Title: **Transposition of Pharmacovigilance Directive 2010/84/EU** **Lead department or agency:** Medicines and Healthcare Products Regulatory Agency **Other departments or agencies:** Department of Health	Impact Assessment (IA) **IA No:** 4011 **Date:** 03/08/2011 **Stage:** Consultation **Source of intervention:** EU **Type of measure:** Secondary legislation **Contact for enquiries:** MHRA Central enquiry point info@mhra.gsi.gov.uk

Summary: Intervention and Options

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

Pharmacovigilance is the process of monitoring a medicine's effects on the general population once it has been authorised for use. Without the information provided by pharmacovigilance, patients can not be expected to determine fully for themselves how safe medicines are. This information asymmetry provides the justification for government intervention. The European Commission reviewed current Pharmacovigilance framework in the EU in 2008, and decided that it does not solve the information asymmetry as efficiently as possible. The Commission concluded that the framework places unjustified burdens upon industry, and that it does not focus effort at the greatest risk. The Directive must be transposed into UK law by 2 July 2012, under government guidelines.

What are the policy objectives and the intended effects?

The policy aims to remove unjustified costs placed upon industry by regulators under the current European legal framework, through the use of worksharing and harmonised processes. The policy also aims to ensure that pharmacovigilance resource is expended (in both the pharmaceutical industry and the MHRA) in a targeted way at areas of greatest risk to patients. The intended effect is to alleviate burdens upon industry whilst at the same time maintaining public health, and reducing the numbers of adverse drug reactions in the general population.

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

Option 1: Status quo
This option is used as a comparator to act as a baseline for current costs of Option 2. It considers the current UK legal framework for pharmacovigilance.
Option 2: Implement the Directive
The Directive contains several discrete interventions, affecting different parts of the industry's pharmacovigilance activities. These proposals have been incorporated into one option, but in effect contain several sub-options where the UK has the chance to maximise the benefit of implementing the Directive. This option also contains a number of derogations, which have been used to benefit the pharmaceutical industry wherever possible. **This is our preferred option.**

Will the policy be reviewed? It will be reviewed. **If applicable, set review date:** 7/2017 **What is the basis for this review?** Duty to review. **If applicable, set sunset clause date:** Month/Year	
Are there arrangements in place that will allow a systematic collection of monitoring information for future policy review?	Yes

Ministerial Sign-off For consultation stage Impact Assessments:

I have read the Impact Assessment and I am satisfied that, given the available evidence, it represents a reasonable view of the likely costs, benefits and impact of the leading options.

Signed by the responsible Minister: ..... Date: .....

Summary: Analysis and Evidence

Policy Option 2

Description:

Implement the Directive

Price Base Year 2011	PV Base Year 2011	Time Period Years 10	Net Benefit (Present Value (PV)) (£m)		
			Low: -25.3	**High:** 57.7	**Best Estimate: 16.2**

COSTS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Cost (Present Value)
Low			2.0	**17.1**
High			7.1	**60.9**
Best Estimate	0.7		4.5	**39.0**

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

Costs to pharmaceutical industry of increased reporting requirements for ADRs, completion of post authorisation safety and efficacy studies and introduction of new processes. Costs to the MHRA in terms of extra burden for administering new systems, publishing further pharmacovigilance data to the public, and audits of its national pharmacovigilance system.

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

Possible minor impact upon health for reduced additional monitoring requirements, but as detailed there is no evidential link between pharmacovigilance changes and cost to public health, and for this reason the exact costs cannot be quantified.

BENEFITS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Benefit (Present Value)
Low	0		4.1	**35.5**
High	0		8.7	**74.8**
Best Estimate	0		6.4	**55.2**

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

Reduction in literature monitoring requirements for industry, removal of DDPS, and harmonisation of several processes allowing reduced reporting requirements.

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

Possible minor impact upon health for several areas, including infringement notices and introduction of RMS - but as detailed there is no evidential link between pharmacovigilance changes and benefits to public health, and for this reason the exact benefits cannot be quantified.

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

Limited responses to industry questionnaire have resulted in a very limited data set.
The Commission has assumed that the directive is a more efficient way to solve the issue of information asymmetry of medicines, but this cannot accurately be measured using the data available.
The Directive contains multiple elements, the details of which will be decided by working parties at the European Medicines Agency. These are unlikely to be finalised by the time this Directive is implemented, and will have a significant impact on the costs and/or benefits of the proposed measures.
A greater focus on benefit:risk may lead the industry to change the specialists that it employs - from scientists to physicians.

Direct impact on business (Equivalent Annual) £m):			In scope of OIOO?	Measure qualifies as
Costs: 4.5	**Benefits:** 3.7	**Net:** 0.8	No	NA

Enforcement, Implementation and Wider Impacts

What is the geographic coverage of the policy/option?			United Kingdom		
From what date will the policy be implemented?			02/07/2012		
Which organisation(s) will enforce the policy?			MHRA		
What is the annual change in enforcement cost (£m)?			£0		
Does enforcement comply with Hampton principles?			Yes		
Does implementation go beyond minimum EU requirements?			No		
What is the CO_2 equivalent change in greenhouse gas emissions? (Million tonnes CO_2 equivalent)			**Traded:** 0	**Non-traded:** 0	
Does the proposal have an impact on competition?			No		
What proportion (%) of Total PV costs/benefits is directly attributable to primary legislation, if applicable?			**Costs:** 0	**Benefits:** 0	
Distribution of annual cost (%) by organisation size (excl. Transition) (Constant Price)	**Micro**	**< 20**	**Small**	**Medium**	**Large**
Are any of these organisations exempt?	No	No	No	No	No

Specific Impact Tests: Checklist

Set out in the table below where information on any SITs undertaken as part of the analysis of the policy options can be found in the evidence base. For guidance on how to complete each test, double-click on the link for the guidance provided by the relevant department.

Please note this checklist is not intended to list each and every statutory consideration that departments should take into account when deciding which policy option to follow. It is the responsibility of departments to make sure that their duties are complied with.

Does your policy option/proposal have an impact on…?	**Impact**	**Page ref within IA**
Statutory equality duties[1] Statutory Equality Duties Impact Test guidance	No	All
Economic impacts		
Competition Competition Assessment Impact Test guidance	Yes	24
Small firms Small Firms Impact Test guidance	Yes	25
Environmental impacts		
Greenhouse gas assessment Greenhouse Gas Assessment Impact Test guidance	No	n/a
Wider environmental issues Wider Environmental Issues Impact Test guidance	No	n/a
Social impacts		
Health and well-being Health and Well-being Impact Test guidance	No	25
Human rights Human Rights Impact Test guidance	No	n/a
Justice system Justice Impact Test guidance	Yes	24
Rural proofing Rural Proofing Impact Test guidance	No	n/a
Sustainable development Sustainable Development Impact Test guidance	No	n/a

[1] Public bodies including Whitehall departments are required to consider the impact of their policies and measures on race, disability and gender. It is intended to extend this consideration requirement under the Equality Act 2010 to cover age, sexual orientation, religion or belief and gender reassignment from April 2011 (to Great Britain only). The Toolkit provides advice on statutory equality duties for public authorities with a remit in Northern Ireland.

Evidence Base (for summary sheets) – Notes

Use this space to set out the relevant references, evidence, analysis and detailed narrative from which you have generated your policy options or proposal. Please fill in **References** section.

References

Include the links to relevant legislation and publications, such as public impact assessments of earlier stages (e.g. Consultation, Final, Enactment) and those of the matching IN or OUTs measures.

No.	Legislation or publication
1	Pharmacovigilance Directive 2010/84/EC - http://tiny.cc/crzba
2	Directive 2001/83/EC - http://tiny.cc/ow70l
3	Commission Impact Assessment on Pharmacovigilance - http://tiny.cc/c7uyy
4	

+ Add another row

Evidence Base

Ensure that the information in this section provides clear evidence of the information provided in the summary pages of this form (recommended maximum of 30 pages). Complete the **Annual profile of monetised costs and benefits** (transition and recurring) below over the life of the preferred policy (use the spreadsheet attached if the period is longer than 10 years).

The spreadsheet also contains an emission changes table that you will need to fill in if your measure has an impact on greenhouse gas emissions.

Annual profile of monetised costs and benefits* - (£m) constant prices

	Y_0	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9
Transition costs	0	0.4	0	0	0.3	0	0	0	0	0
Annual recurring cost	0	2.0	4.1	4.1	6.4	6.4	6.4	6.4	6.4	6.4
Total annual costs	0	2.4	4.1	4.1	6.7	6.4	6.4	6.4	6.4	6.4
Transition benefits	0	0	0	0	0	0	0	0	0	0
Annual recurring benefits	0	0.9	1.8	1.8	10.6	10.6	10.6	10.6	10.6	10.6
Total annual benefits	0	0.9	1.8	1.8	10.6	10.6	10.6	10.6	10.6	10.6

* For non-monetised benefits please see summary pages and main evidence base section

Glossary

ADR **Adverse Drug Reaction(s)**

An unintended consequence of a medicine that is reported to the regulator or marketing authorisation holder by a health professional or patient.

CAP **Centrally authorised product**

A medicinal product authorised through the EU centralised authorisation procedure and results in one marketing authorisation the terms of which apply across all EU member States.

DDPS **Detailed Description of Pharmacovigilance System**

A document that describes the system that the marketing authorisation holder has in place in order to fulfil legal requirements in relation to pharmacovigilance.

EMA **European Medicines Agency**

An Agency of the European Union, responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.

IN **Infringement Notice**

A compliance tool proposed by the MHRA to assist them in ensuring marketing authorisation holders comply with legal requirements in relation to pharmacovigilance.

MAH **Marketing Authorisation Holder**

A company with the right to market their medicine within the UK, the EU, or globally.

Member State

A member state of the European Union that is party to the treaties of the European Union and the obligations that EU membership entails.

MHRA **Medicines and Healthcare products Regulatory Agency**

The UK medicines regulator, responsible for making sure that medicines and medical devices work, and are acceptably safe.

NCA **National Competent Authority**

The authority within the UK that has the responsibility for all aspects of medicines regulation for UK marketing authorisations – this is the MHRA.

PAES **Post Authorisation Efficacy Study**

A study undertaken after a medicine has been authorised for use to provide more information on how effective the medicine is on the condition it is treating.

PASS **Post Authorisation Safety Study**

A study undertaken after a medicine has been authorised for use to provide more information on how safe the medicine is on the population.

PRAC **Pharmacovigilance Risk Assessment Committee**

The Committee at an EU level responsible for pharmacovigilance matters, particularly relating to harmonised and centralised procedures.

PSMF **Pharmacovigilance System Master File**

A file that contains details of the pharmacovigilance system operated by the marketing authorisation holder.

PSUR **Periodic Safety Update Report**

Reports on available safety data that must be made by marketing authorisation holders to the respective national regulators on the safety of their products – at fixed periods and covering defined time points from the point of authorisation.

QPPV **Qualified Person in charge of Pharmacovigilance**

A person employed by an MAH with overall responsibility for establishing and maintaining the MAH's Pharmacovigilance System, and named as such on the authorisation.

RMP **Risk Management Plan**

A plan drawn up by the marketing authorisation holder describing the risk management system introduced for managing the risks inherent in a medicine.

RMS **Risk Management System**

The system introduced for a medicinal product that includes a set of risk minimisation measures and pharmacovigilance activities to optimise the safe use of the product and gather further information on its safety profile.

Signal

Information from any data source that suggests that a medicinal or herbal product may be associated with a new risk or that the magnitude or nature of a known risk may have changed.

One In One Out

The proposals are to transpose European legislation, which will be implemented largely through copy-out, and contain no gold plating. Whilst the proposals will be implemented 19 days early, on 2 July 2012, this is to ensure consistency between the Directive and the accompanying EU Regulation, which comes into force on 2 July 2012. These proposals do not fall within the remit of OIOO, as they implement a Directive.

Sunset Clause

As these proposals are European, they will not carry a sunset clause. A duty to review will be placed within the UK regulation, which will take place by 2 July 2017.

What is the problem under consideration?

Government intervention in pharmacovigilance is justified because, in the complicated world of drug safety, patients can not be expected to work out for themselves how safe a medicine is. This is a problem known as information asymmetry (for a more complete analysis of why government intervenes in pharmacovigilance see the next section). Pharmacovigilance exists to correct information asymmetry as efficiently as possible. The problem addressed by this IA is that the current pharmacovigilance framework is not as efficient as it could be in addressing the information asymmetry.

The European Commission implied in its impact assessment accompanying the Directive that current EU pharmacovigilance policy imposes burdens upon industry that are not justified on public health grounds. They evaluated the current system and surmised that burdens are primarily imposed on industry through convoluted working procedures, lack of proper communication and harmonisation between member states, and an outdated system for recording and reporting of safety signals. We do not believe that the link drawn between pharmacovigilance changes and public health in their calculations can be adequately drawn; however, although we would agree that removal of these burdens is likely to have minimal, if any detrimental effect upon health.

The previous medicines Directive that implemented some pharmacovigilance processes, 2001/83/EC[1] went some way towards harmonising the approach across member states, thereby reducing regulatory burden on the pharmaceutical industry. However, improvements, such as cutting out duplicative reporting procedures across EU member states can still be made, without compromising public health.

The European Commission also believes that insufficient focus is currently placed on structured evaluations of the risk:benefit profile of marketed products. The Commission believes that there is currently insufficient information available to medical practitioners and patients on the risks of medicines and how to minimise the risks. The evidence that the Commission used to support its case comes from the incidence of preventable adverse drug reactions (ADRs). In the UK, the most convincing evidence comes from a 2004 study on patients in two Merseyside hospitals[2]. During the study period (which spanned late 2000 and early 2001), 6.5% of admissions related to an ADR, with the ADR directly leading to the admission in 80% of cases. Over 70% of ADR admissions were deemed to be "possibly" or "definitely" avoidable. Over 2% of patients admitted with an ADR died.

Extrapolating these admissions and average length of stay data to the whole of the whole of the UK (the NHS in England, NHS Scotland and NHS Wales and Health and Social Care in Northern Ireland), we have estimated that the annual cost of hospital admissions directly attributable to avoidable ADRs in 2009/2010 was £508 million[3]. This figure excludes the lost productivity and the pain and suffering of those admitted. We have conservatively estimated that this cost in 2009/10 was £3,188 million[4].

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[1] Directive 2001/83/EC - http://tiny.cc/ow70l

[2] Pirmohamed et al "Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients" BMJ Volume 329, 3 July 2004

[3] The total number of emergency admissions in the UK in 2009/10 (the most recent year for which data is available) was approximately 6,000,000. We took this number, multiplied it by the Pirmohamed 6.5% ADR admissions rate, the 80% directly caused by ADR and the 72% avoidable rate to get the total number of hospital admissions that were directly attributable to avoidable ADRs. We assumed that the cost of each ADR admission was the same as the average long stay non-elective NHS cost in England in 2010 (£2,197) (NHS reference costs).

[4] We conservatively estimated that the average number of QALYs lost to individuals who die prematurely from ADRs is 10. We used the standard Dept of Health QALY value of £60,000.

We have been unable to estimate the cost to the UK healthcare systems and individual patients with ADRs that are dealt with at primary care level.

Our quantified estimate of total harm from ADRs to the UK in 2009/10 is £3,695 million. This is a lower limit estimate of the harm from ADRs.

The Commission's impact assessment for the new Directive does not examine the causality between insufficient information generated by pharmacovigilance systems and costs to healthcare systems and patients. The causality is difficult to prove. While some ADRs are the result of patients ignoring information, other ADRs have their roots in inadequate information used by physicians when prescribing medicines. However, some ADRs are caused by physicians not taking into account known contra-indications and interactions between medicines. There are also cases where the contra-indications and interactions are either not currently known or are under-researched. This last category of ADR cases is the pharmacovigilance problem identified by the Commission. However, there is no evidence on its extent or its susceptibility to improvement.

A more detailed discussion of the background to pharmacovigilance can be found at Annex 3.

Why is Government intervention necessary?

The EU pharmacovigilance regulatory system has been judged by the Commission to place unnecessary and unjustified burdens upon industry that can be replaced with more streamlined processes designed to avoid negatively affecting public health outcomes. Only the EU can remove these burdens through legislative change.

As noted above, government intervention in pharmacovigilance is justified on the basis of information asymmetry – in the esoteric world of drug safety, without the right sort of information, patients can not be expected to determine for themselves how safe drugs are. This asymmetry is addressed by pharmacovigilance, but the current EU framework does not do its job as efficiently as it could. This provides the fundamental reason for corrective action by the EU.

There are two reasons why industry is unlikely to provide sufficient drug safety information. Firstly, the information generated by pharmacovigilance systems is a public good (if you provide it to one person, you can provide to everyone at no extra cost, and consumption of the good by one person does not mean that there is less available for other people to consume). Because patients and practitioners can access pharmacovigilance information without paying for it, the private sector providers of pharmacovigilance information can not capture their full share of the profits, and will, from a societal perspective, undersupply the market. Corrective government intervention is theoretically justified.

Secondly, the pharmaceutical industry has conflicting incentives. In the short term, it can make greater profits by spending less time on pharmacovigilance, because of the cost of pharmacovigilance activities and the possibility that new information on ADRs will affect sales revenue. In the longer term, a pharmaceutical company's ADR record will affect its reputation, its ability to raise capital, and its profitability. This problem of time inconsistency leads to public distrust and is given as a justification for government intervention.

What are the policy objectives and their intended effects?

- Unjustified costs on industry removed
- Pharmacovigilance effort targeted at the greatest risk

The policy aims to alleviate the burdens that currently exist in pharmacovigilance processes whilst at the same time ensuring that public health safety is not compromised.

In line with Commission assumptions, enhanced pharmacovigilance requirements will result in greater targeting of effort by marketing authorisations holders so that the greatest effort is directed at the greatest risk, with the intended effect of reducing ADRs.

What policy options have been considered?

Status quo (or 'do nothing')

This option is the law as it stands at present, with no costs or benefits incurred (as if the Directive had never existed). 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.

The do-nothing option is not a realistic option because of the UK's obligation to adopt EU Directives into national law[5].

Implement the Directive

The Directive contains several discrete interventions, affecting different parts of the industry's current pharmacovigilance activities, as well as those activities currently undertaken by the MHRA. For the sake of convenience, we have incorporated all these proposals into one option, partly because in some cases there is no member state discretion on how to implement the Directive.

Nevertheless, in a number of minor areas, there are some instances where there is discretion in the form of member state derogations. In line with Government guidance on transposition of European legislation, in each area of discretion we propose to choose the option that maximises benefit for UK businesses and shareholders.

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.

Overview of policy measures

The Commission produced proposals in 2008 to improve the EU's current regulatory framework for pharmacovigilance. The UK actively engaged in negotiating on these until December 2010, when they were published as a Directive to be transposed into UK law by July 2012. The main features of the Directive are set out briefly below and explored further in the analysis.

Reductions in the numbers of Periodic Safety Update Reports required

Legislative changes to produce a risk-based approach to what is currently mandatory reporting on safety issues, as well as increase coordination and worksharing between member states in order to reduce burdens upon industry.

Risk Management Plans and Risk Management Systems

A move towards a more holistic approach for risk management, encouraging industry to embed pharmacovigilance principles as a foundation of their business, and to take a proactive approach to safety monitoring. Imposition of a new layer of pharmacovigilance monitoring and responsibility upon industry.

Movement from the use of a Detailed Description of the Pharmacovigilance System to the Pharmacovigilance Master File

Removal of mandatory and repeated updates to marketing authorisations through a shift in how the information is kept and reported by industry.

Additional pharmacovigilance responsibilities

Mandatory audits of the pharmacovigilance systems of both industry and regulators at regular intervals. The possibility of delegation of pharmacovigilance responsibilities between member states.

Revised requirements for Post Authorisation Safety and Efficacy Studies

The strengthening of current requirements to conduct and complete safety studies – now included as specific licence conditions. The introduction of efficacy studies in rare situations in order to collect data on the usefulness of the product where this is still unclear.

[5] Because of an EU fine for each day that the UK would be non-compliant, the UK would be liable for an infinite fine if it continuously failed to implement the Directive. Even the most expensive way of implementing the Directive would look attractive by comparison, and so the "do nothing" option is automatically ruled out.

Additional monitoring arrangements

Minor changes to the UK's current systems to fit with a now harmonised EU system for monitoring new substances more closely, and encouraging reporting of adverse reactions from patients and healthcare professionals.

Centralisation of literature monitoring for certain substances

European plans to decrease the number of journals that the industry currently monitors in order to look for safety signals relating to their products. The European Medicines Agency will perform this function centrally from now on. However, UK industry reporting requirements for literature will remain for literature not monitored by the EMA.

Harmonisation of reporting processes through the use of the EudraVigilance Database

Centralisation of reporting by industry of individual case safety reports to a single EU database, as opposed to many member state databases at present. Coordination of requests for further information from member states. Not due to be functional until early 2015.

Greater accessibility to the public of key safety documents

Duties of industry to provide key safety documents that will now be published on the MHRA's website. Simplification of certain documents to make them more digestible by the general public.

Penalties for failure to meet the conditions of an authorisation

New effective, proportionate and dissuasive penalties to be introduced to ensure compliance with the particulars of the Pharmacovigilance Directive.

Introduction of infringement notices

MHRA proposals to introduce a new regulatory compliance tool to ensure that companies meet their pharmacovigilance responsibilities.

Incremental costs and benefits of implementing the Directive

Assumptions used in the analysis

The standard appraisal period of ten years has been used.

We have assumed that 950 firms will be affected by the Directive. This is based on the number of companies that supply the UK market and we assume that this is representative of the EU as a whole. We have further assumed that none of the companies that supply the UK qualify as small firms. Originator firms (those that bring new patented medicines to market) spend billions of pounds on R&D and require very substantial sales to justify their investments. It is therefore inconceivable that any originator firms are small businesses. It is possible that some generics firms (those that produce out-of-patent medicines) are small businesses. We will ask specific questions during the formal consultation to gather information on generics firm size and, if small generics firms exist, the nature and size of the impacts.

In the short term, the interventions contained in this Directive will affect the profits of all the firms, and we assume the interventions will ultimately be felt through changes to the returns to the capital of the firms' investors. This analysis is mainly 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. The World Health Organisation estimated that in1999 the UK had a 6% share by value in world pharmaceutical production[6]. Taking this figure as our baseline, we have assumed a range of plus and minus 3% to reflect the substantial uncertainty we feel about the exact proportion. We have also made two further adjustments. Firstly we have assumed that some branded manufacturer profits are spent on rent seeking behaviour, such as competitive advertising that increases a firm's share of a market without increasing overall societal welfare. We have assumed that

[6] http://apps.who.int/medicinedocs/en/d/Js6160e/3.html#Js6160e.3 The basis for this calculation is not clear and it might not be based on UK shareholding.

branded manufacturers spend 15% of profits in this way[7]. Manufacturers of unbranded medicines generally do not engage in this sort of rent seeking. We have assumed that overall, 7.5% of profits are spent on rent seeking.

The second adjustment is made to account for the marginal utility of income to UK shareholders. We have assumed that UK pharmaceutical industry shareholders are on average in the fourth quintile of the UK's wealth distribution. The Treasury Green Book recommends a distributional weighting of 0.75 for this quintile.

These adjustments yield a range of between 2.1% and 6.2%.

In the longer run, we can expect all changes to company profits to be passed on to buyers. However we have assumed that this effect is not felt until after our ten year appraisal period ends.

We have applied a zero weighting to impacts on overseas interests (most of which belong to wealthy individuals). In our summary section, however, for the sake of transparency, we have presented our estimates of the cost to the global pharmaceutical industry from the changes that will be effected by the Directive.

In estimating incremental costs and benefits, we have made various assumptions about staff costs.

- A pharmaceutical industry average annual salary of £70,000 and a senior annual salary of £105,000[8] have been used (supplied by a pharmaceutical firm and assumed to be representative of the industry). These yearly salaries have been converted to hourly rates assuming a 215 day working year, and a 7.5 hour working day. Non-salary costs are assumed to add 30%. These assumptions yield average staff costs of £56 per hour and senior staff costs of £85 per hour.

- MHRA annual staff time is assumed to cost £55,300 or £33,600 depending on the seniority of staff required. We have assumed a 220 day working year, a 7.2 hour working day, and 30% non-salary costs. These assumptions yield hourly rates of £45 and £28.

Reductions in the numbers of Periodic Safety Update Reports (PSURs) required

What is currently in place and how does it work?

The current system under 2001/83/EC requires that Marketing Authorisation Holders (MAHs) collect information on adverse reactions on each and every medicine that they are currently marketing. This information is collected and assessed, and then submitted to the MHRA (and other member states where the products are centrally authorised across the EU) at regular intervals. A single report may cover all products containing the same active substances (for instance, all paracetamol products), and are intended to provide a continuously updated picture of the worldwide safety of a medicinal product.

What's wrong with the current system?

The submission of PSURs is seen to be one of the areas where burdens upon industry could be significantly reduced – currently the ongoing cycle of collation and submission, assessment by the MHRA and subsequent changes to the safety profile is seen as onerous when applied across the spectrum of different categories of medicines. The repetitive nature of the work and stringent requirements relating to how and when these reports are submitted has been highlighted by the Commission as unnecessary in their analysis of the current system. When PSURs are submitted to individual member states, each of these states can query and ask for further information, which can lead to significant duplication of effort across the 27 European Member States.

What has the Commission done to intervene?

The Commission aims to reduce the numbers of PSURs submitted by industry to various regulators. They will look at how much risk each medicine carries and decide the frequency of reporting upon this basis. For generic medicines (those medicines where the 'exclusivity' of the developer has expired, allowing others to copy the drug, e.g. ibuprofen), medicines for which the risks are well known, homeopathics and traditional use registered products (e.g. St John's Wort), it is unlikely that PSURs will be required in future, because their effects and use are well known.

[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] Figures sourced from industry contacts

National regulators, such as the MHRA will still have the power to require the production of PSURs in future where specific safety concerns have been identified.

For those still required to submit information on PSURs, the work will be coordinated among the national regulators of the member states in future. Worksharing between member states will mean that there is a single centralised request for further information. MAHs will only need to respond to one set of queries on each PSUR for all of Europe.

PSUR reports will also be submitted electronically to the EU's central repository (the European Pharmacovigilance Issues Tracking Tool, or EPITT) by MAHs to further reduce burdens.

What costs and benefits arise from the new approach?

This area of the legislation should see a reduction in the number of mandatory PSURs required by regulators from industry, and thus will most heavily affect UK businesses in terms of a lift in costs. It will be especially helpful to those elements of the pharmaceutical industry whose main trade is in generics, registered traditional use products, and homeopathics, although the innovative sector (those producing new medicines) will also receive a fair proportion of the benefits.

The list of products that will require PSURs in future is currently being determined by a working group in the European Medicines Agency, and thus there is some uncertainty surrounding how extensive this list might be. The UK will encourage as short a list as possible through participation in EMA working groups. We expect the central reporting database, EPITT, to be available for use by the time these proposals are transposed into national law on 2 July 2012, so benefits should begin to accrue immediately.

We have assumed that there will be no negative health impact to these changes, as further ADRs will not arise as a direct result of a reduction in reporting requirements by industry. Any possible negative health impact will be negated by the alternative and parallel systems that the Commission intends to put in place as part of the Directive, including the more holistic approach to pharmacovigilance under risk management systems. However, this is merely an assumption – we have not been able to obtain evidence to prove a direct evidential link between any pharmacovigilance change and the numbers of deaths due to ADRs. We have estimated that ADR harm would have to increase by approximately 0.04% in order for the estimated benefits to industry to be offset by health losses. We are not claiming that this would happen in practice.

Private Sector benefits (cost savings)

On average, the MHRA reviews 4,500 PSURs per year at present. We have taken this figure as representative of all PSURs produced by the pharmaceutical industry for the EU market. The costs provided by industry of preparing, reviewing and submitting a PSUR (assuming a single request for further information from member states) is £5,756[9]. We cannot definitively answer how many PSURs will no longer be required under the new system, but the MHRA does not expect to request a large number of PSURs per year under the new Directive. Based on the work currently taking place in the EMA working group, the UK is lobbying for around 75% of current submissions to no longer require a PSUR. Assuming that this is achieved, only 25% of marketing authorisations will continue to do so. These assumptions, and our 2.1% - 6.2% UK impact assumption, yield annual UK benefits of between £0.404 million and £1.213 million starting from July 2012. The NPV is between £2.881 million and £8.642 million (annualised at between £0.335 million and £1.004 million).

Member states can also ask for further information for each PSUR, and industry estimates that between 0-3 of these requests are received per application, costing between £0 and £10,560[10] per application. This situation is mirrored across Europe, as the majority of PSURs are submitted to multiple member states. Further benefit should therefore accrue from an increase in worksharing between member states, leading to a single set of queries arising from any PSUR submission and a single response required from MAHs in response to these queries. The benefit likely to accrue from this is a reduction in the number of requests for further information – the range of worksharing costs will now be between £0 and £3,520 per application. These assumptions and our UK shareholding assumption yield estimated annual UK benefits of between £0 and £1.978 million. The NPV is between £0 and £14.093 million (annualised at between £0 million and £1.637 million).

Total UK benefits for the PSUR changes are given below

[9] Industry supplied figures: 90 hours @ £56 for preparation of a PSUR, followed by 8hrs @ £85 for review and clearance of the PSUR.

[10] Unjustified figure supplied by industry – responding to a single request for information - £3,520.

Total UK benefits from PSUR changes	Annual (£million)	NPV (£million)	Annualised (£million)
Lower	0.404	2.881	0.335
Upper	3.191	22.735	2.641
Midpoint	1.798	12.808	1.488

Risk Management Plans and Risk Management Systems

What is currently in place and how does it work?

Risk Management Plans were introduced as part of Directive 2001/83/EC as a way of providing a more planned, focussed and proactive approach to the monitoring of pharmaceuticals within the general population (as opposed to the previous, reactive approach, which relied heavily upon ADR reports). They are important, as they are currently the primary tool by which MAHs and the MHRA agree plans for individual monitoring of each pharmaceutical product placed upon the market.

RMPs are currently required for all new active substances, as well as in a variety of other situations where the safety profile of the medicine needs to be more carefully monitored, and are assessed by the MHRA. RMPs also contain the details of extra requirements that may have been imposed upon MAHs, such as the requirement to carry out post-authorisation safety studies.

What's wrong with the current system?

The Commission's view was that risk management plans as currently formulated focus on individual products and the minutiae of their operation. They detract from a more coordinated and holistic approach that regulators would like to encourage MAHs to move towards. Risk management plans have also been very technical documents in the past, and are unlikely to be understood by the general public, who are increasingly interested in medicines information available.

What have the Commission and the MHRA done to intervene?

The new requirements surrounding the Risk Management System are a detailed description of activities above existing Risk Management Plans for individual products, to be set up and adhered to by the MAH. They are a new requirement placed upon MAHs to ensure that a more proactive approach is taken towards the collection and use of pharmacovigilance data, and are designed to focus industry to embed risk management systems into their culture. Elements of the Risk Management System are now conditions of the marketing authorisation (allowing action to be taken against the MAH if they fail to conduct these key elements).

Risk Management Plans are to be made more accessible to the public and healthcare professionals, and lay summaries (in plain English) of these are to be prepared by MAHs and will be published as publicly accessible documents.

In certain circumstances (currently unknown), where it is judged by the marketing authorisation holder that they do not have to submit an RMP as part of their application, they will instead need to provide a justification of this decision to the MHRA. Clarification from the EU will also be sought as to the procedure for maintaining RMPs where they already exist upon introduction of the Directive.

We have assumed that the proposals will have an unquantifiable positive effect upon public health, as an approach towards embedding pharmacovigilance as a main part of each company's business should lead them to spot safety signals arising from ADRs more promptly and/or frequently. We assume that this would translate into faster action to revise safety data and disseminate it to the public and healthcare professionals, resulting in a reduced level of ADRs. However, we have been unable to ascertain direct links between pharmacovigilance system changes and health benefits, and are aware that there is no monitoring available to the MHRA that will allow us to test this assumption to the degree of accuracy required.

Private Sector costs

The Directive may ultimately require companies to produce more RMPs than they currently do. However, negotiations are on-going, and this outcome is far from certain. We have therefore not included an estimate of the cost implications but will update the IA if changes in RMP frequency requirements emerge.

Lay summaries (descriptions of the risk management plan in plain English) will need to be prepared for all new RMPs. From data provided by industry, we have estimated that this will cost an extra £340[11] in administrative burden. Around 200 applications are received by the MHRA each year that require risk management plans, and we have assumed that this is representative of RMP requirements in the EU as a whole. These assumptions yield annual costs to the UK of between £0.001 million and £0.004 million.

Each firm supplying the EU market will now require a Risk Management System (RMS) to sit over its RMPs. The one-off cost per firm is estimated to be £10,158[12]. The total one-off discounted cost to the UK is estimated to between £0.194 million and £0.582 million.

Each of the 950 firms will also be required to update RMS annually on their progress in meeting authorisation conditions, estimated to cost £621[13] per review. These assumptions yield annual UK costs estimates of between £0.012 million and £0.037 million.

It is unclear how often MAHs will be required to submit a justification to the MHRA where they have decided that a full RMP is not required. There is some concern from the MHRA that this may be an area where burdens are increased by proposals from the European Medicines Agency – in the past, the MHRA had only requested justification from an MAH 'as appropriate', whereas there seems to be movement towards this becoming a *de facto* mandatory submission. Industry estimates the cost of each justification will be £1,020[14] in administrative burden.

The key elements of risk management plans will now also be a condition of the MAH's authorisation – leading to the chance that the MHRA will take action against the MAH if they fail to meet the conditions of their RMP. This is explored in more detail under the 'penalties for failure to meet the conditions of a marketing authorisation' section below.

Total UK costs from RMP and RMS changes	One-off (£million)	Annual (£million)	NPV (£million)	Annualised (£million)
Lower	0.201	0.014	0.292	0.034
Upper	0.603	0.041	0.875	0.102
Midpoint	0.402	0.027	0.583	0.068

Benefits to public health

The Commission has produced an impact assessment on the Pharmacovigilance Directive that considers the impact of avoidable adverse drug reactions upon the healthcare systems in Europe, particularly on hospital admissions.[15] However, the IA provides no evidential link between the numbers of avoidable ADRs and the efficacy of the RMP and RMS changes in preventing the ADRs. We have trawled the literature for further evidence but have found nothing. We therefore feel unable to provide estimates of the benefits of these changes[16].

However, to put the scale of the costs into context, the RMP and RMS changes would have to reduce the UK's ADR costs by less than 0.002% in order for the benefits to justify the costs. Note that we are not claiming that this reduction would be achieved in practice.

Derogation for Risk Management Plans

If the MHRA does not avail itself of a derogation within the Directive, and instead requires all UK Marketing Authorisation Holders to produce risk management plans for products that were authorised before 2 July 2012, we would expect there to be added costs. The MHRA has records of around 28,400 authorisations for medicinal products on the UK market at present, and industry has supplied us with the

[11] Industry estimate – 4hrs @ £85

[12] Industry estimate – 150 hrs @ £56 and 20 hrs @ £85

[13] Industry estimate – 5hrs @ £56 and 4hrs @ £85

[14] Industry estimate - 5hrs @ £56 followed by 8hrs @ £85

[15] Commission impact assessment on Pharmacovigilance: http://tiny.cc/byjw9

[16] If we had a monetised estimate of the ADR costs that better pharmacovigilance could prevent, we could have provided an estimate of the amount of harm that the RMP and RMS changes would have to prevent in order to justify their costs. However, even then we would have been unable to make a reasonable judgement on how likely this amount of harm reduction would be realised, not least because other factors that are beyond the scope of the changes, such as information dissemination and patient and practitioner behaviour, would also determine the desired outcome.

costs of preparing and submitting a risk management plan as part of our calculations above, and we would estimate, based on knowledge of the discussions ongoing at the EMA at present, that around a third of these would need to comply with the RMP requirements and continue to comply with the annual requirements. The remaining two thirds would need to prepare and submit a justification for not producing an RMP

However, it should be noted that it is difficult to tell whether other member states will exercise this derogation – therefore meaning that those who trade in Europe (this is a significant proportion, estimated to be 85%) may still need to prepare risk management plans for some other member states. We therefore assume that no significant cost savings will arise from the utilisation of this derogation.

MHRA and Department of Health (DH) Costs

The MHRA will need to enforce the new authorisation conditions, as well as assess RMPs for each new product as well as updates to RMP requirements. It is expected that this will require adjustment to fees, but any changes to fees will be costed and consulted upon separately, and is not expected to take place until the 2013/14 financial year, in order to allow data to be collected by the MHRA on what levels of fee adjustment may be necessary. We expect there to be associated administrative and resource costs to industry in preparing the paperwork for such fees changes. The scale of these costs is currently uncertain, but we would judge them unlikely to materially affect the proposals put forward by this impact assessment. A separate consultation exercise will take place in 2012, which will be accompanied by its own impact assessment, and the MHRA will have gathered enough information to accurately identify costs at this point.

Movement from the use of Detailed Description of the Pharmacovigilance System (DDPS) to the Pharmacovigilance Master File

What is currently in place and how does it work?

The Detailed Description of the Pharmacovigilance System (DDPS), which is submitted at the time of an application for a marketing authorisation, broadly summarises key pharmacovigilance activities undertaken by the MAH in order to meet legislative requirements. These activities range from a record of the contact details of the Qualified Person responsible for Pharmacovigilance (QPPV) through to an effective pharmacovigilance system for monitoring the safety of every authorised medicine. The current Directive introduced this record and required its submission with every licence application.

What's wrong with the current system?

Due to the size of global pharmacovigilance systems, the DDPS is often very complicated and can take a significant time to compile and review. Currently, MAHs need to supply full details of the DDPS with each marketing authorisation application and certain variations; this is considered to be unnecessary duplication of information as often the pharmacovigilance system operated by the MAH will be identical across different products. Furthermore, as the DDPS is a document supporting the authorisation, any slight modification to the document requires submission of a variation to the NCA as variations are required where any change to the marketing authorisation is proposed. Submission of a variation application to make minor changes to a DDPS, which may not have a significant impact on the operation of a pharmacovigilance system, currently have considerable resource implications for MAHs and NCAs.

What have the Commission and the MHRA done to intervene?

The new Directive removes the need for applicants to submit a DDPS and instead requires them to submit summary information about the pharmacovigilance system (QPPV details and the location of the master file). The detailed description of the pharmacovigilance system is contained in the Pharmacovigilance System Master File, which is submitted *at the request* of competent authorities. This allows MHRA to choose under which circumstances it may be appropriate to request and review the master file. A move from a requirement to submit the DDPS to the use of the Pharmacovigilance System Master File should bring about a great deal of cost savings. Under the new system, the master file is prepared and maintained in a current state by companies and covers the pharmacovigilance system irrespective of the number of authorised products. The only sections of the Pharmacovigilance System Master File that MAHs need to notify as part of the marketing authorisation application will be the location of the file itself and the details of the QPPV, although European Medicines Agency Working groups are looking at ways to further reduce this burden at present.

The new Directive demands that the move from DDPS to Master File be made, at a maximum, three years after the introduction of the Directive in 2015. The MHRA proposes to make this move more quickly and allow marketing authorisation holders the opportunity to make the switch from the

implementation of the Directive in July 2012. This should provide cost savings for those marketing authorisation holders that currently have DDPS requirements, reducing the variations burden on both industry and competent authorities.

Private Sector costs and benefits

The pharmaceutical industry has provided us with an outline of the costs of the DDPS system at present – it is estimated that preparing a new DDPS for each product costs £4,402[17], and there are 2,900 new applications received by the MHRA per year (which we take as representative of the EU as a whole). The DDPS also needs to be regularly updated, and although many of these variations are fee free, we have estimated from data provided by industry that the administrative burden associated with each update is £168. We believe that there is a stock of 15,060 DDPSs. Industry reports that on average there are 6 updates per DDPS every year. These assumptions yield annual UK cost saving estimates (starting in 2015) of between £0.584 million and £1.752 million, with an NPV of between £2.807 million and £8.421 million.

Instead of individual DDPS for each product, a single master file will be required for a company's portfolio of products (and their risk profile). Industry has provided us with figures to estimate how much this new system will cost to set up and prepare – it is estimated that this will be a one-off cost of £2,144[18] for each pharmaceutical company (total cost based on 950 eligible companies. Maintenance of the master file will be ongoing, with an additional estimated cost of £1,129 per annum[19] for each company starting in 2015. These assumptions yield estimated UK costs that have an NPV of between £0.144 million and £0.433 million (which can be annualised at between £0.017 million and £0.050 million)

The master file must be submitted to the MHRA upon request (estimated in 10% of all cases – see below) – and notifications of major changes must be made available to us, however the need for MAHs to submit Summaries of Pharmacovigilance Systems for inspection purposes will be removed for those MAHs operating a Pharmacovigilance Master File, which should deliver a net reduction in regulatory burden.

Under the new Directive, the QPPV must *operate* and reside in the EU from now on, and inform the MHRA of their name and address - this is not anticipated to impose any greater cost than under the present system, particularly as EMA working groups are working to simplify this process.

All of the respondents to the MHRA's questionnaire said that they would be very unlikely to ever submit a variation to change the location of the master file, as it is now electronic. Thus no extra cost is anticipated from this change.

UK private sector net benefits from DDPS and Master File changes	One-off (£million)	Annual (£million)	NPV (£million)	Annualised (£million)
Lower	-0.042	0.562	2.663	0.309
Upper	-0.127	1.685	7.989	0.928
Midpoint	-0.085	1.124	5.326	0.619

The MHRA will experience costs savings from not having to deal with DDPSs. We have assumed that each new DDPS requires 5 hours of Grade 7 time to review and that each updated DDPS requires 1 hour of Grade 7 time. This yields annual cost savings of £4.870 million, which start in 2015. The present value is £22.872 million (annualised at £2.719 million).

The MHRA will experience new costs of dealing with master files, but only in cases where this is the first marketing authorisation in Europe, there are significant issues with the drug in question, or safety concerns. The MHRA representative from the EMA working group estimates that this will happen in no more than 10% of all marketing authorisations. We have assumed that each new Master file requires 5 hours of Grade 7 scrutiny, and that annual updates require 3 hours of Grade 7 time. These costs start in 2015. The present value of these costs is £0.185 million (annualised £0.021 million).

Health impacts

We have assumed that there will be no impact upon health, either negative or positive, arising from these proposals. Updates to the DDPS are almost universally an administrative burden imposed upon

[17] Industry figures - £440 unjustified, £3,480 is 40hrs @ £56 for preparing the DDPS and 12hrs @ £85 for reviewing the DDPS

[18] Industry figures – 20hrs @£56 (assuming that DDPS can be used as a base) for preparation of master file, and 12 hrs @ £85 for clearance at a senior level

[19] Industry figures - £440 unjustified, £1,200 is 20hrs @ £56

industry, and have limited impact upon public health. The Pharmacovigilance System Master File will continue to be reviewed at regular inspection intervals by MHRA inspectors, which will continue to identify any areas for action at the same rate as previously. Links between pharmacovigilance and improvements to public health are tenuous, however, so we cannot test this assumption. We have estimated that ADR harm would have to increase by approximately 0.02% in order for the estimated benefits to industry to be offset by health losses. We are not claiming that this would happen in practice.

Additional transitional proposals

To ensure that benefits are realised as soon as possible, the UK is currently working on proposals that will aim to remove the need for MHRA to receive DDPS from MAHs from the implementation date of 2 July 2012. We are considering permitting MAHs to transfer from DDPS to master file before the final implementation date of 2015, and not asking to see the DDPS from 2012. These proposals have yet to be finalised, but the present value of the savings to the UK would likely be between £1.492 million and £2.985 million (annualised at between £0.173 million and £0.347 million). When these arrangements are finalised, we expect to be able to report a regulatory "Out".

Additional Pharmacovigilance responsibilities

What's wrong with the current system?

There is a perception from the Commission that not enough time is taken by both industry and regulators to regularly evaluate and update their pharmacovigilance systems to ensure that they are fit for purpose. This was implied by their 2008 impact assessment on how the pharmacovigilance system could be improved. Issues with pharmacovigilance systems operated by marketing authorisation holders are reported regularly as a result of MHRA Good Pharmacovigilance Practice inspections.

It is also accepted that in some cases one member state may have a particular expertise that can be brought to bear on pharmacovigilance monitoring, but at the moment there are no provisions that allow one member state to undertake the pharmacovigilance monitoring responsibilities for a product in another country.

What have the Commission and the MHRA done to intervene?

Under Directive 2010/83, MAHs will now be required to audit their pharmacovigilance system at regular intervals. The appropriate frequency of this audit should be determined by the MAH (although the Commission may establish a minimum frequency) and it is expected that this would be determined by a number of factors, including the number/extent of changes to the pharmacovigilance system and company changes (e.g.. mergers). A risk-based model may be utilised to determine the frequency and scope of audits, and inspectors will review the rationale for the frequency of such audits at regular intervals.

As well as a responsibility of the marketing authorisation holder, there is now also a duty upon the MHRA to regularly review its own pharmacovigilance monitoring system from 21 September 2013. This is not an independent audit, but instead one to be carried out by the MHRA themselves (led by personnel who are independent of the operational activities to be audited).

The Directive also allows the MHRA to delegate responsibility for pharmacovigilance tasks for certain products or substances to another member state. The MHRA would be extremely unlikely to ever do this, although it does give the MHRA the opportunity to take responsibility for another member state's pharmacovigilance tasks, although this is likely to be limited in the guidelines produced by the European Medicines Agency.

Private Sector costs

In reality, the vast majority of companies already operate a quality assurance programme which includes performing audits that focus on one or more aspects that make up the pharmacovigilance system. For global Pharma, the number of audits relating to the pharmacovigilance system conducted per year could be 10 or more, whereas a UK-only company, an audit once every two to three years may be sufficient. The industry has provided us with data from which we have estimated the cost for a single audit at £677[20]. It is noted that this is limited to the length of the audit and does not include preparation and reporting time and travel/accommodation costs of the auditor. These assumptions yield a present value

[20] Industry estimate – auditing of 12hrs @ £56

of UK costs at between £0.032 million and £0.095 million (annualised at between £0.004 million and £0.011 million)

MHRA and Department of Health (DH) Costs & Benefits

The MHRA will need to conduct a review of its own pharmacovigilance system once every two years beginning in 2013. We have assumed, based upon previous audits of other systems that each audit takes 40 hours of Grade 7 time. These assumptions yield a present value cost of £0.006 (annualised at £0.001 million)

We cannot, at present, quantify what taking on another member state's responsibilities for pharmacovigilance monitoring might cost – this would be very much based on the circumstances, the member state and the type of medicine involved. However, this it is unlikely to present much opportunity cost – in most cases we would be already monitoring the product in question.

Public Health benefits

The Commission's impact assessment on the Pharmacovigilance Directive considers the impact of avoidable adverse drug reactions upon the healthcare systems in Europe, particularly on hospital admissions. However, the IA provides no evidential link between the numbers of avoidable ADRs and the efficacy of the auditing changes in preventing the ADRs. We have trawled the literature for further evidence but have found nothing. We therefore feel unable to provide estimates of the benefits of these changes.

However, to put the scale of the costs into context, the new audit requirements would have to reduce the UK's ADR costs by less than 0.0002% in order for the benefits to justify the costs. Note that we are not claiming that this reduction would be achieved in practice.

Revised requirements for Post Authorisation Safety and Efficacy Studies

What is currently in place and how does it work?

The requirement for certain MAHs to conduct Post Authorisation Safety Studies (PASS) is not new, and was introduced under Directive 2001/83/EC. These studies are often required where clinical trials have not adequately identified the risks inherent in the medicine, and may be useful in identifying previously unsuspected adverse reactions or to confirm the safety profile of the medicine under normal conditions of use. PASS may not be conducted in such a way that promotes the medicine involved.

What's wrong with the current system?

There is widespread acceptance within the pharmaceutical community that PASS studies are rarely completed, and if so are not of a quality which allows conclusions on the safety profile of the medicine to be adequately drawn.

The system is also costly for industry, who need to respond individually to requests from member states when further information is required. This can mean a number of duplicative submissions to up to 27 member states to answer their queries on the PASS studies.

What has the Commission done to intervene?

The new Directive introduces a harmonised guiding process for and regulatory submission of non-interventional (those likely to have the lowest risk) PASS studies. All PASS studies will now be considered at an EU level, which will mean that MAHs will only need to respond to a single set of queries on their studies from all of the EU. There should not be a rise in the numbers of PASS studies required. There will be greater amounts of guidance available and more emphasis on the completion of PASS in order to benefit public health.

Post Authorisation Efficacy Studies (PAES) are a new addition to the regulatory suite, and allow Member States to request that MAHs perform further trials to prove that their medicine treats the condition for which it is prescribed under normal conditions (e.g. when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly).

These are anticipated to be a very rare occurrence, for which guidance is being drawn up by the European Medicines Agency.

PASS and PAES will now be conditions of a marketing authorisation, enabling the MHRA to take stepped regulatory action against those who fail to meet these requirements.

Private Sector costs

From our involvement in the EMA working group developing these proposals, we do not expect the number of PASS studies to increase as a result of this new legislation. The details are currently being decided at a European Medicines Agency working group, and more information will be forthcoming at a later date. However, we are expecting the rigour of PASS studies to increase, leading to higher costs per PASS. Currently we do not have any information on how much more costly each PASS will be. The Commission's IA assumed a 25% cost increase although provided no evidence to support this assumption. In order to provide an estimate, we have adopted the Commission's assumptions, but will use the consultation as an opportunity to refine our estimate. The Commission's IA reports survey results from which it has estimated that £310 million is spent annually by the industry on PASSs. Applying the Commission's 25% increase and our estimate of the UK share of costs yields a present value of between £11.504 million and £34.514 million (annualised at between £1.337 million and £4.010 million)

Industry will now be required to submit an abstract of the final PASS study report alongside a final submission as part of the conditions of their marketing authorisation.

The MHRA does not expect to impose post-authorisation efficacy studies as part of a condition of authorisation very often. We estimate that PAESs will be required between once and twice a year for the whole industry. Industry estimates that the costs of PAES studies range from £2.64m to £12.32m.[21] These assumptions yield present value costs of between £0.391 million and £10.961 million (annualised at between £0.045 million and £1.273 million).

Both PASS and PAES will be included as part of the risk management plan, will be monitored through the master file, and will become conditions of the marketing authorisation. For this reason, it is expected that these will be completed in better time and to a greater level of data quality than currently takes place. This will benefit patients and the public, as well as industry, who will benefit from better information about the performance of substances within the population and be able to better target existing medicines. The costs and benefits here are again very difficult to estimate, but should be more readily estimated before the proposed regulations are laid.

Public Health benefits

The Commission's impact assessment on the Pharmacovigilance Directive considers the impact of avoidable adverse drug reactions upon the healthcare systems in Europe, particularly on hospital admissions. However, the IA provides no evidential link between the numbers of avoidable ADRs and the efficacy of more robust PASSs. We have trawled the literature for further evidence but have found nothing. We therefore feel unable to provide estimates of the benefits of these changes to public health.

However, to put the scale of the costs into context, the PASS and PAES changes would have to reduce the UK's ADR costs by less than 0.14% in order for the benefits to justify the costs. Note that we are not claiming that this reduction would be achieved in practice.

Additional monitoring arrangements

What is currently in place and how does it work?

In the UK, we currently have a scheme called the 'Black Triangle' (▼), a symbol that is placed upon medicines packaging to denote that the medicine is under a period of intensive monitoring. Typically, the black triangle is applied to new medicines where the side effects are not fully known, and it is intended to both inform prescribers and patients that less is known about the medicine than in some other cases, and to encourage them to be vigilant and report any adverse reactions to the medicine.

What's wrong with the current system?

The UK's black triangle system is a national system, and quite unique within Europe at present. The Commission has decided, from evidence supplied by the MHRA, that additional monitoring would be a useful regulatory tool for all of Europe.

What has the Commission done to intervene?

The new Directive 2010/84/EU creates an 'additional monitoring scheme' that closely mirrors the UK's current systems. The major change is that it will now be applied across Europe evenly to a set list of

[21] Based upon estimates for a typical interventional clinical trial in more than one European country

substances - which may be slightly different from the UK's current list, requiring adaption or phased transition. Medicines information will need to be updated to take account of the specifics of the additional monitoring scheme.

Private sector costs

We expect that in future, fewer products will be covered by additional monitoring than are currently by the Black Triangle Scheme in the UK, although this is still being decided by an EU working group. Industry has calculated that on average it costs an extra £4,700[22] per annum for products that are on the black triangle scheme at present. Industry have also supplied us with a figure of 5% cost saving likely to take place due to the changing requirements brought about by the new Directive.

Medicines information will need to be updated to take account of the specifics of the additional monitoring scheme. This involves updating the Product information Leaflet and the Summary of Product Characteristics with specific text and the symbol for additional monitoring from the new Directive, which the EU has estimated will take 24 hours of work per product - calculated to be £1,600 per product.

While MHRA knows the number of substances that are covered by the UK's Black Triangle scheme, we do not know the number of products this involves. We will ask a specific question to industry bodies during the consultation and provide an estimate of the costs in the next iteration of this IA.

The MHRA may from time to time request that additional products be added to the list (subject to EU agreement) once the list has been developed by the European Medicines Agency – we would expect this to happen only very infrequently.

Public health impact

The systems surrounding the black triangle scheme in the UK are very similar to those put forward by the Commission under additional monitoring arrangements. However, any reduction in the numbers of those medicines covered by the scheme could conceivably lead to a higher level of ADRs – as safety signals for new products not being intensively monitored could lead to a slight lag in the action taken upon them. We assume that this would only happen exceedingly rarely, but note that as the link between pharmacovigilance and increases in public health cannot be proven by our analysis, nor any that we can locate, there remains a possibility that the impacts could be greater (or lesser).

MHRA and Department of Health (DH) Costs & Benefits

The MHRA will be required to publish a list of those products covered by the additional monitoring scheme, although we do not expect this to cost us anything further in terms of resource compared to the current system, as a list of Black Triangle Scheme products is already produced and made publicly available by the MHRA.

Centralisation of literature monitoring for certain substances

What is currently in place and how does it work?

As part of their marketing authorisation, MAHs must at present perform literature monitoring to ensure that any extra studies or individual case reports printed among certain journals are taken into account as part of their continuous evaluation of the safety profile of the drug. They must also report to the competent authorities a subset of individual case safety reports identified and also incorporate information on published studies in PSURs that may have a bearing upon the safety profile of the medicine.

What's wrong with the current system?

The monitoring of hundreds of journals and many other forms of media for specific entries on certain medicines is an onerous task for the industry. This is particularly a problem for the generics industry – many of whom are duplicating effort (sourcing and reporting the same reports), and are small businesses who expend resource in outsourcing the literature monitoring role to companies who perform it for them.

What has the Commission done to intervene?

The new Directive removes the obligation to monitor for a set list of medicines (extent yet to be determined), and obliges the European Medicines Agency to perform this task in future. The reports will be entered onto a centralised system known as the EudraVigilance database. However, whilst the

[22] Unjustified figure supplied by industry

monitoring elements have been reduced, MAHs will still be required to report to the EMA on reports contained within any other literature where these concern their products.

Private Sector costs and benefits

The burden of literature reporting will be reduced, as MAHs will not be required to report ADRs published in the literature for certain substances from publications reviewed by EMA, throughout the EU. The costs for this task will move from businesses to the European Medicines Agency. Whilst the new legislation may reduce burden in terms of reporting of suspected ADRs from the literature, MAHs will still be required to review the scientific and medical literature to detect any new safety data that concerns their products and factor these data into their ongoing safety monitoring. If MAHs have reporting responsibilities outside of the EU, the same literature may nevertheless have to be monitored for reportable ADRs, depending on how quickly EMA make available each reportable case through EudraVigilance. Finally, following budget constraints within Europe, the EMA is considering ways in which this role could be reduced or removed.

Some benefits would unambiguously arise if the European Medicines Agency makes the reports on EudraVigilance available to all via their web-portal. This is not likely to aid larger companies, who already contract agencies to conduct literature monitoring for them, but may have a positive impact on smaller companies, who may not need to purchase these articles from web archives in future. The purchasing of articles online typically costs £10-12 per article, and industry contacts that are smaller companies have estimated that on average they would have to purchase 75 of these per year. The EU estimate (according to the Pharmacovigilance Directive's impact assessment) on the size of the pharmaceutical market would put 20% of companies as having fewer than 100 employees. These assumptions yield annual benefits to the UK of between £0.003 million and £0.010 million starting in 2015.

Health impact

We have assumed that there will be no negative impact upon public health arising from these proposals. Literature monitoring forms a very small part of the total monitoring of safety signals that companies perform, added to which is the fact that reporting of these signals will still have to take place. Essentially, the industry will receive and process the same number of reports as they had in the past, and no safety signals will be missed, leading to no change in public health.

Harmonisation of reporting processes through the use of the EudraVigilance Database

What's wrong with the current system?

At present, there is no reliable database in the EU that can store essential information, such as adverse drug reactions and is accessible to all. The EudraVigilance database already exists, but is not fully functional, or fit for purpose. The Commission views this central information repository as an essential step towards ensuring that harmonisation of member states' systems and decisions takes place.

What has the Commission done to intervene?

As mentioned by a number of other areas above, the Commission proposes to further develop its existing EudraVigilance database, so that it can be used a single portal for receipt of reports (such as Adverse Drug Reaction reports (ADRs)) from MAHs, as well as simultaneously transmit these safety update reports to the competent authorities in which the marketing authorisation is held. This single reporting portal should significantly reduce the amount of duplicate reporting that MAHs currently undertake. However, the portal is unlikely to go live until 1 January 2015, to ensure that it is fully functional (and to give it time to be independently audited as such).

Added to this, and an area of real benefit, is that because of worksharing arrangements, there will be a single request for further information on these ADRs (rather than at present, where up to 27 member states can request further information), and MAHs will only need to reply to this single request.

The MHRA will continue to run the UK's existing national Yellow Card Scheme in order to encourage healthcare professionals and patients to report ADRs directly to the MHRA. This ensures that a link is kept between prescribers, patients and the MHRA, as well as the already well established link between industry and the MHRA. It also aims to preserve wider access to reports that might not have been captured or notified to the MAH and gives the MHRA a broader view of the safety profile of any given substance within the general population.

Private Sector benefits from harmonised reporting

The impact of these proposals varies widely – the Commission IA expects that some companies will see little benefit, others as much as 80% from improved worksharing and reduction in duplicate reporting. During MHRA's informal consultation Industry has estimated a likely benefit of £69,000[23] per year per company for these proposals. These assumptions yield annual benefits of between £1.439 million and £4.318 million starting in 2015 (present value of between £6.918 million and £20.753 million).

Private sector costs from having to report non-serious ADRs

Non-serious ADRs in Europe will now also need to be reported to EudraVigilance, whereas in the past this had not been the case. This will increase the numbers of reports that will need to be sent by companies to EudraVigilance, and according to an industry source, will likely cost £48,400[24] per year per company in increased reporting. This is based on additional expedited reporting in certain cases, tighter timelines for reporting non-serious ADRs, more systematic review and recording of the ADRs themselves and checking these non-serious ADRs against clinical databases. This assumption yields annual costs to the UK of between £0.534 million and £1.603 million starting in 2015 (present value of between £4.599 million and £13.798 million).

Currently, ADRs reported by industry to the regulator are required to be confirmed by a health care professional; however MAHs will be required to report all ADRs irrespective of health care professional confirmation from July 2012. Therefore, it is likely that the impact on companies who predominantly market over-the-counter products (e.g. mouth ulcer products, indigestion tablets, cough syrups etc.) will be greater. These companies receive a greater proportion of non-serious ADRs that are unlikely to be confirmed by a healthcare professional, as a proportion of their total ADR dataset and would have to expend more resource on the reporting of ADRs, as a proportion of their current workload relating to reporting.

Public Health benefits from reporting of non-serious ADRs

Greater attention being given to non-serious ADRs by industry could conceivably lead to safety signals being addressed earlier, thereby avoiding further ADRs relating to the same issue. The Commission's impact assessment on the Pharmacovigilance Directive considers the impact of avoidable adverse drug reactions upon the healthcare systems in Europe, particularly on hospital admissions. However, the IA provides no evidential link between the numbers of avoidable ADRs and the efficacy of reporting of non-serious ADRs. We have trawled the literature for further evidence but have found nothing. We therefore feel unable to provide estimates of the benefits of these changes.

However, to put the scale of the costs into context, the new non-serious ADR requirements would have to reduce the UK's ADR costs by less than 0.03% in order for the benefits to justify the costs. Note that we are not claiming that this reduction would be achieved in practice.

Greater accessibility to the public of key safety documents

What's wrong with the current system?

The Commission would like to encourage greater transparency of the safety profiles of medicines in circulation. The general public is increasingly able to access and use information to make informed decisions on the medication that they are prescribed, and greater accessibility to these documents, as well as drafting them in a way that can be understood by the layman will encourage them to do so.

What has the Commission done to intervene?

Various documents are now to be posted upon the national web portals of the MHRA and the European Medicines Agency – for the former, this will be;

- Public Assessment Reports;
- Summaries of Product Characteristics;
- Patient Information Leaflets;
- Lay summaries of Risk Management Plans;
- The list of those products subject to additional monitoring; and

[23] Industry estimate 1FTE reduced to 0.2FTE because of the proposals

[24] 1. Additional expedited reporting of approx. 3000 non-serious cases/year for 5'/case -> approx. 0.2 FTE -> 15000 €;.2. Reconciliation of non-serious study cases with clinical databases: effort multiplied by factor 10, ca. 0.5 FTE -> 40000 €; 3. higher costs of additional reconciliation could be prevented by switching to inter-company E2B reporting and automatic acknowledgement of receipt. Further costs were supplied by respondent, but are disputed by MHRA, as they are duplication of current practice.

- Information to healthcare professionals and the public on ways to report suspected ADRs via the web.

MHRA, Department of Health (DH) and wider Government Costs & Benefits

It is likely that greater access to certain key safety documents will have a beneficial effect – both in terms of their confidence in medicines and knowledge that safety is continually being assessed by the pharmaceutical industry and the Government. This may also have the beneficial effect of encouraging further reporting from those who have suffered ADRs. These reputational costs are difficult to quantify and are therefore listed only qualitatively. However, the MHRA already has a good reputation in the EU, as we already accept patient reports and follow up with enquiries, as well as proactively work to encourage such reporting.

There will be a minor incremental cost to the MHRA of publishing these documents, expected to be the equivalent of 24hrs per annum of an HEO's time. These assumptions yield an annual cost of £662 (present value £4,715)

Penalties for failure to meet the conditions of an authorisation

What is the situation at present?

The UK already has a series of penalties that apply to failure to meet the conditions of a marketing authorisation granted by the MHRA. The most severe penalties that we can impose for these failures is: on summary conviction (in a Magistrate's Court), to a fine (not exceeding the prescribed sum); on conviction on indictment (in Crown Court), to a fine or to imprisonment for a term not exceeding two years or to both.

What has the Commission done to intervene?

The Pharmacovigilance Directive requires that:

'Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties'

Further penalties are proposed as part of these transposition measures, although many are based upon previous or similar penalties. The costs of these will be determined at a later date with the aid of the Ministry for Justice (see the Justice Impact Test section below). The MHRA operates a step-wise process to tackling non-compliance, therefore it is very unlikely that these penalties would be used as a first option by the MHRA and only in rare circumstances would this be considered; if a breach of an obligation results in significant harm to patients or is considered to be in the public interest. The MHRA has so far never brought a case based upon pharmacovigilance offences only.

Introduction of infringement notices

What's wrong with the current system?

Criminal prosecution is a challenging, time-consuming and resource-intensive option. Investigations with a view to criminal prosecution for pharmacovigilance offences have been conducted (most notably the Seroxat investigation[25]), but, to date, no case has been brought to court. The pursuit of a criminal penalty for the majority of offences committed within the area of pharmacovigilance is unlikely to be in the public interest. They cost too much to the justice system, are based upon an extremely technical piece of law, and cost the MHRA a great deal of resource in terms of bringing evidence to a prosecutable criminal standard of proof. Instead, the MHRA is more likely to take action against the Marketing Authorisation (e.g. variation, suspension or revocation) and/or require detailed commitments from the MAH in the form of a Corrective and Preventative Action plan.

How does the MHRA propose to intervene?

The MHRA considered a number of civil sanctions that would complement the existing and new criminal sanctions proposed by the Directive. These were rejected as disproportionate options.

The MHRA instead intends to use the 'infringement notice' – a notice sent to an organisation where MHRA has objective grounds to consider a breach of an obligation has occurred. This would specify the steps that the organisation must take and in what timeframe, in order to rectify the non-compliance and

[25] MHRA press release on Seroxat investigation: http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con014162.pdf

also take steps to prevent a further case of non-compliance. This notice would be made publicly available and it would also be sent to the EMA and the European Commission.

Private Sector costs and benefits

It should be noted that no additional regulatory requirements would be created by introducing the infringement notice, so there will be no impact on the vast majority of MAHs that are compliant. It is not envisaged that this would place additional burden on industry; the only cost to non-compliant MAHs would be the cost to comply with existing requirements.

MHRA and Department of Health (DH) Costs

The introduction of the infringement notice process would place some additional administrative burden on the MHRA, but it is anticipated that these notices would only be used in a small number of cases (approximately 4 per year). It is proposed that the existing Inspection Action Group (IAG) would determine whether an infringement notice was appropriate in the first instance. Since IAG already discuss and administer warning letters and the Inspectorate holds company meetings, this burden is likely to be negligible.

Public health impacts

The only foreseeable change to public health might be a minor benefit as those companies that are persistent in their non-compliance become compliant more quickly. This would result in their pharmacovigilance systems becoming more effective, and the chance that specific ADRs are turned into safety signals that affect the way the medicine is prescribed. This in turn might lead to a reduction in ADRs. However, this assumption is tenuous at best, and given the lack of evidence that we have been able to source between these proposals and public health, the impact is unquantifiable.

Summary and net benefits

The table below sets out the costs and benefits proposed by the scheme. We acknowledge that there are gaps in our analysis. We will address these gaps through the consultation process.

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	PV	Annualised
Transition costs	0.0	0.4	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.7	0.1
Annual recurring costs	0.0	2.0	4.1	4.1	6.0	6.1	6.1	6.1	6.1	6.1	38.5	4.5
Total annual costs	0.0	2.4	4.1	4.1	6.2	6.1	6.1	6.1	6.1	6.1	39.0	4.5
Transition benefits	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Annual recurring benefits	0.0	0.9	1.8	1.8	10.6	10.6	10.6	10.6	10.6	10.6	55.1	6.4
Total annual benefits	0.0	0.9	1.8	1.8	10.6	10.6	10.6	10.6	10.6	10.6	55.1	6.4
Net benefits	0.0	-1.5	-2.3	-2.3	4.4	4.5	4.5	4.5	4.5	4.5	16.1	1.9

This summary table should be read with some caution. In several sections of this IA[26], we have acknowledged that we have been unable to estimate the public health benefits of measures that introduce new burdens on the private and public sectors. The table below summarises the costs of the burdens for which we have been unable to estimate benefits.

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	PV	Annualised
Transition costs	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0
Annual recurring costs	0.0	2.0	4.0	4.0	6.0	6.0	6.0	6.0	6.0	6.0	38.1	4.4
Total annual costs	0.0	2.2	4.0	4.0	9.4	9.4	9.4	9.4	9.4	9.4	55.0	6.4

To put the scale of the costs into context, the new cost imposing measures would have to reduce the UK's ADR costs by less than 0.12% in order for the benefits to justify the costs. Note that we are not claiming that this reduction would be achieved in practice.

Having put these costs into context, we should do the same for the cost savings (benefits) that accrue to industry (annualised estimate £3.751 million). Throughout this IA we have assumed, plausibly we

[26] "Risk Management Plans and Risk Management Systems", "Additional Pharmacovigilance responsibilities", "Revised requirements for PASS and PAES" and "Harmonisation of reporting processes through the use of the EudraVigilance database".

believe, that these cost saving measures have no impact on public health. However, we should allow for the possibility that the assumption is wrong. We have estimated that ADR harm would have to increase by 0.1% in order for the cost savings to be offset entirely by ill health effects. Again, note that we are not claiming that this increase would occur in practice.

We estimate that the NPV to the global pharmaceutical industry is -£158 million (annualised at -£18.3 million)

The key uncertainties that exist in our analysis surround:

- the cost increases imposed by the requirement to conduct more robust Post Authorisation Safety Studies and Post Authorisation Efficacy Studies (present value of UK costs estimated at between £11.9 million and £45.5 million, annualised at between £1.4 million and £5.3 million). We will address this uncertainty during the consultation.
- the evidence that links changes in pharmacovigilance to changes in ADR harm.

In conclusion, we have estimated costs and cost-savings attached to a wide variety of discrete pharmacovigilance activities, each of which has the potential to change the harm caused by ADRs. The evidence that links relatively small changes in pharmacovigilance activities to ADR harm is too weak to complement our cost change estimates with the estimated value of changes in public health. Our estimated NPV of £14.4 million is therefore unlikely to represent the true balance between costs and benefits of this package of pharmacovigilance measures. We have pointed out what scale of health changes would be required for the costs and cost-savings to yield a £0 NPV but have been unable to comment on the likelihood of these changes occurring in practice.

Principal evidence sources

The most extensive survey of the costs and benefits of pharmacovigilance was last conducted by a European Commission Impact Assessment in December 2008, which accompanied their initial proposals for changes to the pharmacovigilance legislation. Where possible, these figures have been incorporated into this impact assessment, appropriately scaled down and adjusted for the size of the UK market and the time that has passed since the survey was carried out.

The MHRA has also engaged with a group of industry stakeholders to verify the figures put forward by the impact assessment – where these have been found not to match, current industry estimates have been favoured.

Finally, other sources have been used where there are gaps in knowledge – such as medical studies and literature on pharmacovigilance, as well as verifiable sources posting figures on external websites.

Equalities

Pharmacovigilance and adverse drug reactions are areas that are not confined to any single area of the general public, and affect all equally. The MHRA currently makes sure that the information on its website and the reporting systems that it encourages the public to use are as accessible to the public as possible, and will continue to do so in future. We will also continue to look for ways to strengthen the reporting and receipt of timely information from all sections of the public on the safety of medicines.

Risks

The figures provided were sourced through a questionnaire sent to industry, and have been averaged along the responses given. However, responses were limited, and so the sample of answers retains a fair degree of potential inaccuracy. For this reason, respondents will be encouraged to reply to the consultation with further information on the costs and benefits of this proposal in order to further augment our current calculations.

There is a great deal of work ongoing at the European Medicines Agency to determine the detail on how many of the procedures introduced under the Pharmacovigilance Directive will operate in future. The complexity or simplicity of those procedures and the roles of the industry and regulators will determine the costs and benefits of these proposals. Whilst the proposals are being progressed as quickly as possible, many will not be finalised by the point at which this consultation impact assessment is

published, and some will not be decided until after the UK's transposition arrangements come into force. There is therefore a real and unavoidable lack of knowledge that arises from continued development of these proposals in Europe.

A greater focus on the benefit:risk balance, as provided for by 2010/84/EC, may lead to more pharmaceutical companies employing physicians instead of scientists. In general, physicians verify the conclusions drawn on active substances by scientists, and an increased focus on benefit:risk will raise their profile. The MHRA does not mandate how these decisions should be made within pharmaceutical companies, or by whom, but it is worth noting that a shift in emphasis could affect the types of people employed by these businesses in future.

Specific impact tests

Justice Impact Test

The transposition of the Pharmacovigilance Directive could introduce some new and updated offences relating to pharmacovigilance activities. The Ministry of Justice has been approached about the introduction of offences, and has agreed that the MHRA should engage with them to justify their introduction following the close of the public consultation on the proposed text.

Competition impact assessment

EU markets for originator medicines that contain innovative active substances are to some extent national. Originator companies attempt to segment markets using their control over the distribution of their products. Nevertheless parallel exports and imports have some impact on making the markets EU-wide. These markets experience strong dynamic but little static competition. Development of these medicines is always associated with high research and development costs.

EU markets for generic, off-patent medicines are largely EU-wide and experience some static competition based on price.

The costs of pharmacovigilance are without doubt a barrier to entry into both originator and generic markets. The scale of the changes brought in by the Directive is significant compared with the overall cost to industry of its pharmacovigilance activities. The EU estimates that pharmaceutical firms spend annually Euros 832.7 million on meeting the current EU pharmacovigilance requirements. We have estimated that the changes brought in by the new Directive are expected to increase this amount by approximately Euros 70 million (this is the total amount to the 950 firms that supply the EU market, and not the adjusted amount that measures UK impact) .

We therefore conclude that there will be some impact on increasing barriers to entry. We expect this only to affect competition in the generics sector. The originator sector has several much more substantial barriers to entry connected with scientific knowhow and the huge R&D costs of bringing drugs to market. We therefore do not expect that the changes brought about by the Directive will alter competition in originator markets.

Answering the competition assessment questions, we believe that the measures:

1. Are unlikely directly to limit the number or range of suppliers

2. May indirectly limit the number or range of suppliers in generics markets. However, the bulk of the impact will not be felt generics suppliers because their products' safety profiles are well understood (their medicines have been prescribed for many years)

3 Are unlikely to limit the ability of suppliers to compete

4 Are unlikely to reduce suppliers' incentives to compete vigorously

Small Firms impact test

We have assumed that none of the companies that supply the UK qualify as small firms. Although the EU has estimated that 20% of all firms that supply the EU market have fewer than 100 employees, we have assumed that any UK firms with fewer than 50 employees (an unknown proportion of the 950), have annual turnovers greater than £6.5 million and hence do not count as small firms under the UK definition. We believe that this assumption is plausible because of the nature of the businesses

involved. Originator firms (those that bring new patented medicines to market) spend billions of pounds on R&D and require very substantial sales to justify their investments. It is therefore inconceivable that any originator firms would have turnovers of less than £6.5 million. Generics firms (those that produce out-of-patent medicines) operate in highly competitive environments where margins are small. These firms therefore rely on large sales to cover their fixed costs. We therefore believe that it is unlikely that any generic firm will have a turnover of less than £6.5 million. Nevertheless, we will test our assumption by asking specific questions during the consultation.

Health impact test

The impact upon health has been considered in a specific impact test, although as outlined in previous discussions, we cannot define an adequate link between these specific pharmacovigilance system changes and increases to public health through a reduction in ADRs. 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.

Annexes

Annex 1 should be used to set out the Post Implementation Review Plan as detailed below. Further annexes may be added where the Specific Impact Tests yield information relevant to an overall understanding of policy options.

Annex 1: Post Implementation Review (PIR) Plan

A PIR should be undertaken, usually three to five years after implementation of the policy, but exceptionally a longer period may be more appropriate. If the policy is subject to a sunset clause, the review should be carried out sufficiently early that any renewal or amendment to legislation can be enacted before the expiry date. A PIR should examine the extent to which the implemented regulations have achieved their objectives, assess their costs and benefits and identify whether they are having any unintended consequences. Please set out the PIR Plan as detailed below. If there is no plan to do a PIR please provide reasons below.

Basis of the review: [The basis of the review could be statutory (forming part of the legislation), i.e. a sunset clause or a duty to review , or there could be a political commitment to review (PIR)]; There will be a statutory duty to review after five years, in July 2017.
Review objective: [Is it intended as a proportionate check that regulation is operating as expected to tackle the problem of concern?; or as a wider exploration of the policy approach taken?; or as a link from policy objective to outcome?] The objective will be to check that the regulation has transposed the Directive with the minimum burden to industry possible, whilst maintaining the integrity of the EU harmonised proposals. Particular focus will be given to any mismatch between UK and EMA approaches that have arisen in the intervening period.
Review approach and rationale: [e.g. describe here the review approach (in-depth evaluation, scope review of monitoring data, scan of stakeholder views, etc.) and the rationale that made choosing such an approach] The review will take place as a scope review of the MHRA data on pharmacovigilance, as well as engagement with industryto provide a critical review of the transposition, and an evaluation of how other member states implemented the Directive. The rationale is that this should give us a broad-spectrum analysis of the impacts of the Directive incorporating different stakeholder viewpoints.
Baseline: [The current (baseline) position against which the change introduced by the legislation can be measured] The current situation in the UK (with the pharmacovigilance legislation as it currently stands, prior to July 2012) is considered the baseline.
Success criteria: [Criteria showing achievement of the policy objectives as set out in the final impact assessment; criteria for modifying or replacing the policy if it does not achieve its objectives] Success will be an implementation of the Directive that is not subject to infraction proceedings, and that as far as possible is adapted to changes proposed by the European Medicines Agency. An alleviation of current defined burdens upon industry, and a movement towards a more risk-targeted approach for pharmacovigilance will also be key success criteria.
Monitoring information arrangements: [Provide further details of the planned/existing arrangements in place that will allow a systematic collection systematic collection of monitoring information for future policy review] The MHRA has an ongoing data collection function for pharmacovigilance, and will continue to engage with the industry on pharmacovigilance concerns. We are also present on EMA working groups and in other European for a.
Reasons for not planning a review: [If there is no plan to do a PIR please provide reasons here] N/A

Annex 2

Measuring the Opportunity Cost of NHS Spending

The total NHS budget is fixed, in a given period. Any funds committed to new policies must therefore be reallocated away from some other use, elsewhere in the NHS. To fully reflect the impact of a particular policy, it is important to consider the effect of reallocating funds away from this alternative use. The impact of reallocation is the policy's true cost – or "opportunity cost" – that must be measured in Impact Assessments.

To calculate the impact of reallocating funds to a new policy, it is necessary to determine how much benefit would have been realised from the alternative use of those funds. This can be done using DH's standard estimates of the amount of benefits generated by NHS treatments "at the margin" that may be withdrawn if the availability of funding is reduced. These marginal treatments have been estimated to provide health benefits - measured in Quality Adjusted Life Years (QALYs) - at a *cost* of £25,000 per QALY. Importantly, however, society is currently estimated to *value* these QALYs more than twice as highly - at £60,000.

This 2.4:1 ratio of benefits to costs implies that the alternative use of a given quantity of NHS funds will generate benefits valued 2.4 times as highly. This means that any policy which involves spending from the NHS budget will deprive society of benefits worth 2.4 times as much (before the policy's own benefits are taken into account). Similarly, any cost saving measure that releases NHS budget to be spent elsewhere is expected to provide benefits valued at 2.4 times the cost saving.

To correctly reflect the cost impacts of policies and programmes, all effects on the NHS budget should therefore be multiplied by 2.4 in order to calculate their true cost to society. This adjustment reflects the amount of benefits lost by diverting spending to the policy in question – and it follows that the policy should itself generate greater benefits, in order to provide an overall positive impact.

Example

A policy to provide a new service will incur costs of £2m, which will fall on the NHS budget. It is expected to generate patient benefits worth £3m. What is the net benefit?

At first glance this policy might appear good value for money, as the benefits to society outweigh the costs to the NHS. But we know that costs to the NHS do not equate one-for-one with costs to society – and it is the net impact on society that should be calculated. Because we estimate that society's benefits from spending an extra £1 in the NHS are worth £2.40, the withdrawal of £2m from the NHS budget, as proposed in this policy, would deprive society of benefits worth £4.8m. So the social costs of the policy are £4.8m – and these outweigh the social benefits of £3m, giving a negative net benefit of -£1.8m.

Annex 3: Background to Pharmacovigilance

Pharmacovigilance is the monitoring of a medicine once it has reached general population in order to interpret safety reports that identify potential changes to the way that the medicine should be used. Whilst extensive testing takes place in clinical trials during the development of a medicine, the way that medicines will react with a minority level of patients in the population is never known, and unforeseen side effects cannot be accurately measured during small samples such as are used in human trials. Pharmacovigilance, along with the regulatory structure for medicines that exists today, was brought about in part due to the Thalidomide tragedy of the 1960s, where safety signals regarding the effects of Thalidomide on unborn children were not interpreted quickly enough to prevent an estimated 10,000 children being born worldwide with limb defects.

Medicines safety signals are often in the form of adverse drug reaction (ADR) reports sent to medicine Marketing Authorisation Holders (MAHs) and national authorities (in the UK's case the Medicines and Healthcare products Regulatory Agency, MHRA) from patients and healthcare professionals. The UK also has an advanced system of reporting compared to many other European Member states. This is known as the Yellow Card scheme, and allows professionals and members of the public to report to the MHRA any suspected ADRs. If the available data received from safety reports points to a problem– for instance that a large number of people taking the medicine find that they are having increased levels of gastro-intestinal problems, then a decision is made by the MAH or MHRA that the safety profile of the medicine has changed, and the MAH would be compelled to make changes to the information associated with the product. A number of other steps may also be taken, including requirements to undertake further studies on the medicine. MAHs are also responsible for scrutinising the performance of their product in the population through the monitoring of medical literature.

Safety reporting, recording and monitoring is therefore a very important function of both pharmaceutical companies and the MHRA. The more data that is received and processed, combined with timely action taken; the smaller the risk to patients from medicine. The rules surrounding the harmonised processes for this were first laid out in Directive 2001/83/EC, and allow for a number of different areas to be set up to monitor and identify safety signals. Some significant areas that are mandated are;

- Risk Management Plans – these are submitted by MAHs as part of their applications for a marketing authorisation, and are designed to give an overview of key areas for safety monitoring that will not have been identified by the relatively small numbers of patients exposed to the medicine as part of the clinical trials development process. RMPs encourage proactive monitoring of safety signals, and allow an opportunity for the company to tailor their pharmacovigilance plans to an individual product; and
- Periodic Safety Update Reports – as the name suggests, these are safety reports on products submitted routinely by companies to the MHRA in order that those products that are newer or require closer monitoring are carefully scrutinised – so that the latest safety information can be passed to patients.

However, it is clear that more can be done to maximise the number of safety signals that are received, whilst at the same time streamlining and harmonising the pharmacovigilance system, which should bring about benefits for the pharmaceutical industry. There are a number of significant areas that currently cause difficulties for companies and regulators (and by extension, patients), and the size of the problem was last estimated during the Commission Impact assessment that accompanied the draft Pharmacovigilance proposals in December 2009 [ref]. These were carried out as a view of the whole of the EU pharmaceutical market, and concentrated on the costs to society arising from avoidable adverse drug reactions. The study outlined the impact that ADRs have on the EU – they are suspected to be the fifth most common cause of death in the EU, accounting for 3-10% of all hospital admissions. The study estimated that between 100,000 and 200,000 deaths are caused by ADRs in the EU every year, and that there is a €79bn annual societal cost. Avoidable ADRs (those that might have been identified through better reporting, or thorough reduction in prescriber error) were estimated as 30%, of which the Commission hoped between 1% and 10% of all currently avoidable ADRs, at a health saving of between €237m and €2.4bn.

The pharmaceutical industry is global, and so benefits from harmonised procedures across member states wherever these are in place. The existing EU Directive 2001/83/EC made significant advances in simplifying and harmonising pharmacovigilance processes, but these can still be very costly for businesses, and could be streamlined in order to make real public health gains. The European Commission undertook to look at the existing legislative structure surrounding pharmacovigilance in 2007, and published their first draft proposals in December 2008. These have been extensively

negotiated by the MHRA and other member state representatives in the European Council, and agreed in the European Parliament in late 2010 (as 2010/84/EU).