholesalers operate on a national basis, while the other 8 operate regionally[15]. Full-line wholesalers had 71% of the market share in 2005[16] and compete for pharmacy business on the basis of reliability of supply, frequency of delivery and price discounts.

207. "Short-line" wholesalers (the vast majority of the 1,750 total) are much smaller. Having a much smaller scope of medicines allows short-line wholesalers to keep their costs low. They compete largely on price and generally do not offer the same reliability and frequency of delivery as full-line wholesalers. Short-line wholesalers had approximately 13% of market share in 2005[17].

208. The geographical scope of medicines wholesaling markets is constrained by the costs of distribution and therefore we assume that these markets are regional in nature.

209. Answers to the standard OFT competition assessment questions:

Q. Would the proposal directly limit the number or range of suppliers?

A. No. The proposal does not alter the amount of business available to suppliers or groups of suppliers

Q. Would the proposal indirectly limit the number or range of suppliers?

A. No

Q. Would the proposal limit the ability of suppliers to compete?

A. No.

Q. Would the proposal reduce suppliers' incentives to compete vigorously?

A. No.

Exporters to third countries

210. Firms in this sector form part of the global distribution network of medicines. By definition, their markets are not in the EU, and the distribution services that these firms provide are for overseas customers. From what we can gather, this sector experiences considerable competition.

211. Answers to the standard OFT competition assessment questions:

Q. Would the proposal directly limit the number or range of suppliers?

A. No. The Directive does not alter the amount of business available to suppliers or groups of suppliers

Q. Would the proposal indirectly limit the number or range of suppliers?

A. Yes. The Directive will increase the costs of smaller companies disproportionately. Also, firms in non-EU countries will not bear the same GDP costs as their EU counterparts

Q. Would the proposal limit the ability of suppliers to compete?

A. No.

Q. Would the proposal reduce suppliers' incentives to compete vigorously?

A. No.

Active Substance distributors

212. These firms provide distribution services for active substance manufacturers. Their markets are international, and, from what we can gather, competition between firms is strong.

Q. Would the proposal directly limit the number or range of suppliers?

A. No. The Directive does not alter the amount of business available to suppliers or groups of suppliers

Q. Would the proposal indirectly limit the number or range of suppliers?

A. Yes. The Directive will increase the costs of smaller companies disproportionately. Also, firms in non-EU countries will not bear the same GDP costs as their EU counterparts

Q. Would the proposal limit the ability of suppliers to compete?

A. No.

Q. Would the proposal reduce suppliers' incentives to compete vigorously?

A. No.

Brokers

213. These firms provide brokering services between medicines wholesalers, particularly internationally. We do not know the state of competition in this sector.

Q. Would the proposal directly limit the number or range of suppliers?

A. No. The Directive does not alter the amount of business available to suppliers or groups of suppliers

Q. Would the proposal indirectly limit the number or range of suppliers?

A. Yes. The Directive will increase the costs of smaller companies disproportionately. Also, firms in non-EU countries will not bear the same GDP costs as their EU counterparts

Q. Would the proposal limit the ability of suppliers to compete?

A. No.

Q. Would the proposal reduce suppliers' incentives to compete vigorously?

A. No.

Pharmacies involved in distance selling

214. Pharmacy companies that offer distance selling are usually associated with major pharmacy chains. They compete for business with high street chemists on the basis of convenience. The scope of their markets is national.

Q. Would the proposal directly limit the number or range of suppliers?

A. No. The Directive does not alter the amount of business available to suppliers or groups of suppliers

Q. Would the proposal indirectly limit the number or range of suppliers?

A. No

Q. Would the proposal limit the ability of suppliers to compete?

A. No.

Q. Would the proposal reduce suppliers' incentives to compete vigorously?

A. No.

Active substance manufacturers

215. The scope of these markets is international, and competition between firms is strong, and is based on quality and price.

Q. Would the proposal directly limit the number or range of suppliers?

A. No. The Directive does not alter the amount of business available to suppliers or groups of suppliers

Q. Would the proposal indirectly limit the number or range of suppliers?

A. No. Although the Directive will impose additional registration and inspection costs on EU active substance manufacturers relative to their international competitors, we believe that these costs are not significant enough to affect competition. We think it unlikely that EU firms will incur significantly greater GMP costs as a result of the Directive.

Q. Would the proposal limit the ability of suppliers to compete?

A. No.

Q. Would the proposal reduce suppliers' incentives to compete vigorously?

A. No.

Justice Impact Test

216. The transposition of the Falsified Medicines Directive is likely to introduce some new offences relating to the various activities mandated by the Directive. The Ministry of Justice has been informed about this and is currently looking at the offences and is expected to clear the offences by the end of January 2012. We have been in contact with them and we do not foresee any difficulties introducing the offences.

Health impact test

217. As outlined in previous discussions, we cannot define an adequate link between these specific GDP and GMP changes and reductions in harm. We have estimated that the harm to health from counterfeits is on average 21 lost QALYs per year. We have not been able to link the Directive evidentially with a reduction in this harm. For this reason, the public health benefits of the proposals have been considered 'not important' using the criteria of the Department for Health's health impact assessment.

Equality assessment

218. The measures that are introduced by this Directive are directed mainly to certain persons working in the area of medicines - wholesale dealers, manufacturers and pharmacists and are not confined to any particular area of the general public. Where information on the MHRA's website seeks to encourage the public to report, for example, concerns about whether medicines they receive may be counterfeit, this information is made as accessible as possible. The responses to the consultation did not highlight any equality concerns.

Annex A

Rationale for UK apportionment of multinational firm costs

1. Assessing the UK economic welfare effects of costs and benefits to multinational firms (such as large pharmaceutical firms) is not straightforward. Whichever approach is taken, significant assumptions have to be made. The RPC has challenged the methodology that DH has been using and has requested that a cross-Whitehall consensus on the correct approach is found. A meeting between the Treasury Green Book Team, and BIS,DH and MHRA economists will take place in January 2013 to continue efforts to c achieve this consensus. In the meantime, the DH methodology is used in this IA and is explained below.

2. On the assumption that firms are effective at minimising costs at each level of output, in the short to medium term, the interventions contained in this Directive will affect firms' profits. The effects of intervention will therefore be felt through changes to the returns to the capital of firms' investors. This analysis is interested in how the interventions will affect UK citizens, and hence we need to know the proportion of UK shareholding in the firms that supply the EU market. Unfortunately, we know little about this proportion.

3. In the longer term, we would expect profits in pharmaceutical firms to normalise around the risk adjusted capital market average rate of return, as markets shift capital around in response to differentials in rates of return across investments. When this happens, it is not clear what the welfare effects of the intervention will be. Pricing of patented pharmaceuticals in the UK is based on the health value that the medicines provide and is not related to firms' costs. Consequently, originator firms can not pass regulatory cost changes on to buyers[18]. The only option for firms is to adjust their levels of output in some way. At the margin, this might mean spending more or less on R&D and/or rent-seeking. The welfare effects of these adjustments are extremely difficult to predict. For instance, by itself, spending less on rent-seeking would have no welfare impact whatsoever because the activity is economically wasteful. By contrast, spending less on R&D might have welfare impacts that are felt in the future, albeit that firms would cut marginal R&D that is likely to have low social value.

4. One simplification is to assume that shareholders bear the cost of the changes throughout the whole of the ten year appraisal period. There is a reasonable rationale for this position. Pharmaceutical firms that engage in substantial R&D look at the expected costs and benefits of a project, and if they decide to undertake it, they fund the R&D. If all goes well, after ten years or more a marketable product emerges. If we impose some additional cost on these firms, it means they get less profit once the drugs are launched. It's too late for them to do anything about it in respect of the pipeline of drugs that are already in development - and which will emerge over the next ten years or more. So their profits on these will be reduced. But they will factor the increased costs into their future decisions to invest. So in ten or more years' time everything will be back to normal, as the increased costs are factored in to investment decisions[19].

Evidence for distribution weighting

5. On the assumption that shareholding is a linear function of wealth, the following calculation for the distributional weight applies to UK share ownership.

Quintile	% of wealth*	Green Book weight**	weighted contribution to overall multiplier for shareholders
5	59%	0.5	0.295
4	20%	0.8	0.16
3	13%	1	0.13
2	6%	1.3	0.078
1	1%	1.9	0.019
		overall multiplier	**0.682**

* from http://www.hmrc.gov.uk/stats/personal_wealth/menu.htm

** from page 94, http://www.hm-treasury.gov.uk/d/green_book_complete.pdf

Note this is an over-estimate because a) there will be an additional concentration of wealth, probably highly significant, within the top quintile (top decile has 45%); b) the weightings used are the most conservative cited in the Green Book

Endnotes

[1] Counterfeit packs and PILs with authentic product inside – this is a counterfeit medicine by every used definition

[2] Total numbers exported from the UK are still being corroborated through paper trail examination - figures estimated

[3] Note that we have not uprated this figure to put it into current prices. However, drug prices are notoriously flat over time and hence there is not point in making the adjustment. This approach is adopted throughout this IA.

[4] http://www.oft.gov.uk/shared_oft/reports/comp_policy/oft967.pdf

[5] PSSRU unit cost estimate of a 17.2 minute GP consultation

[6] The World Health Organisation estimated that in 1999 the UK had a 6% share by value in world pharmaceutical production. http://apps.who.int/medicinedocs/en/d/Js6160e/3.html#Js6160e.3

[7] Gagnon and Lexchin (2008). "The cost of pushing pills: a new estimate for pharmaceutical promotion expenditures in the US" PLoS Med 5 (1)

[8] The EU can levy a fine for each day that the UK would be non-compliant. In theory therefore, the UK would be liable for an infinite fine if it continuously failed to implement the Directive.

[9] These figures are derived by searching for firms with addresses in the UK and EU that are named on UK Marketing Authorisations for finished form medicinal products. They are probably an over-estimate of the number of firms, given inconsistencies in the way that addresses are recorded.

[10] This approach is simplistic. Some active substance manufacturers in the UK are probably subsidiaries of multinational firms.

[11] Estimated using OECD statistics for 2008 and 2009. The 3.4% is a slight overstatement of the UK share because there is some missing data in the OECD database. However, this is not likely to have resulted in a large error.

[12] There may be some double counting in this figure due to discrepancies in the way that company addresses are recorded. Nevertheless we believe that this figure is reasonably accurate.

[13] The average age of the UK population is 39. The average number of QALYs that a person of 39 can expect is 30. Using the standard Dept of Health value of £60,000 as the maximum society is willing to gain a QALY, the premature death of an average person can be valued at £1.8 million.

[14] Information from MHRA databases on the number of wholesaling authorisations

[15] OFT "Medicines Distribution. An OFT market study" 2007

[16] Macarthur Donald (2007) "European Pharmaceutical Distribution: Key Players, Challenges and Future Strategies" SCRIP reports, BS1353, Informa UK Ltd. The British Association of Pharmaceutical Wholesalers, which represents all full-line wholesalers, claims that its members currently provide 90% of the medicines in the UK, although the basis for this figure is not clear.

[17] Regarding the remaining market share, MacArthur reports that in 2005, self-distributors (vertically integrated pharmacy businesses) and manufacturers using direct to pharmacy distribution arrangements accounted for 13% and 3% of market share respectively.

[18] Unless perhaps there is some adjustment in the quality of service that the pharmaceutical firms provide.

[19] This approach ignores (at least) two important factors. First, decisions on R&D actually happen on a continual basis - and there will be some ongoing projects at the margin that would be stopped as a result of the increased costs, thereby reducing the profit impact. Second, there will probably be some reduction in spending on post-launch rent seeking, which will also have the effect of reducing the profit impact. These two factors should be explored properly when time permits. At the moment we believe that the figure of 6% is an over-estimate of the impact.