EXPLANATORY MEMORANDUM TO

THE MEDICINES FOR HUMAN USE (MANUFACTURING, WHOLESALE DEALING AND MISCELLANEOUS AMENDMENTS) REGULATIONS 2005

2005 No. 2789

1. This explanatory memorandum has been prepared by the Medicines and Healthcare products Regulatory Agency, on behalf of the Department of Health and is laid before Parliament by Command of Her Majesty.

This memorandum contains information for the Joint Committee on Statutory Instruments.

2. Description

2.1 This instrument replaces, as respects medicinal products to which the relevant EU legislation applies ("relevant medicinal products"), the existing regulations which implement the EU legislation (Directive 2001/83/EC) relating to the manufacture of and wholesale dealing in medicinal products for human use in the United Kingdom. It also implements the provisions of Directive 2004/27/EC (which amends Directive 2001/83/EC) relating to the manufacture of and wholesale dealing in medicinal products in the United Kingdom. It also makes related amendments to the Medicines Act 1968 and to other related enactments.

2.2 In replacing, for relevant medicinal products, the legislation which implemented Directive 2001/83/EC, (the Medicines (Standard Provisions for Licences And Certificates) Regulations 1971, as amended (SI 1971/972)), the opportunity has been taken to clarify certain measures which implement some of the requirements of the 2001 Directive or to align them more clearly with the provisions of Directive 2001/83/EC which they implement.

3. Matters of special interest to the Joint Committee on Statutory Instruments

3.1 This instrument has been laid before Parliament less than 21 days before it is due to come into force (30th October 2005). The instrument was prepared and ready in draft last week, but it was not possible, in the time available, to obtain the necessary seals of the Department for Health, Social Services and Public Safety, Northern Ireland, and the Department for Agriculture and Rural Development, Northern Ireland, so as to enable the instrument to be laid more than 21 days before coming into force. The Department recognises that it should have allowed additional time for obtaining those seals.

3.2 As explained in paragraph 4.3, this instrument is one of a number of statutory instruments which implement Directive 2004/27/EC. The final date for transposition of the Directive is 30th October 2005, as set out in Article 3. Failure to transpose by that date would place the United Kingdom in breach of

its obligations under Community law. The Department's view was that, despite the delay in laying, the instrument should come into force on 30th October 2005, in order to ensure adequate and timely implementation of the Directive.

3.3 As set out in paragraphs 7.2 and 7.3 , the proposals for amendment of the legislation relating to manufacturing and wholesale dealing of medicinal products have been widely consulted on by the Medicines and Healthcare products Regulatory Agency. Companies in the pharmaceutical industry, who are the main stakeholders affected by the instrument, are aware of the proposed changes and expect them to be implemented on 30th October.

4. Legislative Background

4.1 The instrument is made under section 2(2) of the European Communities Act 1972 and sections 18(1), 47(1) and 129(1) and (5) of the Medicines Act 1968. It implements certain provisions of Directive 2004/27/EC ("the 2004 Directive") which amends Directive 2001/83/EC on the Community code relating to medicinal products for human use ("the 2001 Directive"). It also clarifies the implementation in the domestic legislation of certain requirements of the 2001 Directive and, in some cases aligns the wording of the domestic legislation more closely with the wording of the 2001 Directive.

4.2 The 2001 Directive is the main piece of EC legislation governing medicinal products for human use and consolidated most of the previous EC legislation in the area. The provisions of the 2001 Directive are implemented in the UK by the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 (as amended) and as respects the manufacture of and wholesale dealing in relevant medicinal products, by the Medicines (Standard Provisions for Licences and Certificates Regulations 1971 (as amended).

4.3 The provisions of the 2004 Directive will be implemented in the UK by: the Medicines (Marketing Authorizations Etc.) Amendment Regulations 2005; the Medicines for Human Use (manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005; the Medicines (Homoeopathic Medicinal Products for Human Use) Regulations 2005; and the Medicines (Advertising Amendment) Regulations 2005. Separate explanatory memoranda have been prepared for each statutory instrument. A Transposition Note in relation to the implementation of the 2004 Directive is attached.

5. Extent

5.1 This instrument applies to all of the United Kingdom.

6. European Convention on Human Rights

6.1 The Minister of State for Quality and Patient Safety, the Rt. Hon Jane Kennedy MP, has made the following statement regarding Human Rights:

In my view the provisions of the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendment) Regulations 2005 are compatible with the Convention rights.

7. Policy background

7.1 The Government's overriding objective when negotiating the new legislation was to further guarantee the public health protection of UK citizens through effective regulation of medicines for human use. We also aimed to rationalise the regulatory system to bring about grater harmonisation between member Sates and prepare the regime for enlargement of the EU. These Objectives were achieved.

7.2 Following agreement of the 2004 Directive in March 2004, the Government consulted widely on our proposed implementation of these measures, bearing in mind the need for a harmonised approach to certain provisions across the EU. The Government also consulted on certain areas where it considered that the legislation which implemented the requirements of the 2001 Directive as respects the manufacture of and wholesale dealing in relevant medicinal products would benefit from clarification.

7.3 Forty-four responses were received on the consultation – most of which related to the provisions being implemented by The Medicines (Marketing Authorisations Etc) Amendment Regulations 2005. Further information can be found in section 3(ii) of the attached Regulatory Impact Assessment (Appendix A). Whilst forty–four responses (of which 31 offered substantive comments) were received from consultees on the main body of proposals, there were none at all in respect of the additional changes to legislation in relation to manufacturers and wholesale dealers. This implies that the industry is content with the nature and scope of the proposals. A second full Regulatory Impact Assessment relating to the proposed changes implementing the review and other changes to legislation is attached (Appendix B).

7.4 Manufacturing and Wholesale Dealing activity in the United Kingdom is currently regulated by the Standard Provisions Regulations 1971[1] (which have been amended nine times over the years). Those regulations are disapplied as respects relevant medicinal products by this instrument which replaces them as respect those products.

7.5 This instrument provides that those obligations which implement requirements of the amended Directive will be compulsory provisions of manufacturer's and wholesale dealer's licences. It also prescribes further provisions for such licences which are not obligations set out in the Directive. These fall into a non-compulsory category and may be imposed at the discretion of the licensing authority.

[1] The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971, as amended (S.I. 1971/972)

7.6 In preparing the new regulations the drafting of the obligations which appeared in the Standard Provisions Regulations has been modernised and clarified in certain places. No obligations which did not appear in the Standard Provisions Regulations are being imposed on licence holders other than those which arise directly from requirements of the 2001 Directive (as amended).

7.7 The following summarises the main effects of the replacement (for relevant medicinal products) of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 by the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 by reference to the relevant Article of the 2001 Directive as amended by the 2004 Directive.

Article 46, 46a and 47 – manufacturing

7.8 These Articles reflect new Community requirements on pharmaceutical companies to adhere to the principles of Good Manufacturing Practice (GMP) in the manufacturing processes (production and quality control) of active substances used as starting materials. The requirement is for manufacturers to use as starting materials only active substances which have been manufactured (including total and partial manufacture and import, re-packaging or re-labelling) in accordance with the detailed guidelines on GMP for starting materials. These provisions for manufacturers and importers have been implemented in the Regulations, which require manufacturers and importers to only use active substances as starting materials that have been manufactured in accordance with GMP. The Regulations create a new offence such that a person who sells or supplies an active substance that does not comply with GMP practice commits an offence.

Articles 49 and 50 – obligations (qualifications and experience) on the Qualified Person

7.9 These are minor amendments to the obligations relating to the qualifications and experience required of a Qualified Person.

Article 51 – duties of the Qualified Person

7.10 This extends the need for full batch analysis and testing (or re-testing) in a Member State to product imported from third countries (i.e. outside the Community), - whether or not the product was originally manufactured in the Community.

Article 76 – distribution

7.11 Distributors that import medicinal products from other Member States are required to notify both the Marketing Authorisation (MA) holder and the

competent authority of the member state to which the product is imported of the intention to import.

Article 81 - distribution

7.12 This is a new provision which places an obligation on the MA holder and the relevant distributor of a medicinal product to ensure appropriate and continued supply of the product to pharmacies and other authorised suppliers, in order to meet patients' needs. It is linked with the new Article 23a, which places requirements on the MA holder to inform the competent authority of the various activities associated with the availability of the product on the market. These Regulations impose this obligation on distributors of relevant medicinal products. The Medicines (Marketing Authorizations Etc) Amendment Regulations impose an equivalent obligation on marketing authorization holders.

Article 111 – inspections

7.13 The amending Article gives the competent authority the power to carry out inspections (which may be unannounced) at the premises of manufacturers of active starting materials, or at the premises of MA holders or any firms employed by the MA holder where there are grounds for suspecting non-compliance with the GMP principles set out in the amended 2001 Directive. No specific implementing measures are required for this as the licensing authority has the necessary inspection powers by virtue of section 111 of the Medicines Act 1968. The amending Article provides for the European Pharmacopoeia to ask the Commission or the European Medicines Agency to request an inspection of a starting material manufacturer, when the material is subject to a European Pharmacopoeia monograph. Section 111 of the Medicines Act 1968 has been amended to provide powers of entry in order to inspect in these circumstances.

Other changes to legislation

Good Manufacturing Practice

7.14 An amendment to existing UK legislation is being made, making it a general requirement for holders of a manufacturing licence to comply with the principles of GMP set out in Commission Directive 2003/94/EC.

Import from third countries

7.15 Directive 2001/83/EC treats imports from third countries[2] as being part of the manufacturing framework, so requiring a manufacturer's licence. However, the UK implementation of this requirement is currently via the wholesale dealer framework. Accordingly, the Medicines and Healthcare products Regulatory

[2] The member states of the European Union, plus Iceland, Norway and Leichtenstein

Agency (MHRA – the UK licensing authority) issues Wholesale Dealer Import licenses to applicants.

7.16 The new Regulations change the licensing arrangements for third country import and make the relationship between manufacturing and import much clearer. Accordingly, the Regulations now provide that import from a third country requires a manufacturer's licence for import. This moves the issue from the provisions relating to wholesale dealing to those relating to manufacturing, consistent with the approach in the 2001 Directive. Existing licenses will be "rolled over", creating no additional burden on industry.

Wholesale distribution

7.17 Article 80(g) of the 2001 Directive imposes a requirement on wholesale dealers and importers to comply with the guidelines on good distribution practice (GDP). Although this obligation is adhered to by the industry in practice, there is no such requirement currently present in UK legislation. Accordingly, the legislation relating to wholesale distribution is being amended as part of the overall consolidation exercise to impose such a specific obligation on holders of wholesale dealer's licences.

7.18 These regulations also impose a similar requirement on manufacturers to comply with the guidelines on good distribution practice when they distribute medicinal products manufactured under their manufacturer's licence.

Export to EC/EEA countries

7.19 The existing wholesale dealing provisions are consistent with Directive 2001/83/EC, which has the effect that export to another Community Member State is a form of wholesale distribution. Export from the UK to another Member State of the European Community thus requires a wholesale dealers' licence (WDL) by virtue of section 49A of the Medicines Act 1968. However, export to European Economic Area States which are not members of the EC is also covered by the Directive - by virtue of the EEA Agreement.

7.20 Therefore, a minor amendment is being made to the relevant sections of the Medicines Act to clarify that a wholesale dealer's licence is required for export to all EEA States - not just the member states of the European Community.

Time limits for licence applications

7.21 Articles 43-45 and 78 of Directive 2001/83/EC concern the examination of licence applications and the time limits for granting a manufacturer's or wholesale dealer's licence. These are: 90 days for processing a full licence application; 30 days for a variation to a licence – plus any period of time when the clock stops due to further necessary information being required by the licensing authority. The Medicines Act does not currently specify the time limits for considering applications for manufacturer's licences or wholesale

dealer's licences; although in practice the MHRA has an obligation to comply with the limits set out in the Directive, an amendment to the Medicines Act is therefore made in the regulations to require that the licensing authority adhere to these time limits.

8. Impact

8.1 Two Regulatory Impact Assessments are attached to this memorandum.

8.2 The impact on the public sector is judged to be low – the new Regulations will, in the main, apply to pharmaceutical companies in the private sector.

9. Contact

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DRAFT FULL REGULATORY IMPACT ASSESSMENT (RIA)

1. Title of proposal

The Medicines (Marketing Authorisations Etc.) Amendment Regulations 2005; the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005; The Medicines (Homoeopathic Medicinal Products for Human Use) Amendment Regulations 2005; and the Medicines (Advertising Amendments) Regulations 2005.

2. Purpose and intended effect of measure

(i) Objectives

The attached four statutory instruments together implement amending Directive 2004/27/EC, which is part of the legislation arising from the Review of EU Medicines Legislation. The Government's overriding objective when negotiating the Review of EU Medicines Legislation was to further guarantee the public health protection of UK citizens through the effective regulation of medicines for human use. We are confident that the agreed package of measures meets this objective.

The Government therefore supported the Commission's stated objectives for the Review, which place public health protection at the forefront of their proposals to reform the regulatory regime in relation to medicines for human use:

- To guarantee a high level of health protection for European Union citizens, in particular, by making safe, innovative products available to patients as quickly as possible.
- To guarantee tighter surveillance of the market, in particular by strengthening pharmacovigilance procedures.
- To complete the Internal Market for pharmaceuticals while taking globalisation into account.
- To set up a legal framework which fosters the competitiveness of the European pharmaceutical industry.
- To take the opportunity to rationalise and, if possible, simplify the regulatory system, thereby improving its consistency, profile and transparency.
- To take the opportunity to prepare the regulatory system for Enlargement of the EU

(ii) Background

(ii)a EU legislative framework

In relation to the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005, this RIA is concerned only with the provisions of the statutory instrument that implement Directive 2004/27/EC.

There is an extensive body of EU legislation regulating the safety, quality and efficacy of medicines for human use dating back to 1965. After a recent codification exercise this legislation is now contained mainly in two pieces of legislation: Regulation 2309/93EC and Directive 2001/83/EC. The legislation sets out the rules and procedures for:

- authorising human medicinal products at National and Community level, and the issue of a MA;
- maintaining standards in manufacture, distribution and supply;
- monitoring the safety of marketed products (pharmacovigilance);
- providing information to patients.
- EC Regulation 2309/93/EC also establishes the European Medicines Evaluation Agency (EMEA).

(ii)b Review of EU legislation

In 2004, Member States (MS) and the European Parliament reached agreement on revisions to the body of EU medicines legislation. This included a new Regulation (726/2004/EC) which replaces 2903/93/EC and Directive 2004/27/EC which amends Directive 2001/83/EC relating to the Community code for medicinal products for human use.

Regulation 726/2004 has a transposition date of 20 November 2005, by which time the provisions will apply in all MS. Directive 2004/27/EC must come into force in all MS by 30 October 2005, although MS are able to implement early any of the provisions should they wish.

Following a full public consultation (reference MLX 309) and circulation of a separate RIA, the Government chose to implement early three provisions from amending Directive 2004/27/EC (Articles 1(21), (44), (45) and (54)) are therefore excluded from this exercise (ie Articles 23, 59(3, and 61(1) of Directive 2001/83/EC as amended). These provisions were implemented by the Medicines Use (MA and Miscellaneous Amendments) Regulations 2004 (SI 2004/3224).

Although this RIA focuses on the implementing measures associated with the transposition of amending Directive 2004/27/EC, they must be seen in the context of the broader objectives of the review – which also relate to provisions agreed in Regulation 726/2004. In many ways, these provisions complement those in the amending Directive. Paragraph 5 illustrates the costs and benefits associated with the provisions introduced by the Regulation. Although MS have no influence over the way in which these provisions are implemented, paragraph 5 serves to demonstrate the balance achieved by MS.

(iii) Rational for Government Intervention

The changes to the legislation are intended to strengthen the protection of public health of EU citizens through the effective regulation of medicines for human use whilst improving the competitiveness of the UK/EU pharmaceutical industry. The following measures have been identified as providing the greatest public health impact and therefore serve as the focus for this RIA:

1. More effective market surveillance of medicinal products on the UK and EU markets by:

    a) The introduction of a more robust and integrated approach to pharmacovigilance (by sharing safety data between MS and a common approach to the collection, verification and presentation of information on Adverse Drug Reactions (ADRs).
    b) Increased frequency of Periodic Safety Update Reporting (PSUR)
    c) The extension of good manufacturing practice to new areas, such as Active Pharmaceutical Ingredients (APIs).
    d) The introduction of the ability of the competent authorities to carry out unannounced inspections by the competent authority of manufacturers of APIs

2. Effective provision of appropriate high-quality information to patients by:

    a) Reordering the information to be included in the Summary of Product Characteristics (SPC).
    b) Introducing requirements for Marketing Authorisation (MA) holders to include the name of the medicinal product in Braille on the outer packaging, and make the patient information leaflet available on request from patients' organisations in formats appropriate for blind and partially sighted people.
    c) The publication of Assessment Reports generated following the granting of MAs for new products will improve the transparency of decision making.

3. Increasing the attractiveness of the EU/UK pharmaceutical market by:

    a) More effective and timely procedures for assessing MA applications by refining the Mutual Recognition Procedure (MRP) to take into account lessons learned in the 7 years since its introduction in 1998 and the introduction of an alternative Decentralised Procedure.
    b) Increasing the competitiveness of the EU regulatory regime by harmonising data and market exclusivity periods across the Community at 8 and 10 years respectively, with the possibility of an extension to 11 years if certain valuable criteria are met.
    c) The introduction of legislative definitions of 'generic' and 'reference' medicinal products, which will bring greater clarity and certainty in operating the rules for both the innovative and generics sectors of industry.
    d) The introduction of a provision to allow the development of generic copies of medicinal products and other products without infringing patent protection in force in the UK.
    e) Deregulatory measures, such as refining the renewals process. MAs must now be renewed after 5 years, and again after a further 5 years if justified on pharmacovigilance grounds. Following this, they will be valid indefinitely. This has been complemented by increasing the frequency of PSUR, which is a

less bureaucratic and more safety focussed means of ensuring public health protection.

The above measures are indicative of the range of provisions that have been agreed that support the Commission and Government's objectives for the reform. Failure to implement some or all of the agreed provisions will represent a missed opportunity to improve the quality and effectiveness of the current regulatory system, and the UK would be susceptible to infraction proceedings for failure to implement an EU Directive. Failure to implement would also lead to a fragmented system across the EU, as these provisions rely on a co-operative approach between Member States. This would jeopardise public health protection. In addition, these new provisions prepared the regime for enlargement of the EU from 15 to 25 MS. The new provisions offer real public health benefits to UK and EU citizens, whilst offering incentives to both the innovative and generics industries to invest in the development of products in the EU. This will bring medium and long term benefits to the UK/EU citizens through the development of new medicines.

3. Consultation

(i) Within Government

An inter-departmental meeting took place in October 2001, at which officials from a range of departments and the devolved administrations discussed the Commission's original proposals. The agreed position was then endorsed at Ministerial level. Further written consultation with other Government departments took place in May 2003 and December 2003 via the Ministerial Committee on European Policy.

There has been consultation within Government at official level on the implementation of the agreed legislation. However, the provisions on which this RIA is based are specific to medicines regulation and do not generally impact on other departments, besides the Department for the Environment, Food and Rural Affairs, which is responsible for the regulation of medicines for veterinary use and the implementation of the corresponding veterinary Directive (2004/28/EC). Bilateral discussions have taken place with DEFRA to ensure consistency in implementation. In respect of the new provision at Article 10(6) of the amending Directive, an approach was agreed with the Patent Office, DTI and DEFRA. This requires an amendment to the Patent Act. Discussions also took place with the Department of Health on a range of issues and the agreed approach is reflected in the consultation letter and RIA. Liaison has also taken place with the Cabinet Office Better Regulation Team and Small Business Service whilst constructing the consultation document and RIA.

(ii) Public Consultation

A formal public consultation exercise on the Commission's original proposal was concluded in May 2002 (MLX 282). In total, 66 responses were received from a range of organisations, including consumer and patient representative bodies and the associations representing the interests of the innovative, generic and over-the-counter medicinal products.

Stakeholder meetings with the 3 main industry trade associations have taken place approximately every 3 months since publication of the Commission's proposals and have continued through the implementation phase. In addition, the MHRA regularly meets the industry's Herbal Forum.

A second formal written consultation took place from 22 March 05 – 16 June 05 (MLX 317). The consultation sought views on the UK's proposals for implementation of amending Directive 2004/27/EC – the consultation included a Partial RIA. 44 responses were received from consultees, of which 31 offered substantive comments. The three main industry trade associations responded, as did organisations representing the interests of the herbal and homoeopathic industries. Comments were received on a range of issues – in particular on data exclusivity, renewals, sunset clause and patient information leaflets (including Braille). A number of respondents enquired about the publication of guidance on the new procedures. In many cases, discussions are ongoing at EU level (as there is a need to ensure a common approach in most areas), but we hope to be in a position to issue either EU or UK guidance by October 05. The comments received have been reflected in this RIA where appropriate.

4. Options for implementation

Three options have been identified:

Option 1 – fail to implement the amending Directive

Option 2 – implement the provisions in advance of the final date of transposition

Option 3 – implement the provisions on the final date of transposition

Option 1 – do not implement the provisions. As this is EU legislation, the UK has no option but to implement the agreed provisions. In addition, the new measures provide a significant opportunity to the UK/EU to refine and improve the current regulatory regime in the medicines field, so implementation remains desirable. A number of the agreed provisions enable a greater degree of harmonisation between MS, so failure to implement would significantly hinder the operation of the updated regulatory regime and single market for pharmaceuticals.

Option 2 – implement the provisions in advance of the final date of transposition. A thorough assessment of the possibility of introducing the provisions early was conducted by the MHRA and examined by the Government. This included the potential public health benefits associated with early implementation, the fact that certain provisions were linked in the legislation and therefore could not be implemented in isolation, and the need to keep a balance between the interests of the generics and innovative industries as the legislation as a whole does, and a harmonised approach with other MS where necessary.

Following the analysis and circulation of a consultation document with RIA, it was decided to proceed with the implementation of three individual provisions that offered

public health benefits. The Government looked again at the possibility of implementing certain provisions before the final date of transposition.

Option 3 – implement the provisions on the final date of transposition. As outlined under Option 2, following a full analysis (relating to public health benefits/linked provisions in the legislation/harmonised procedures across the EU), the Government considers that the remaining provisions should be implemented by the final date of transposition. This will ensure that the linked provisions in the legislation are implemented in unison, and that a co-ordinated approach is maintained with other EU MS for those measures that require for effective operation a harmonised approach. The Government does not consider that any remaining provisions would offer public health benefits if implemented early.

5. Costs and Benefits

5(i) Sectors and groups affected

The pharmaceutical industry is broadly split into two sectors - the innovative (research and development) and generics industries. There are also specialist distribution and wholesale companies. Around 3000 organisations and companies exist in the pharmaceutical sector in the UK, and because of the wide-ranging nature of the agreed provisions, all areas of the industry will be affected.

Since the 1940s, a significant proportion of the global innovative pharmaceutical industry, whether British or foreign owned, has been based in the UK. To illustrate this:

- Some 70 000 people are directly employed in the UK, with as many as 250 000 others dependent on the industry's presence in this country[3].
- Pharmaceuticals are one of Britain's leading manufacturing sectors. Industry exports in 2002 were £10.03 billion, creating a trade surplus of £2.6 billion[4].

The generics industry is also an important sector of the UK industry in terms of contribution to the economy and the use of generic products in the NHS. To illustrate this:

- the British Generic Manufacturers Association (BGMA) has estimated the total turnover in the generics manufacturing sector to be about £350m[5].
- the likely market size of the generics wholesale industry is about £5.4 billion[6].

Pharmaceutical distributors that import medicines from other MS will be affected by only a very small number of the requirements, MHRA is not aware of an authoritative estimate of the market share of this sector.

[3] ABPI webiste (at 28 January 2004)
[4] ABPI website (at 28 January 2004)
[5] OXERA Fundamental Review of the Generic Drugs Market p 146
[6] OXERA Fundamental Review of the Generic Drugs Market p 159

The herbal industry is also affected by these provisions. The value of the UK market has been variously estimated at between £75m and £105m in 2002. There are thought to be several dozen UK manufacturers operating in the area, mostly micro, small or medium sized businesses.

5(ii). Benefits

Option 1 – no practical benefits would be derived from not implementing the measures, as they offer a real opportunity to safeguard public health of EU/UK citizens by the more effective regulation of medicinal products.

Option 2 – there are no benefits associated with implementation of Option 2, for the reasons outlined in Section 4. This would have resulted in a fragmented regulatory regime that would have had detrimental effects on public health protection.

Option 3 – in addition to the technical matters associated with implementation (addressed under Section 4 – 'Options') the benefits to patients of implementing these measures are wide-ranging and numerous. The benefits have been examined in relation to their economic, environmental and social implications where applicable.

There are significant benefits for the UK economy in ensuring that the UK based innovative pharmaceutical industry continues to thrive. It contributes significantly to the UK economy, providing £4.7billion[7] of the UK's national income in 1998 (latest available figures) It also attracts significant R&D resource, receiving about 10%[8] of world R&D expenditure during the 1990s. Likewise the UK economy and National Health Service benefit from a large and attractive generic products sector with the majority of prescriptions now written generically.

This section addresses the relevant issues covered in the rationale for Government intervention section and outlines with benefits associated with those provisions.

1. More effective regulatory tools in the licensing and ongoing safety monitoring of medicinal products on the UK and EU markets by:

a) The introduction of a more robust and integrated approach to pharmacovigilance (by sharing safety data between MS and a common approach to the collection, verification and presentation of information on ADRs). The formal introduction of the risk-benefit principle; the requirement for an environmental risk assessment for all products; the requirement for a pharmacovigilance and risk management plan at the time of applying for a MA; greater transparency in the licensing process. Patients and the public will benefits from the clearer expression of the decisions taking on the licensing and ongoing safety of products. Greater transparency will bring greater public confidence in decision making and the inclusion of environmental risk factors in the assessment process will enable all aspects of risk to be addressed.

[7] Competitiveness and Performance Indicators 2001: p.10 PICTF
[8] Competitiveness and Performance Indicators 2002: p.47 PICTF

b) Increased frequency of PSUR will enable, the more regular review of safety aspects identified during a products lifecycle, balancing the removal of the requirements for 5 yearly renewal with the confidence the public can have in ongoing surveillance

c) Patients take it for granted that the medicines they take are manufactured to the highest standards, free of contamination. The industry is responsible for ensuring that appropriate standards for manufacture are met and responsibility remains with the regulatory authorities to make sure (by inspections) that they are. The extension of good manufacturing practice to new areas, such as APIs, will enhance the quality of medicinal products by ensuring greater batch to batch consistency. There will also be a higher level of assurance that the APIs will be of the required quality. Manufacture in accordance with Good Manufacturing Practice (GMP) provides a better level of assurance of quality than testing alone can provide. There will be a commercial advantage for manufacturers of APIs that hold a current GMP certificate issued by a MS.

d) All manufacturers will be required to apply the same GMP controls as stipulated in Annex 18 to the European Community guide to GMP, thus giving a level playing field. The introduction of unannounced inspections of manufacturers of APIs will make investigations into suspected defective APIs quicker and more effective. It will also aid investigation of suspected bad practices. API manufacturers will be aware that they must comply with good manufacturing practice at all times and not just during inspection.

2. Effective provision of appropriate high-quality information to users of medicinal products by:

a) Reordering the information to be included in the SPC. This will ensure that patients and healthcare professionals are able to clearly interpret the information on the Patient Information Leaflet (PIL) which will reduce the incidence of misuse of medicines.

b) Introducing over a 5 year period requirements for MA holders to include the name of the medicinal product in Braille on the outer packaging, and make the patient information leaflet available on request from patients' organisations in formats appropriate for blind and partially sighted.

c) The publication of the Assessment Reports (as required by Article 21(4)) will bring the benefit of increasing the transparency of the regulatory approval process for new product authorisations and their subsequent significant changes

3. Increasing the attractiveness of the EU/UK pharmaceutical market by:

a) More effective and timely procedures for assessing MA applications by refining the MRP to take into account lessons learned and the introduction of the alternative Decentralised Procedure. For both of these procedures a Co-ordination Group will be set up (replacing the informal Facilitation Group) which, amongst other roles, will be able to examine major public health

concerns related to specific applications. The benefit expected is that more procedures will have successful outcomes and that long arbitration referrals will be avoided.

b) Increasing the competitiveness of the EU regulatory regime by harmonising market exclusivity periods for original products across the Community at 10 years, with the possibility of an extension to 11 years if certain criteria are met. This will replace the different 6 or 10 year periods of data exclusivity applied in different MS. (This period is presently 10 years in the UK.) The new periods will apply to new product MA applications submitted after 30 October 2005.

   MA applications for generic versions of those products can be submitted at 8 years. When the 8 years data exclusivity received has expired, generic product companies will then have two or more years for completion of subsequent MRP or Decentralised procedures in readiness for placing on the market at year 10 or 11 or at patent expiry if later. However in the UK, if original products continue to gain similar lengths of supplementary patent protection, access to the market will still be governed in most cases by expiry of that protection (usually sometime after year 11 on the market) rather than by expiry of the data or market exclusivity periods. Therefore the benefit for generic product companies lies in the earlier granting of authorisations rather than earlier access to the market.

c) The introduction of definitions of generic and reference medicinal products will bring greater clarity to both the regulator and industry, allowing simpler and timelier assessment of MA applications from the generics sector. The amendment of Article 6 now puts into the legislation the guidance previously issued by the Commission by establishing a 'global' marketing authorisation concept, thereby denying additional periods of data exclusivity for any variant or line extension of the original product with the same active principle (as had been UK practice in some cases until 2004.)

   Likewise, the concept of 'essentially similar' products is to be replaced by a legislative definition of a 'generic' which is a broader definition in that it will include products containing different versions of the active moiety which have the same safety and efficacy. Since this again reflects the current practice suggested by guidelines, there is little additional benefit.

   The inclusion of a definition of 'similar biological product' in the amended legislation again reflects the previous understanding of what would be required to authorise such products from the biotechnology sector as they now begin to approach the expiry of data exclusivity periods.

   Of some potential benefit however is the amendment within Article 10 which allows authorisation of generic products of reference products which are no longer authorised but had been authorised for the requisite period. This will allow access to the market for generic products even though the reference product had been withdrawn for commercial (as distinct from safety) reasons.

Furthermore, where the reference product had never been authorised in the UK but had been authorised for the data exclusivity period in another MS, a generic version can be authorised in the UK if the MHRA receives the necessary documentation and reports of that other MS. Use of this provision in the UK is however likely to be rare.

d) The introduction of a provision to allow the development of generic and other products without infringing patent protection in force in the UK. Previously the development by generic product companies of processes to produce active substances, formulate and package them into finished products for laboratory and clinical testing could not be carried out in those countries in which a patent was in force as these were considered infringing activities. Medicinal product patents (with supplementary protection where granted) usually last beyond expiry of the data exclusivity period. Therefore, in order to develop generic alternatives and be ready to submit an MA application on expiry of the data exclusivity, required generic companies to carry out those activities in countries where no patent protection was in force. This has had the effect of 'exporting' such work outside of the UK and outside of the expanded Community.

   The provision to be introduced in Article 10(6) allows those product development activities to be carried out in the UK and other countries where a patent is still in force, as long as the studies and trials are for the purposes of gaining a marketing authorisation under Article 10. This is expected to have commercial benefit to those generic product companies who wish to carry out such work within the UK or the EU and therefore will bring the associated economic and social benefits in terms of employment and investment. Furthermore if the commercial benefits are reflected in lower product prices then the element of price competition compared to innovative companies or generic companies not using this provision will increase.

e) Deregulatory measures, such as the refining of the renewals system will be complemented by increasing the frequency of PSUR, which is a less bureaucratic means of ensuring public health protection. The removal of the automatic requirements for a second and subsequent renewal means that resource used for renewal assessment can be better targeted at the safety of medicines on the market, enhancing patient safety

Conclusion

All of these measures can bring real public health benefits to patients. Some of the benefits will be immediate, such as the provision to patients of further information about medicinal products, leading to greater patient understanding about medicines. An understanding of the risks and benefits associated with using medicines will result in greater patient involvement in the treatment of their conditions.

Other provisions will bring benefits in the medium and long term, such as increasing the attractiveness of the EU regulatory regime, leading to increased availability of innovative and generic medicines. In terms of equity and fairness, the application of common standards in the authorisation of medicinal products is essential to both

fairness and public health protection. Equal treatment for MA holders operating within the EU Single Market is safeguarded by the Community legislation which underpins MS regulatory regimes. The implementation of the Directive does not have an impact on issues of race equality or implications for rural areas.

5(iii). Costs

(i) Compliance costs

Option 1 - failure to transpose this legislation would result in infraction proceedings being brought against the UK leading to an economic cost to the UK competent authority. The social costs associated with not implementing the legislation would be significant as the measures offer real public health benefits to UK citizens.

Option 2 – implement the provisions in advance of the final date of transposition. There would be costs to the pharmaceutical industry in complying with these provisions early, proportionate to the fees charged during the additional period of implementation. A thorough assessment of the possibility of introducing the provisions early was conducted by the MHRA and examined by the Government. The provisions that were amenable to early implementation were subject to a separate consultation (MLX 309) and RIA. Early implementation of any additional provisions would result in a disjointed EU regulatory regime, which would be detrimental to public health protection in the UK. There would be costs associated with setting up systems to comply with the UK interpretation of the Directive provisions, and additional capital costs on realigning systems should Member States take a different approach to the UK following discussions in EU meetings during the implementation phase..

Option 3 – the costs associated with implementing the new measures have been expressed in terms of economic, environmental and social costs where applicable.

1. More effective market surveillance of medicinal products on the UK and EU markets by:

a) the introduction of a more robust and integrated approach to pharmacovigilance (by sharing safety data between MS and a common approach to the collection, verification and presentation of information on ADRs). The UK is looking to adopt a pragmatic approach to reduce the potential burden on small and medium sized companies in complying with the requirement to submit electronic ADRs. The compliance costs to companies with a large number of MAs is estimated at £100,000. For smaller companies a standard IT solution is available 'off-the shelf' from a third party provider at approximately £25,000. In view of the potentially disproportionate costs for small companies with products likely to attract relatively low numbers of ADRs, we propose to allow the current method of reporting ADRs to continue. Following a request from a Marketing Authorisation Holder (MAH), the MHRA would convert the ADRs into an acceptable electronic format to enable transfer of data to the EMEA database and other MS as necessary.

The MHRA would provide this service on a contract basis and a fee would be charged to recover MHRA costs.

b) Increased frequency of PSUR taken with the refining of the renewals system is a deregulatory measure, which will reduce costs of MAHs. PSURs are a less bureaucratic and more safety orientated means of protecting public health. Savings will be achieved by MAHs as resources will be redirected from the production of a renewals dossier to other areas.

c) The extension of good manufacturing practice to new areas, such as APIs

GMP is that part of quality assurance which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the MA or product specification. GMP is concerned with both production and quality control.

We have identified 30 UK companies which manufacture active substances used as APIs. These firms, and similar companies throughout the EEA, will be directly affected by the new provisions in the amending Directive. The MHRA does not licence overseas (i.e. outside the EEA) manufacturing sites supplying the UK, but they are inspected when named on specific MAs. These overseas inspections focus on the products to be imported, and the standards applied are the same as those applied in the UK. There is no legal requirement to notify the licence holder of an intention to visit and inspections may be pre-arranged or unannounced.

While the new inspection requirements for API manufacturers bring inspection, the issuing of certificates and the use of sanctions on to a statutory basis for the first time, it should be remembered that the UK has been using the standards set out at Annex 18 to the European Community guide to GMP – in the context of voluntary inspection of API manufacturers - for a number of years. These standards were the subject of extensive (worldwide) consultation and they are well established principles to which the industry generally adheres. Thus, we expect the new provisions to account for minimal additional cost to manufacturers. Indeed, the quality of APIs is currently the responsibility of the dosage form manufacturer so there is already a cost of compliance.

Since 1997, the MHRA has carried out 67 voluntary inspections of manufacturers of APIs, 41 of which have been performed on full scale API manufacturers. Of these, only one company did not meet the standards required, suggesting that companies are indeed observing GMP requirements already. The table below shows the trend of inspection activity since 1997:

Table 1

Year	**Number of inspections**
1997	1
1998	2
1999	4
2000	6
2001	11

2002	14
2003	13
2004	16
Total	67
Type of manufacturer	
API for Clinical Trials	6
Biological API for Clinical Trials	10
Full scale API	40
Excipient	8
Specific risk materials	2
Total	66*

* one site not given a classification

NB. The figures quoted in tables 1 and 2 are for chemical/biotech API inspections only.

For the future, the MHRA will devise a rolling programme of inspections for API manufacturers, and this is likely to be established, first of all, on a risk-based or "for cause" approach – with a final decision on inspection frequency and future strategy to be decided in due course. Companies should, however, be reassured that the future inspection regime will not be any more onerous than that which currently exists for GMP – i.e. bi-annually (or three-yearly for overseas sites – those outside the EEA).

Fees are charged for routine scheduled inspections. Additional inspections may also be carried out, for example, to follow up deficiencies raised previously, following reports of defective products, or to follow up information received from external sources (e.g., "whistleblowers"). For manufacturers of APIs, GMP inspection costs are expected to be in the range of £2,500 to £10,000 (rounded figures) depending upon the size of the site – i.e. smaller operations employing fewer staff generally require less inspector time on-site, therefore resulting in a lower inspection fee. This arrangement mirrors the current GMP fee structure for non-sterile manufacture, which is felt to be the most equitable way forward. It is expected that the inspection fee will include the issue of the GMP certificate, although if extra or multiple copies are required for any reason, a charge may then be made.

The cost impact on companies of the new requirements is judged to be negligible - the table below sets out how inspection costs are likely to be broken down by size of company (using 2004 fee levels):

Table 2

Description	**No. of companies**	**No. of employees**	**Inspection cost (£)**
Small	5	0-10	2,481
Medium	18	10-60	4,601
Large	15	60-250	5,557
Extra large	3	>250	9,525

The table shows that the majority of companies affected by the new requirements fall within the "medium – large" bracket. These will typically be manufacturers of

multiple APIs, and are therefore thought to be able to absorb easily the necessary inspection costs (which themselves are firmly within the middle of the fee range).

Brokers, who re-package or re-label APIs, are another sector that will be included in future inspection arrangements. At present, these are not picked up at all by the inspection regime and the MHRA has not received any request from manufacturers to undertake inspections in this area. It is therefore impossible to predict what future activity (and associated cost impacts) might arise.

Herbal API Inspection

Although the figures quoted in tables 1 and 2 above are for chemical/biotech API inspections only, the costs to herbal API manufacturers of GMP inspections will follow the same formula. The GMP provisions will apply to herbal products with a marketing authorisation or that will be registered in the future under Directive 2004/24/EC.

Reliable and qualitative information on the size and composition of the herbal API manufacturing sector is not currently available. However, across the EU as a whole, including the UK, there are many hundreds of authorised herbal medicines. If the picture shown at Table 1 of general compliance with the GMP requirement is replicated in the herbal API manufacturing sector in the UK and more widely in EU there may be many herbal API manufacturers in UK or elsewhere in EU who are already at or near the required standard. On this basis it would seem relatively unlikely that manufacturers of registered herbal medicines would be faced with an unmanageable loss of choice of suppliers of APIs or significantly higher costs. The picture in relation to those herbal API manufacturers who may have hitherto supplied only the unlicensed herbal sector may be more variable.

As with chemical and biotech APIs, the Agency does intend devising a rolling programme of inspections for herbal API manufacturers, and this is likely to be established, first of all, on a risk-based or “for cause” approach - using evidence from dosage form (final product) manufacturers to determine the breadth and extent of the herbal API sector and of the manufacturing standards in operation. A final determination on inspection frequency and future strategy would then be arrived at in due course.

Generally, given that fees are based on company size and inspector time on site, the proposals may, in time, result in small increases in costs for dosage form manufacturers, particularly where API manufacturers are found to be operating to low standards, where significant improvements to quality systems and standards are judged to be required. However, there are also benefits to be derived - compliance with GMP, supported by advice given by Agency inspectors, for example on quality systems, can result in a range of benefits: less reworking or reprocessing needed, reduced wastage, improved stock control, lower inventory holding costs, fewer complaints, improved productivity, and decreased equipment downtime. The ability to give an assurance of compliance with GMP is likely to be of benefit to herbal API manufacturers who wish to sell materials to herbalists for use in their remedies made up under Section 12(1) of the Medicines Act 1968.

d) The ability to conduct unannounced inspections of manufacturers of APIs materials will aid investigation where companies are suspected of bad practice. However, the evidence from the programme of voluntary inspection over recent years is that manufacturers are already aware that they must comply with good manufacturing practice at all times. The ability to conduct unannounced inspections will be a useful regulatory tool, but it is not expected that it will be widely used. Therefore, the associated costs are expected to be at a low level.

2. Effective provision of appropriate high-quality information to users of medicinal products by:

a) Reordering the information to be included in the SPC. However, costs to the pharmaceutical industry are likely to be minimal as this provision will apply initially only to products for which an MA application was submitted after 30th October 05. For existing products we are proposing that we are proposing that the re-ordering takes place when other regulatory action triggers changes to the SPC. This will manage the new burden to companies.

b) Introducing requirements for MA holders to include the name of the medicinal product in Braille on the outer packaging, and make the patient information leaflet available on request from patients' organisations in formats appropriate for blind and partially sighted. Consultation on the costs associated with the Braille provision has taken place with MA holders. MA holders are predicting a 5%-10% increase in overall costs to comply with this requirement. However, there will be little or no reduction in the production capacity of the packaging machines due to the requirement to print Braille on each carton. For small companies, such as those in the herbal sector, based on the historic pattern of small companies with large products ranges, the relative costs associated with Braille provision could be more significant. However, the MHRA's current feedback is that a number of herbal companies are likely to seek to register products progressively over a number of years. Given size of the task and its cost implication in the light of the proportionate benefit, we propose to allow a longer period for transition than other measures – of 5 years. For specialist pharmaceutical importation and distribution companies the relative cost may also be greater due to their large product ranges and variable batch sizes.

c) The preparation of Assessment Reports by the Agency in a form suitable for publication (including the removal of commercially confidential information) will bring additional costs to the Agency.

3. Increasing the attractiveness of the EU/UK pharmaceutical market by:

a) More effective and timely procedures for assessing MA applications by refining the Mutual Recognition Procedure to take into account lessons learned and the introduction of the alternative Decentralised Procedure. The single-stage Decentralised Procedure offers a potentially faster and surer route to gaining MAs in many MS (compared to the two-stage National + MRP)

Small companies may however find that there is an additional regulatory resource cost in managing short timescale procedures across many MS.

b) Increasing the competitiveness of the EU regulatory regime by harmonising market exclusivity levels across the Community at 10 years, with the possibility of an extension to 11 years if certain criteria are met.

c) The introduction of definitions of generic and reference medicinal products will bring greater clarity to both the regulator and industry, allowing simpler and timelier assessment of MA applications from the generics sector. Because these definitions are broadly in line with Commission guidance and recent judgments of the European Court of Justice it is unlikely there will be any cost implications.

d) The introduction of a provision to allow the development of generic and other products without infringing patent protection in force in the UK. Though commercial benefits may accrue to those generic product companies who wish to develop their products in the UK and the EU under this new provision, it is unlikely that there will be any direct and proportionate increase in costs for those companies whose products are being copied.

e) Deregulatory measures, such as the refining of the renewals system will be complemented by increasing the frequency of periodic safety update reporting, which is a less bureaucratic means of ensuring public health protection.

(ii) Other costs

One-off costs fall largely to the pharmaceutical industry and the EMEA. However, there will also be some additional costs to the MHRA, which are generally passed on to the pharmaceutical industry through new or increased fees (see Appendix A).

In the pharmaceutical industry, there will be costs associated with re-training regulatory affairs staff in the reformed regime.

The requirement that all new MA applications must include an assessment of risk to the environment will add to the costs of preparing an application dossier. Since previously such risk assessment was usually only required for new active substance applications, this additional cost will now also fall on applicants for generic products. We estimate that the additional cost would not exceed 2% of the cost of producing the other data for the application dossier but would particularly welcome feedback from the industry on this cost.

There are no costs in relation to issues of equity and fairness.

(iii) Costs for a typical business

Businesses range from single person wholesale dealers to multi-billion pound international manufacturing and marketing businesses. For human medicinal

products, the authorisation process is a rigorous one. The data needed to demonstrate safety, quality and efficacy must be submitted to the Competent Authorities and the dossier assessed before a product is authorised for use. Inspection of manufacturing sites, the wholesale and distribution networks and monitoring the safety of products in use are key parts of the regulatory system.

Fees

In the UK, the costs associated with fulfilling our regulatory responsibilities are generally recovered via the payment of fees for serviced provided. Proposals to introduce or revise our current fees schedule are subject to a separate public consultation, which began in on 17th June 05 (MLX 324).

Provisions introduced by Regulation 726/2004/EC

A number of measures will be introduced into the UK when the Regulation comes into force across the EU on 20th November 05. The provisions are designed to complement those agreed in the amending Directive, resulting in a package of new measures that provides real public health benefits to patients, and which creates a more attractive regulatory environment for the pharmaceutical industry.

For example, the scope of the Centralised Procedure was extended to require its use for all products containing new active substances used to treat HIV/AIDS, cancer, neuro-degenerative disease, diabetes. It also now includes orphan medicinal products. In addition, human products used to treat auto-immune diseases and other immune dysfunctions and viral diseases will be added after 4 years, at which time a review may also take place. This represents potential reduction in costs for the pharmaceutical industry as a single MA for these products will be valid for use throughout the EU (currently they have to pay national MA fees to each MS in which they wish to market their products).

The new Regulation also allows MS to supply on 'compassionate use' grounds to certain groups of patients, unauthorised human medicinal products required to use the Centralised Procedure. This will allow patient access to certain unauthorised products, provided there are adequate public health and safety grounds (this does not interfere with the UK's current 'named patient supply' arrangements). In addition, for centrally authorised products, a new provision will be introduced that allows the conditional authorisation of medicinal products in exceptional circumstances, provided there are justified reasons (such as the product treats only a very limited population). The conditions under which the authorisation is made would be reassessed on an annual basis. These provisions will bring public health benefits to patients in the UK.

The structure of EMEA Management Board and scientific committees were revised to take account of the enlarged membership of the EU. The new structures provide one representative per MS, whereas the current system provides for 2 representatives per MS, so marginal savings will be achieved by the MHRA through reduced membership (associated travel costs etc).

Finally, the Commission has agreed to establish the circumstances, in which small and medium-sized companies may pay reduced fees, defer payment of fees or receive administrative assistance.

It should also be noted that the provisions of the amending Directive, on the whole, also apply to Centrally Authorised products.

6. Consultation with small businesses: the Small Firms' Impact Test

Because of the highly specialised nature of the pharmaceutical industry, the majority of MAs are held by the larger companies. However, there are a number of smaller operators in the market, predominantly in the herbal and homoeopathic sectors.

Discussions with the Herbal Forum, which represents UK manufacturers' associations, indicate that, overall, their concern is one of cumulative impact: that the cost of some of these measures is additional to the cost this particular sector is facing at the same time as a result of Directive 2004/24/EC. Their main concern is the cost of implementing the requirement to include the name of the medicinal product in Braille on the outer packaging. Other areas of potential concern identified, depending on implementation, were electronic reporting of ADRs and frequency of PSURs, and GMP for APIs. In ongoing discussions about detailed implementation the MHRA has sought to ensure that implementation is proportionate and reflects awareness of regulatory impact issues. For example, in EU discussions on guidance covering PSURs the UK has raised the issue of whether the initial six monthly frequency of reporting following a product authorisation would in all cases be necessary for registered traditional herbal medicines. In addition, the MHRA proposes to establish an alternative method of submitting ADRs, which meets the objective of the provision but reduces the burden on those businesses for whom the cost of introducing electronic reporting would be disproportionately expensive.

7. Competition Assessment

Most of the agreed changes amount to "fine tuning" of procedures and provisions that are already well established and, consequently, are not considered to introduce any significant competition issues. The competition filter test has been carried out in relation to the markets considered most likely to be affected.

On the basis of the filter test, a simple competition assessment, rather than a detailed assessment is required. No other competition issues have been identified.

Simple Competition Assessment

The UK pharmaceutical industry is broadly split into two sectors: the innovative (research and development, including biotechnology) industry and the generics industry, with a number of manufacturers of herbal and homoeopathic products and pharmaceutical importers. Around 3000 organisations and companies exist in the pharmaceutical sector in the UK, a significant proportion of which carry out activities that will be affected by these proposals. Although there are some major players in the UK pharmaceutical industry, the MHRA considers that no single company has more

than 10% of the market share, no two companies have more than 20%, and no three have more than 50% market share.

The introduction of the new provisions is unlikely affect the market structure and size and number of firms in the UK pharmaceutical industry. As the measures are broadly applicable to both main sectors of the pharmaceutical industry, the effects on competition will be negligible, whereas the public health benefits of implementation are significant. The effect of these changes on the herbal sector should overall be relatively modest, although the impact of the requirement for Braille could be significant for some small companies. Of greater significance is the impact of aggregate regulatory changes affecting the sector and this will be addressed in more depth in the RIA on Directive 2004/24/EC. The introduction of systematic regulation into this sector of the UK market may lead to a degree of consolidation as some herbal companies, for example small ones lacking an existing infrastructure to enable them to operate within a regulated environment, may decide to pool expertise, for example via merger.

Existing firms and new and potential firms will have to comply with the new requirements. Therefore, the setting up and on-going running costs associated with these changes will not discriminate against new firms wishing to join the market. In addition, the MHRA does not consider that the introduction of these requirements will constrict firms in their ability to choose the price, quality, range or location of their products. The new provisions were agreed with the principles of the Single Market in mind and so will lead towards greater flexibility in the choice of location of pharmaceutical firms.

8. Enforcement and sanctions

The competent authorities of the Community (EMEA) and MS enforce the Regulation and Directive. In the UK, the competent authority is the MHRA. It already has a range of civil and criminal powers at its disposal to enforce the regulatory regime. In addition, we are proposing to introduce the following sanctions:

Directive 2004 27/EC

Various obligations have been identified in the amending Directive as obligations relating to marketing authorisations which require enforcement by means of a criminal offence. We are proposing to amend the current schedule of criminal offences relating to marketing authorisations (Schedule 3 to the MA Regulations) to create the following criminal offences. The relevant provisions of Directive 2001/83/EC are indicated in brackets:

a) Placing a generic medicinal product (i.e. one granted by reference to data submitted for an earlier innovative product) on the UK market before the market protection period set out in the Directive (10 or 11 years) has elapsed (Article 10)
b) Failure by marketing authorisation holder to notify MHRA of actual placing on the market of a medicinal product and any cessations or interruptions in supply (1st and 2nd paragraphs of the new Article 23a)

c) Failure by a marketing authorisation holder to provide the MHRA with information re. volume of sales and prescriptions (final paragraph of Article 23a)
d) Failure by marketing authorisation holder to ensure, within the limits of his responsibilities, appropriate and continued supplies of his product to pharmacies and other suppliers, to meet the needs of patient in the UK (Article 81)
e) Communication of information relating to pharmacovigilance concerns to the public (i) without prior or simultaneous notification to MHRA or (ii) where information misleading or is not presented objectively (Article 104(9))

The new obligations in Article 23 have already been implemented and Schedule 3 to the MA Regulations amended accordingly[9].

In addition to obligations relating to MAs, we have considered the obligations in relation to the manufacture and wholesale distribution of medicines. At present, section 45 of the Medicines Act 1968 makes it a criminal offence to manufacture medicinal products or supply such products by way of wholesale dealing, otherwise than in accordance with the provisions of a relevant licence granted under the Act. We propose to impose the following additional obligations on holders of such licences; it will be an offence under section 45 to breach these obligations:

- The holder of a UK manufacturer's licence will be required to use active substance "starting materials" which have been manufactured in accordance Good Manufacturing Practice (GMP);
- The holder of a UK manufacturer's licence who also supplies products by way of wholesale dealing, shall be required to comply with the principles of "good distribution practice" and other relevant obligations imposed on holders of wholesale dealer's licences

We are re-drafting the existing provisions which impose requirements to ensure full compatibility with the Directive. Breach of the re-drafted provisions will be an offence under section 45 – but the obligations under the new provisions are not substantially different from those at present.

Our regulations will also create a number of other free-standing offences –

- Offence to breach regulation 3(1)(a) of the MA Regulations - which provides that no person may distribute a "relevant medicinal product" by way of wholesale dealing unless it is authorised, or subject to an exemption or exception in the Community legislation (e.g. specials);
- Offence for possession of a POM (Prescription Only Medicine) with intent to supply contrary to the restrictions in Medicines Act 1968 (i.e. that, subject to various exemptions, a POM may be supplied only from a pharmacy and in accordance with the prescription of a doctor or other independent prescriber);

[9] See regulation 3(4) of the Medicines (Marketing Authorisations and Miscellaneous Amendments) Regulations 2004 (S.I. 2004/3224).

Regulation 726/2004/EC

The following obligations have been identified in the Regulation as new obligations for centralised MAs requiring specific provision for enforcement in the UK. MS are required to set the penalties for infringement of such obligations. To ensure consistency across the regulatory regime we are also proposing to extend the current schedule of criminal offences (Schedule 3 of the MA Regulations) to cover these additional obligations.

a) Duties relating to the public communication of information relating to pharmacovigilance concerns – Article 24(5);
b) Duty to collect information from targeted patient groups at the request of the EMEA – final paragraph of Article 26
c) Duty to ensure appropriate and continued supply of the product to pharmacies and other authorised suppliers – Article 81
d) Duty to inform the EMEA of the date that products are placed on the market and any interruptions in supply to the market at least 2 months before the interruption – Article 13(4)

In addition, references in Schedule 3 of the MA Regulations to obligations under the existing provisions governing centralised MAs (Regulation 2309/93) will be updated to references to the equivalent obligations under Regulation 726/2004.

Homoeopathic Regulations

As part of the implementation of Directive 2004/27/EC, we will be substantially amending the Medicines for Human Use (Homoeopathic Medicinal Products for Human Use) Regulations 1994. These provide for the licensing of homoeopathic medicinal products by means of certificates of registration. At present, marketing a product without such a certificate, or breaching a certificate, are offences under the Medicines Act 1968. The amendments to the 1994 Regulations will create a free standing enforcement regime, including a new schedule of offences (attached at Appendix B). Although the offences are new, they either replace the existing offences under the Medicines Act 1968, or are identical to the existing offences in the MA Regulations relating to marketing authorisations. The penalties for breach of the new offences will be the same as for the existing offences under the Act and the MA Regulations.

9. Implementation and delivery plan

The MHRA has liaised extensively with stakeholders since the new legislation was adopted in April 2004. A number of stakeholder meetings took place during the implementation phase to keep those with an interest fully informed of the changes. The UK has played an active role in discussions at EU level since the adoption of the legislation, with a view to producing robust guidance on the operation of the new procedures. The MHRA is holding a training seminar on the 21st September 05 to provide further information on the new procedures and to give stakeholders another opportunity to seek clarification on the new provisions. Over 110 people have confirmed their attendance.

10. Post implementation review

Article 86 of Regulation (EC) No 726/2004 requires the European Commission to publish a general report on the operation of the EU medicines regime under both the Regulation and the two Directives (on human and veterinary medicines respectively) at least every ten years. The UK will examine this report against our own experiences of the new regime.

11. Summary and recommendation

Option	Benefits per annum	Costs per annum
1	There are no benefits associated with not implementing this Directive, as this would lead to a dis-harmonised approach across the EU.	There will be costs associated with any fines imposed by the Commissions as a result of infraction proceedings against the UK. There will be significant social costs, as failure to implement the new provisions will represent a lost opportunity to further safeguard the public health of UK/EU citizens. It would also lead to a fragmented system, which would jeopardise current levels of public health protection in the UK.
2	There would be no benefits per annum as this would have led to a dis-harmonised approach across the EU that would have resulted in confusion – possibly jeopardising public health protection in the UK.	This would have led to a fragmented approach across the EU, giving rise to economic costs to stakeholders of implementing new systems early. There would also be a high possibility that industry would have to reinvest in the one-off changes to systems when a harmonised approach was achieved across the EU. Social costs would also be evident – patient safety would be jeopardised as the UK would be operating to different procedures to the other Member States.
3	Significant social benefits will be brought about through increased public health protection (for example by more effective surveillance of	The requirement to express the name of the product in Braille on the outer packaging will bring economic costs to MA holders

	medicinal products on the UK market, inspection of active pharmaceutical ingredients used as starting materials, increased transparency of decision making and more effective authorisation procedures which will get products to market more quickly). Information on environmental risks must now be submitted with the MA application. Economic benefits are represented by more streamlined procedures which get products to market more quickly. Harmonised periods of market and data exclusivity, which will increase investment in the EU/UK market. Streamlining of the renewals system will bring savings to industry. The economic savings to the industry associated with the provisions of Regulation (EC) 726/2004 are significant. The scope of the Centralised Procedure was extended to require its use for all new active substances used to treat HIV/AIDS, cancer, neuro-degenerative disease and diabetes. This enables companies to market those products throughout the EU with a single MA, issued by the EMEA. Previously, companies would have to apply for MAs for all Member States, at significant cost. Current fees for MAs issued at the EMEA are as follows: EURO 232 000 basic fee (1 strength associated with 1 pharmaceutical form) + EURO 23 200 for each additional strength and/or pharmaceutical form. The UK currently charges £80,586 for an assessment of these applications. This would result in the granting of a UK MA, which would need to be	(MA holders are predicting a 5%-10% increase in overall production costs to comply with this requirement). However, there will be little or no reduction in the production capacity of the packaging machines due to the requirement to print Braille on each carton. Compliance with the requirement to submit electronic ADRs (for companies with a large number of MAs) is estimated at £100,000. For smaller companies a standard IT solution is available 'off-the shelf' from a third party provider at approximately £25,000. In view of the potentially disproportionate costs for small companies with products likely to attract relatively low numbers of ADRs, we propose to allow the current method of reporting ADRs to continue, with the MHRA providing the conversion to electronic forma and charging a fee. For manufacturers of Active Pharmaceutical Ingredients, GMP inspection costs are expected to range from £2500 - £10000 per inspection, depending on the size of the manufacturing site. We are also proposing to introduce a number of new fees related to new service activities carried out by the MHRA. These are subject to a separate consultation (MLX 324). The proposed fees are attached at Appendix A to this RIA. The fees will be charged directly to the companies who seek and receive the service being provided. There is no element of cross-subsidisation involved. The fees

	mutually recognised (at significant cost to the company per MS MA applied for) in other MS to enable more widespread marketing of the product.	are proposed at levels that are consistent with existing fees for other similar work already undertaken by the MHRA. The level of fees will be monitored to ensure they are set at the right level and proposals will be made to adjust them at a later date if not.

The Government recommends option 3. The implementation of the remaining provisions of Directive 2004/27/EC by the final date of transposition offers the best opportunity to further protect the public health of UK citizens.

12. Declaration and publication

I have read the Regulatory Impact Assessment and I am satisfied that the benefits justify the costs.

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Date: 5th October 2005

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Appendix A

PROPOSED NEW FEES ASSOCIATED WITH AMENDING DIRECTIVE 2004/27/EC

1. ***Decentralised procedure where the UK is the Reference Member State (RMS)***

1.1. This new licensing procedure will combine, within a single application, National assessment with a modified mutual recognition procedure in which the UK has been chosen as the reference member state by the applicant for this procedure. Under this procedure, UK will be responsible for assessing the product and provide an initial assessment report to be "mutually recognised" by other concerned member states in a process analogous to the current outgoing mutual recognition procedure.

1.2. It is proposed that fee amounts should be set as the combination of National plus Outgoing Mutual Recognition fees - first wave. The proposed fees are therefore £115,098 for Major Application; £31,219 for Abridged Complex and £11,813 for Abridged Standard. (These figures include the increases to fees due to come in on 1 July 2005).

2. ***Decentralised procedure where the UK is the Concerned Member States (CMS)***

2.1. In these cases UK would be assessing applications in the Decentralised Procedure but with the aid of the Assessment Report from the RMS. The amount of work involved should therefore be similar to that when UK is CMS in an Incoming Mutual Recognition Procedure.

2.2. However, because of time restrictions we would be unlikely to be able to make significant savings of assessment effort as we can in the existing Mutual Recognition Procedure. With the much shorter time scale proposed for CMS to assess the applications after the receipt of the RMS assessment report, the UK will have to evaluate the applications independently and ahead of the RMS report. In addition the relatively short time scales, especially during the latter part of the new procedure, may require a greater concentration and dedication of assessment and support resource, in particular for approval of patient information

2.3. It is proposed therefore that these applications (Major, Complex, Standard and Simple) should be to charge at the full National rate (i.e. Major @ £80,698; Abridged Complex @ £22,366; Abridged Standard @ £8,272 and Abridged Simple @ £2,337) because a full assessment will be required. (These figures include the increases to fees due to come in on 1 July 2005).

3. ***Hybrid applications***

3.1. Directive 2004/27/EC expands the scope of what was previously known as the "proviso" paragraph, (this was the final paragraph of Article 10(1)(a)(iii)) to include all applications which do not meet the strict definition of a generic product. This includes those applications presenting the results of new pre-clinical and/or clinical data. This could occur where either, simple bioequivalence cannot be demonstrated or, those applications are for changes to the therapeutic indications, strengths, pharmaceutical

forms, routes of administration or active substance compared to an authorized reference product. It is proposed to amend the definition of a complex application to cover all applications made under the expanded "proviso". The usual fee for a Complex application of £22,366 will then apply. (This figure includes the increases to fees due to come in on 1 July 2005).

4. ***European Reference Products***

4.1. A company will be able to submit an abridged application for a product making reference to an original MA granted in another member state where the reference product has not been authorized in the UK. The UK would then be required to request all appropriate documentation from that other Member State in order to assess and determine the "Euro-generic" product application for the UK. As a matter of UK policy, assessment of the "Euro-generic" application will consist of an assessment of its own product quality and generic equivalence data, together with an assessment of the pre-clinical and clinical data of the reference product as for a Major application. It is expected that we will have the benefit of the other MS Assessment Report in a similar situation to the current Incoming Mutual Recognition procedures.

4.2. It is proposed to charge for these "Euro-generic" applications the same fee as for Incoming Mutual Recognition (CMS) applications. The fees proposed will be Major/NAS application £56,218, a Complex application £15,689 and a Standard application £5,820. (These figures include the increases to fees due to come in on 1 July 2005).

4.3. It is anticipated that such applications to the UK will be few.

5. ***Fees for Inspections of Active Pharmaceutical Ingredients (API) Manufacturers***

5.1. Directives 2004/27/EC and 2004/28/EC, which amend 2001/83/EC and 2001/82/EC respectively, place an obligation on marketing authorisation holders to use as starting materials only active substances which have been manufactured in accordance with detailed guidelines for GMP of starting materials. The new Directive provides a legal basis for competent authorities to undertake inspections of manufacturers of active substances used as starting materials.

5.2. The inspections of manufacturers of active substances will involve manufacturing sites, assembly sites and storage sites both in the UK and overseas. Inspection of API sites are QA process-based inspections and so are similar to those of finished dosage forms.

5.3. Where the sterility of a medicinal product depends on the sterility of the starting material ie where a sterile API is aseptically incorporated into the finished dosage form, the process of sterilising the material is deemed to be part of the manufacturing process and these manufacturers have always required a manufacturing licence. These inspections have been charged at the same rate as that for a finished dosage form manufacturer.

5.4. MHRA inspectors have been performing voluntary inspections of API sites for some years. Fees for these voluntary inspections have been the same as that charged for sites of similar size that manufacture finished dosage forms, i.e. based on number of employees at the site.

5.5. The current scale of fees for GMP inspections of manufacturers of non-sterile finished dosage form be applied to inspections of API sites.

6. ***Fees for Good Manufacturing Practice (GMP) certificates***

6.1. Directive 2004/27/EC requires that a certificate of good manufacturing practice (GMP) be issued to a manufacturer if the outcome of an inspection confirms compliance with the principles and guidelines of good manufacturing practice.

6.2. The requirement is likely to apply to all sites inspected by the GMP inspectorate. It is therefore proposed that a GMP certificate will be routinely issued following the successful close out of an inspection.

6.3. MHRA already operates a certificate programme with well established fees for certificates of pharmaceutical products (CPP), certificates of manufacturing status (CMS) and certificates of licensing status (CLS)

6.4. Currently certificates are computer generated with fixed fees for routine certificates, emergency issue (within 24 hours) and for repeat issue. GMP certificates will be generated in the same way.

6.5. It is proposed that the GMP inspection fee for all sites be increased by the same amount to cover the routine issue of GMP certificates. This increment will be equal to that of a routine CPP (currently £53.00). Only one GMP certificate will be issued, copy certificates will attract a fee equal to the routine fee for CPP.

Appendix B

SCHEDULE 6 Regulation 7A(3)

OFFENCES, PENALTIES ETC

Offences

1. Any person who, in breach of these Regulations, places a homoeopathic medicinal product on the market without holding a certificate of registration in respect of that product, or otherwise than in accordance with the terms of such a certificate, shall be guilty of an offence.

2. Any person who, in the course of a business carried on by him, sells, supplies, manufactures or assembles, or procures the sale, supply, manufacture or assembly of, a homoeopathic medicinal product, or who has in his possession a homoeopathic medicinal product, knowing or having reasonable cause to believe that the product was or is intended to be placed on the market contrary to paragraph 1 shall be guilty of an offence.

3. Without prejudice to any other sanction which may be available for the enforcement of conditions attaching to certificates of registration, any holder of a certificate of registration for a homoeopathic medicinal product who contravenes any condition of the certificate shall be guilty of an offence.

4. Any person who is or, immediately before its revocation or suspension, was the holder of a certificate of registration who fails to comply with a notice given to him under regulation 10 (withdrawal from the market) shall be guilty of an offence.

5. Any holder of a certificate of registration who fails promptly to—

(a) take any steps reasonably necessary to take account of technical and scientific progress for the purposes of making any changes or amendments as required by Article 23 of the 2001 Directive; or

(b) introduce any changes or make any amendments that may be required in accordance with that Article or paragraphs 3.2(9), 3.2.1.2(c) and 3.2.2.4(c) of Part I of Annex I to the 2001 Directive; or

(c) provide information to the licensing authority as required by the third or fourth paragraphs of Article 23 or the first paragraph of Article 23a of the 2001 Directive; or

(d) submit any application to the licensing authority to make any changes or variation as required by Article 23 of the 2001 Directive;

shall be guilty of an offence.

6. Any holder of a certificate of registration who fails to forward to the licensing authority any data requested by the authority pursuant to the final paragraph of Article 23 or the final paragraph of Article 23a of the Directive—

(a) where the licensing authority have served a written notice on the holder under regulation 7A(4) in relation to the request, within the time specified in that notice;

(b) where there is no such notice, promptly,

shall be guilty of an offence.

7.—(1) Subject to paragraph (2), any person who is the holder of a certificate of registration who fails, not less than two months before an interruption in the placing on the

market of the product to which the certificate relates, to notify the licensing authority that the product is to cease to be placed on the market, shall be guilty of an offence.

(2) A person does not commit an offence under paragraph (1) if he took all reasonable precautions and exercised all due diligence to avoid the commission of the offence.

8.—(1) Subject to paragraph (2), any person who is the holder of a certificate of registration who fails to ensure appropriate and continued supplies pursuant to the second paragraph of Article 81 of the 2001 Directive shall be guilty of an offence.

(2) A person does not commit an offence under paragraph (1) if he can prove—

(a) that he did not know and could not by the exercise of reasonable care have known that the obligation to supply had not been complied with; or

(b) that in all the circumstances of the case it was not reasonable for him comply with the obligation.

9.—(1) Any person who in the course of an application for the grant, renewal or variation of a certificate of registration for a homoeopathic medicinal product—

(a) fails to provide to the licensing authority any information which is relevant to an evaluation of the quality of the homoeopathic medicinal product as required by Article 15 of the 2001 Directive; or

(b) provides to the licensing authority any information which is relevant to an evaluation of the quality of the homoeopathic medicinal product but which is false or misleading in a material particular,

shall be guilty of an offence.

(2) Any person who—

(a) is responsible for placing a homoeopathic medicinal product on the market; or

(b) is the holder of a certificate of registration for a homoeopathic medicinal product;

who provides to the licensing authority any information which is relevant to an evaluation of the quality of the homoeopathic medicinal product but which is false or misleading in a material particular shall be guilty of an offence.

10. Any holder of a certificate of registration who sells or supplies or procures the sale or supply of a homoeopathic medicinal product to which the certificate of registration relates the labelling of which, or any package insert accompanying which, does not comply with the applicable requirements of Title V of the 2001 Directive, shall be guilty of an offence.

11. Any person, other than the holder of a certificate of registration for a homoeopathic medicinal product, who in the course of a business carried on by him, sells or supplies or procures the sale or supply of a homoeopathic medicinal product knowing, or having reasonable cause to believe, that the labelling of the product, or any package insert accompanying the product, does not comply with the applicable requirements of Title V of the 2001 Directive, shall be guilty of an offence.

Penalties

12. Any person guilty of an offence under any of the preceding paragraphs shall be liable—

(a) on summary conviction, to a fine not exceeding the statutory maximum;

(b) on conviction on indictment, to a fine or to imprisonment for a term not exceeding two years or to both.

Miscellaneous

13. Where the holder of a certificate of registration is charged with an offence under these Regulations in respect of anything which has been manufactured or assembled to his order

by another person and had been so manufactured or assembled as not to comply with the provisions of that certificate, it shall be a defence for him to prove—

(a) that he had communicated the provisions relating to the certificate of registration to that other person; and

(b) that he did not know, and could not by the exercise of reasonable care have known, that those provisions had not been complied with.

14.—(1) A person does not commit an offence under paragraph 9 if he took all reasonable precautions and exercised all due diligence to avoid the commission of that offence.

(2) Where evidence is adduced which is sufficient to raise an issue with respect to that defence, the court or jury shall assume that the defence is satisfied unless the prosecution proves beyond reasonable doubt that it is not.

FULL REGULATORY IMPACT ASSESSMENT

1. Title of regulatory proposal

1.1 Implementing the 2001 Review – other changes to UK medicines legislation

2 Purpose and intended effect of measure

Policy objective

To review the implementation of certain EC obligations in current UK medicines legislation

2.1 The MHRA licences manufacturers, importers and wholesale dealers of medicinal products. These licences cover all the main activities associated with the manufacture, import or distribution of medicinal products. This system of licensing is intended to ensure that manufacturers, importers and wholesale dealers have the necessary staff, premises, equipment and facilities to carry out their activities and that they do so to appropriate standards of quality, in accordance with the principles of good manufacturing or good distribution practice.

2.2 In addition to the main 2001 Review provisions, which were discussed fully within the consultation package (MLX317)[10], the Government intends utilising the Review process to re-examine – and if necessary make appropriate changes to legislation – areas where current UK legislation has not clearly or precisely implemented the European Community obligations relating to the manufacture, import and distribution of medicinal products for human use.

2.3 The changes identified for action within the consultation relate to a wider examination of UK compliance with the governing European legislation on manufacture, import or distribution of medicinal products for human use.

2.4 Where there are outstanding issues of compliance with European requirements and, therefore, a need for the Government to make any necessary changes to UK's domestic legal framework, it is intended that these should be included as part of a single package of amending legislation.

Risks

2.5 It is a requirement of Community law that EC legislation should be implemented in an effective, timely and proportionate manner. Where directives are concerned, the Government's policy is to transpose so as to achieve the objectives of the European measure, on time and in accordance

[10] http://medicines.mhra.gov.uk/inforesources/publications/mlx317annexe.pdf

with other UK policy goals, including minimising the burdens on business. The key risk associated with not taking forward the regulatory proposals is that if the UK is found not to be compliant on any aspect of European Community legislation then the UK would be at risk of infraction proceedings by the European Commission for failing to ensure compliance with the relevant Regulation or Directive.

2.6 At European level, cases of alleged infraction are heard by "Infraction Chefs" in the first instance and may, ultimately, be taken to the European Court of Justice by the Commission for trial if their Reasoned Opinion is not adequately answered. Depending on the severity of the non-compliance, this could result in a heavy fine against the MS concerned plus a direction for an immediate amendment to the offending domestic legislation.

Detail

2.7 The detail of the regulatory proposals can be found at Annex D of MLX317 and this regulatory impact assessment should be read in conjunction with that. Briefly, the Government is proposing changes to UK domestic legislation relating to:

- Importation from third countries;
- Export;
- Application requirements;
- Compliance with the principles of Good Distribution Practice;
- Manufacturing (including compliance with Good Manufacturing Practice) and wholesaling;
- Unlicensed medicines;
- New sanctions

2.9 The proposed changes will result in amendments to the Medicines Act 1968. The Standard Provisions Regulations [11] which currently regulate manufacture and wholesale dealing in medicinal products are to be disapplied as respect products to which the 2001 Directive (as amended) applies and replaced by new regulations, the Medicines for Human Use (manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 which will update and clarify the regulatory obligations on manufacturers and wholesale dealers in medicinal products.

3. Consultation

3.1 The Agency is committed to seeking views from as many interested parties as possible and consulted widely on the regulatory proposals. In particular, we asked for opinions on whether:

- The benefits and costs looked reasonable;

[11] The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971, as amended (S.I. 1971/972)

- The assessment of competition effects looked reasonable;
- The enforcement issues are reasonable and fair;
- There are any unintended consequences.

3.2 Whilst 44 responses (of which 31 offered substantive comments) were received from consultees on the main body of proposals contained within MLX317 (the UK's proposals for implementation of amending Directive 2004/27/EC), there were none at all in respect of the additional changes to legislation outlined at Annex D of the consultation document. This implies that the industry is content with the nature and scope of the proposals.

4. Options

4.1 The UK is obliged to implement European legislative requirements. In parallel with the main 2001 Review implementation process, the MHRA undertook a comprehensive review of the wider regulatory framework as it relates to manufacturing, wholesaling and importation. Several areas of weaknesses were identified, where existing UK legislation does not clearly implement European obligations. The Government took the view that certain elements of the UK's domestic legislative framework were sufficiently imprecise as to benefit from further clarification, in order to assist industry and ensure clear implementation of European requirements. This is explained at Annex D of the consultation package. Accordingly, these measures have been taken forward in the context of this wider review of UK medicines legislation. As such, two options have been identified:

Option 1 – Do nothing and rely, as now, on the existing legislation.

Option 2 – Introduce strengthened (amended) legislation to ensure clarity and consistency between European requirements and the domestic measures which implement them.

4.2 A third option would normally be the consideration of a non-regulatory solution but the context of these proposals coupled with the fact that they relate to the UK's overall compliance with the European regulatory framework make this an unworkable alternative.

5. Costs and Benefits

5.1 The new regulatory requirements around manufacture, import and wholesale dealing seek to clarify European requirements. They establish in UK legislation relevant procedures and processes that are already observed (and subject to inspection/enforcement) within the pharmaceutical sector. As such, there are no additional burdens for industry.

5.2 Many of the proposals (for manufacturing, wholesale dealing and importation) will result in amendments to the present Standard Provisions Regulations, which have themselves been amended fully seven times over the years. These instruments will be revoked (insofar as they relate to Manufacturer's Licences

(MLs) and Wholesale dealer's Licences (WDLs), where these relate to medicinal products covered by the 2001 Directive) and replaced by a single consolidated Statutory Instrument – making it easier for companies and licence holders to navigate through a framework of clearer and simplified legislation.

5.3 The one potential cost burden for industry of the proposals is the amendment to the Medicines Act to provide that import from a third country will in future require a (ML). This will move the requirement from the current provisions relating to (WDLs) to those relating to MLs, which is consistent with the approach in the 2001 Directive (and indeed of other Member States).

5.4 At the present time there is an upward cost differential on the respective licence fees of £1200. However, it has already been made clear at consultation that existing (WL) licenses would simply be "rolled over" into MLs and any related costs would be absorbed by the licensing authority. In addition, new (ML) licences for import from third countries (i.e. those applications submitted after 30 October), would continue to be charged at the WDL rate, as happens now.

5.5 There are no other compliance costs associated with the regulatory proposals.

Benefits

5.6 **Option 1** (do nothing) - There are no perceived benefits. UK manufacturers, importers and wholesalers would potentially be placed at a competitive disadvantage (especially where intra-Community trade is involved) the UK regulatory framework remains unclear and there would be continuing problems relating to enforcement of the provisions. This option would also risk infraction proceedings from the Commission.

5.7 **Option 2** - Implementing the proposed changes to legislation would:

- Ensure that UK legislation framework is clear and fully consistent with European requirements;
- Facilitate a greater emphasis on quality processes in manufacturing, wholesaling and importation;
- Clarify existing legislative requirements;
- Remove the risk of the UK incurring infraction proceedings

5.8 There are no distributional impacts to the regulatory proposals. The proposed measures relate to the pharmaceutical industry and will not disproportionately affect vulnerable or already disadvantaged groups.

6. Small Firms Impact Test

6.1 The regulatory proposals will apply equally to small, medium and large businesses. A "significant impact" can be both a high cost and/or a disproportionate cost on small firms, relative to other sized businesses. The Government believes that neither applies in this case because the proposals relate, in the main, to changes in regulatory processes.

6.2 The Government tested these assumptions with consultees and across interested Government Departments (including the Small Business Service). No significant impacts, nor any unintended consequences were identified.

7. Competition assessment

7.1 The UK pharmaceutical industry is broadly split into two sectors: the innovative (research and development, including biotechnology) industry and the generics industry, with a number of manufacturers of herbal and homoeopathic products and pharmaceutical importers. Around 3000 organisations and companies exist in the pharmaceutical sector in the UK, a significant proportion of which carry out activities that will be affected by these proposals. Although there are some major players in the UK pharmaceutical industry, the MHRA considers that no single company has more than 10% of the market share, no two companies have more than 20%, and no three have more than 50% market share.

7.2 The Government's view is that the introduction of the regulatory provisions is unlikely affect the market structure and size or the number of firms in the UK pharmaceutical industry, as the measures are broadly applicable to both main sectors of the pharmaceutical industry. There is unlikely to be any identifiable change to market shares on the basis of these regulatory proposals. The price and range of end products should be similarly unaffected.

7.3 New businesses entering the market will not be affected differently to existing businesses – they will be required to observe the same processes and standards as existing companies and will be subject to regulation and inspection on that basis. Accordingly, there is unlikely to be any additional set-up or "on" costs for new or potential businesses triggered by the new provisions and, in the Government's view the proposals will not cause any impediment to them competing in the market – nor are they likely to affect significantly the current nature of competition within the affected markets. The MHRA sought views on these points within the formal public consultation but no comments were received.

8. Enforcement, Sanctions and Monitoring

8.1 The Government is mindful not to impose an over-cumbersome regime on the industry whilst, at the same time, ensuring that the provisions are properly enforceable by the MHRA.

8.2 The MHRA will be responsible for enforcement of the Regulations. As with the existing arrangements, inspectors and the Agency's Enforcement Group will continue to provide advice to companies on compliance using guidelines prepared by the Agency.

8.3 For the new inspection arrangements, manufacturers of products who do not comply with the new GMP requirements would face suspension or revocation of their licence or, ultimately, prosecution. Penalties are consistent with other Medicines Act offences (i.e. on summary conviction a fine not exceeding

£5,000 or on conviction on indictment an unlimited fine and/or a 2-year prison sentence).

8.4 The offence of "possession (of a POM) with intent to supply" would be a criminal offence. Criminal offences created under section 2(2) of the European Communities Act 1972 are restricted in terms of available punishment by Schedule 2 to that Act – are restricted in terms of available punishment by Schedule 2 to that Act – i.e. not punishable with imprisonment for more than two years or a maximum fine, on summary conviction, of £5000.

8.5 The Government will continuously monitor the impact of the new Regulations and make any necessary changes. Where significant policy amendments are proposed, there will be further consultation to ensure the views of the industry are represented.

9. Implementation and Delivery Plan

9.1 There is no specific delivery plan as such as the proposals merely "tidy-up" existing legislation and pose no additional costs or burdens. The MHRA is nevertheless holding a training seminar on the 21st September 05 to provide further information on the new procedures and to give stakeholders another opportunity to seek clarification on the new provisions. Over 110 people have confirmed their attendance.

10. Post-implementation Review

10.1 There is no specific post-implementation review as such. The Government will, however, continuously monitor the impact of the new Regulations through the established regime of inspections.

11. Summary and Recommendation

Option	Total Benefits	Total Costs
1	There are no associated benefits. UK manufacturers, importers and wholesalers would potentially be placed at a competitive disadvantage if they were unable to demonstrate compliance with European requirements and there would be continuing problems relating to enforcement of the provisions. This option would also risk infraction proceedings from the Commission.	N/A
2	Implementing the proposed changes to legislation would: - Ensure that UK legislation complies fully with European requirements; - Facilitate a greater emphasis on quality processes in manufacturing, wholesaling and importation;	None identified

	-Clarify existing legislative requirements; - Remove the risk of the UK incurring infraction proceedings	

11.1 It is recommended that option 2 be supported and implemented. There are clear benefits for industry from harmonising UK legislation with European requirements. The regulatory proposals will result in clearer, more accurate and more consistent information about the standards to be met by pharmaceutical manufacturers, importers and wholesalers and will provide a level playing field for industry. These regulatory proposals allow the UK to fulfil its Community obligation to implement the provisions of European legislation. The Government plans to implement the changes by 30 October 2005.

12. Declaration

I have read the regulatory impact assessment and I am satisfied that the benefits justify the costs

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Date: 5th October 2005

Minister of State, Department of Health.

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