EXISTING LEGISLATION RELATING TO MEDICINES FOR HUMAN USE

The manufacture, marketing and distribution of medicinal products for human use in the European Community is governed by Directive 2001/83/EC (“the 2001 Directive”). This Directive consolidates a number of earlier EC directives (in particular Directive 65/65EEC) and sets out a comprehensive Community code for medicines for human use. The key requirement is that no product maybe placed on the market in any Member State of the Community, unless it has a “marketing authorisation” granted by a national competent authority under the provisions of the Directive, or a Community-wide authorisation granted by the European Commission under Regulation (EC) No. 2309/93. The Directive sets out rules governing how such authorisations are granted and the basis on which they may be suspended, varied or revoked. The Directive also governs: the manufacture, wholesale distribution and advertising of medicinal products; labelling and patient information leaflets; pharmacovigilance (the monitoring of drug safety); classification of medicinal products (i.e. into products which are subject to medical prescription and those which are not); and supervision and sanctions (for example, provisions regarding inspections by national authorities).

The Directive is also supported by guidance issued by the European Commission in “The Rules governing medicinal products in the European Union” (http://pharmacos.eudra.org/F2/eudralex/index.htm). In particular:

- Volume 2A contains the “Notice to Applicants” which provides guidance on the procedures for MAs and on the content of the dossier of data which must accompany each application for authorisation
- Volume 9 contains guidance on pharmacovigilance, including the reporting of ADRs to medicines

The 2001 Directive is implemented in the UK by various pieces of legislation. In particular:

- The Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994 (S.I. 1994/3144) ("the MA Regulations"), as amended, implement the provisions of the Directive relating to the grant, variation, suspension and revocation of MAs and the obligations of MAHs (including obligations relating to pharmacovigilance, labelling and package leaflets)
- Sections 8 to 24, and 28 to 30, of the Medicines Act 1968, and various orders and regulations under those provisions, including the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (S.I. 1971/972), implement the provisions of the Directive in relation to manufacturing and wholesale distribution
Sections 108 to 126 provide for the enforcement of the Act and the 1994 Regulations, and thereby implement the provisions of the Directive relating to supervision and sanctions


The interpretation and operation of these is explained in various guidance notes prepared by the MHRA. For manufacturers and wholesalers, the relevant Guidance notes are 5, 6 and 13. Those covering advertising, labelling and disease awareness campaigns are 23 and 24, and 25 and 26 respectively. Guidance notes relating to MAs can be found on the MHRA’s web-site at:

http://medicines.mhra.gov.uk/inforesources/publications/guidnotepub.htm

The amendments made by Directive 2004/27/EC will affect the procedures followed by the MHRA. The following sections of the consultation indicate the proposed changes to procedure, as well as the MHRA’s interpretation of the effect of the new provisions.

**Directive 2004/27/EC**

Article 1 of Directive 2004/27/EC sets out the amendments to the 2001 Directive. The amendments, and the proposals for implementation, are explained in more detail below.

**Summary of changes to legislation**

In order to implement the Directive, the relevant provisions of UK legislation would be amended.

**Marketing authorisations**

The amendments made by Directive 2004/27/EC in relation to MAs including requirements for labelling, package leaflets and pharmacovigilance, are contained in Article 1(1) to (12) and (16) to (30), (40) to (53), (73) to (76), (79), (80), (83) and (86). We propose that these provisions would be implemented by amending the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 (“the MA Regulations”). The amending regulations would be made under section 2(2) of the European Communities Act 1972.

The MA Regulations do not set out all the obligations on MAs in detail. Instead, the Regulations provide that authorisations must be granted, varied, suspended or revoked in accordance with the “relevant Community provisions” and that MAHs must comply with the obligations imposed on them by those provisions. To ascertain the precise obligations, the MHRA and the MAH must refer to the European legislation itself. We propose to continue that approach to the drafting of UK legislation relating to MAs, rather than “copying out” the detail of the provisions, or seeking to elaborate the provisions in detail in UK legislation. The definition of “relevant Community provisions” would simply be amended to include a reference to the amendments made
by Directive 2004/27/EC. We would be grateful for your views on whether you agree with this approach.

A number of other changes are however proposed; for example creating new criminal offences for the breach of new obligations.

Manufacturing, wholesale distribution

The amendments made by Directive 2004/27/EC in relation to manufacturing, wholesale dealing and are contained in Article 1(32) to (39) and (55) to (60), (77) and (78). We propose that these provisions be implemented by making regulations under section 2(2) of the European Communities Act 1972 to amend the relevant provisions of the Medicines Act 1968. Regulations would also be made to amend the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (S.I. 1971/972). The changes to implement the Directive would be combined with the other amendments proposed in Annex D.

Advertising

The amendments made by Directive 2004/27/EC in relation to advertising are contained in Article 1(61) to (72). We propose to implement these provisions by amending the Medicines (Advertising) Regulations 1994.

Homoeopathic Regulations

Article 1(12) to (15), (31), (60), (71) and (81) of Directive 2004/27/EC make amendments to the 2001 Directive in relation to homoeopathic medicinal products. We propose to implement these provisions by amending the Medicines (Homoeopathic Medicinal Products for Human Use) Regulations 1994 (S.I. 1994/105).

Other changes

Other miscellaneous changes would be implemented by regulations under section 2(2) of the European Communities Act 1972; i.e.

- The new Article 5(3) and (4) of the 2001 Directive, inserted by Article 1(4) of Directive 2004/27/EC, which requires Member States to lay down provisions to ensure that authorisation holders, manufacturers and health professionals are exempt from civil liability for the consequences of using an unauthorised medicines, or using an authorised medicine outside its licensed indications, where that use is authorised or recommended by the competent authority in the event of a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation
- Article 1(87) which inserts a new Article 127b of the 2001 Directive, requiring Member States to ensure that appropriate collection systems are in place for unused or expired medicines

Format of description of provisions
The provisions have been arranged to follow the life-cycle of the product, from the revised definition of a medicinal product, through the rules governing MA applications and post-licensing activities to manufacture, importation and wholesale distribution. Finally, there are separate sections covering the application of the revised provisions to homoeopathic products, herbal products, and parallel imported products.

For each provision, the Article of the 2001 Directive which is amended or inserted is provided, together with the paragraph of Article 1 of Directive 2004/27/EC which makes the amendment.

CHANGES TO DIRECTIVE 2001/83/EC (as amended by DIRECTIVE 2004/27/EC)


**Articles 1(2) and 2(2) - Definition of a medicinal product (Articles 1(1) and 1(2) of amending Directive 2004/27/EC)**

**Summary**

The definition of a medicinal product in Article 1(2) of Directive 2001/83 EC has been changed. The new definition states that to be a medicine a product must be:

(i) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(ii) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

A new provision has been added to Article 2. Article 2(2) of Directive 2001/83 EC as amended now states that:

“In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a product covered by other Community legislation the provisions of this Directive shall apply.”

Taken together, these provisions are intended to ensure that where doubt exists over whether a product – those on the “borderline” between, for example, medicines and medical devices, medicines and cosmetics, medicines and food supplements etc – should be regulated under medicines or other sectoral legislation, the stricter medicines regulatory regime should apply.
EU discussions

The borderline most likely to be affected is the medical device/medicine “borderline”, because of the change to the definition of a medicinal product. The European Commission held a meeting of MS and other stakeholders in October 2004 to discuss the change in the definition, and has issued a general communication addressing the borderline products but implications for specific products have not yet been determined.

UK implementation

The Government will, acting within the framework of the new provisions, continue to regulate products at the “borderlines” between foods/medicine, cosmetics/medicine or biocide/medicine. The MHRA anticipates that this provision will only impact on the regulation of a very small number of products (those that do not act by pharmacological, immunological or metabolic means) with respect to the borderline between medicinal products and medical devices. These may be reclassified as medical devices. However, the decision on which products are to be reclassified will be subject to the outcome of European discussions to maintain a harmonised approach. The MHRA will revise its Guidance Note 8 to reflect the Commission’s position and the new definitions.


Summary

The definition of “risk to public health” has been replaced by a definition of “risks related to use of the medicinal product”. The definition now has four components – in addition to the current definition which defines risk to public health in terms of the quality, safety and efficacy of the product, the revised legislation provides that risks related to the use of a medicinal product includes any risk of undesirable effects on the environment from use of the product.

Risk-benefit balance

Article 1(28a) defines the risk-benefit balance as an evaluation of the positive therapeutic effects of the product in relation to the risks to patients’ or public health. The environmental component of the definition of risks is excluded from the risk-benefit balance.

Under the new legislation, the risk-benefit balance is considered as part of Article 23 (which enables the competent authority to continuously assess the risk-benefit balance by requesting relevant data from MA holders), and Article 104 (relating to the submission by MA holders of Periodic Safety Update Reports (PSURs). Further information on the application of the risk-benefit balance to these provisions is outlined under the relevant articles.

Environmental risk assessment
Article 8 requires that an evaluation of the environmental risks posed by the product is submitted with the MA application. Article 23 (2nd paragraph) requires MA holders to inform the competent authority of any new information that might influence the evaluation of benefits and risks of the medicinal product – in our view this includes environmental risks as defined under Article 1(28).

**UK implementation**

The assessment of risk-benefit in relation to patients’ and public health from a product will remain unchanged. However, in relation to the new provision, applicants will be required to submit in the dossier an evaluation of potential environmental risks. This requirement is also set out in the list of particulars and documents to be submitted with an application at Article 8(3). The risk-benefit balance applies throughout the life-cycle of the product (see in particular Articles 23 and 104).

**Article 5 – distribution of unauthorised products and arrangements for responding to the release of pathogenic agents, toxins etc (Article 1(4) of Directive 2004/27/EC)**

Article 1(4) of Directive 2004/27/EC replaces the existing Article 5 of the 2001 Directive. New Article 5(1) continues the existing provision under which Member States may allow the supply of unlicensed products to fulfil “special needs”; the existing UK legislation relating to “specials” (Schedule 1 of the MA Regulations) is therefore unaffected.

Article 5(2) and 5(3), however, are new. They enable Member States to adopt measures to respond the suspected or confirmed release of pathogenic agents, toxins, chemical agents or nuclear radiation which could cause harm. They are explained in more detail below.


**Summary**

This new provision will allow MS to authorise on a temporary basis the distribution of unauthorised (that is, products without a MA and not licensed in the normal way) medicinal products in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation.

**UK implementation**

Regulation 3(1) of the MA Regulations prohibits the placing on the market or the distribution of products without an MA, but subject to exemptions or exceptions set out in the “relevant Community provisions”. By amending the definition of that expression, to insert references to the changes made by Directive 2004/27/EC, the UK will be able to rely on this new provision in the event of a suspected or confirmed release of toxins, agents etc., without further changes.
Article 5(3) – addressing liability issues associated with Article 5(2) (Article 1(4) of Directive 2004/27/EC)

Summary

This article requires MS to lay down provisions to ensure that MAHs, manufacturers and health professionals are not subject to civil or administrative liability associated with the use of unauthorised products, or the use of authorised products otherwise than in accordance the authorised indications, in the circumstances described in Article 5(2). The provision is intended to ensure that where a competent authority (in the UK, the MHRA/Secretary of State) recommends or authorises such use, in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation, MAHs, manufacturers and health professionals will not be vulnerable to legal actions against them for injury resulting from such use.

MAHs, manufacturers and health professionals will however still be subject to the provisions of the criminal law. In addition, Article 5(4) provides that liability for defective products provided for by Council Directive 85/374/EEC is unaffected.

UK implementation

We propose to implement this provision by making regulations under section 2(2) of the European Communities Act 1972 to the effect that a MAH, a manufacturer or a health professional shall not be liable in tort for any harm or injury caused to a person, if that harm or injury is a direct consequence of the use of an unauthorised medicinal product, or the use of an authorised product otherwise than for an authorised indication, provided that the use was recommended or authorised by the MHRA and/or the Department of Health in the circumstances set out in Article 5(2). Those companies and individuals would therefore be immune from claims for damages arising from alleged negligence, provided that the court is satisfied that the harm arose as a consequence of the recommended use of the product in question.

The immunity would apply to MAHs, in relation to the use of their products outside the licensed indications. For manufacturers, the immunity would relate to the use of any product manufactured by them. For health professionals, the immunity would apply where they were involved in prescribing or administering the product in question.

We propose that the immunity would not apply in relation to harm arising from use of a product outside the MHRA/DH recommendations.

In accordance with Article 5(4), the immunity would not extend to liability for defective products under section 2 of the Consumer Protection Act 1987. A person harmed by a defective medicinal product may therefore still be able to make a claim under that section, even though its use was recommended by the MHRA/DH.

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1 OJ No. L210, 7.8.1985, p.29
We are considering whether the immunity should cover actions for breaches of contracts; whether the immunity should extend to individual employees or agents of a MAH or manufacturer; and whether any other limitations or restrictions are appropriate, while ensuring that the UK complies with its obligations under Article 5(3). We would be grateful for your views on these points.

PROVISIONS GOVERNING APPLICATIONS FOR MARKETING AUTHORISATIONS (MAs)

As indicated in the summary of changes to legislation (see above), the MA Regulations provide that MA applications must be made and determined in accordance with the “relevant Community provisions”. We propose to amend the MA Regulations by adding references to Directive 2004/27/EC to the definition of “relevant Community provisions”. This would mean that as from 30th October, the changes set out below would have effect in relation to UK MA applications made to the MHRA.

One provision (Article 10(6)) also requires amendment to UK patent law.


Summary

Under the amended legislation, and following the granting of an initial MA, all strengths, pharmaceutical forms, administration routes, presentations and any variations and extensions will be considered as part of the same global MA in particular for the purpose of applying Article 10(1) concerning generic product applications.

EU discussions

In particular, Member States have debated whether a MA based on submission of a new full dossier and with a new brand name should be considered within or outside the initial global MA and whether completely new combination products create a new global authorisation. UK proposals for implementation take account of the outcome of these discussions.

UK implementation

The scope of changes considered to fall within the initial MA will be as described in the amending Directive and will encompass all versions of the original product having the same active substance(s) authorised to the same company, group of companies or their licensees. The data content of the dossier associated with such versions or their designation as extension applications will not be factors in determining whether these form part of the same initial authorisation for purposes of applying Article 10(1). Despite the 'global MA' concept, new PL numbers will still be needed in the UK for line extension products falling within the scope of Annex II of the Variation Regulation (1084/2003/EC) which sets out the type of changes needing a new marketing authorisation application.
In our view, the ‘global MA’ concept under Article 6(1) reflects recent judgments of the European Court of Justice (Case C-106/01 R (on the application of Novartis) v. Licensing Authority and Case C-36/03 R (on the application of Approved Prescription Services) v. Licensing Authority) and therefore will not change current UK policy with regard to data exclusivity for existing or new products and their line extensions.

Article 8 – Documents to be submitted with MA applications (Article 1(7) of Directive 2004/27/EC)

Summary

Article 1(7) amends Article 8 of the 2001 Directive, which sent out the information which must accompany a MA application. The effect is that a number of additional items must be submitted with the MA application, the most significant of which are:

- an evaluation of potential environmental risks posed by the product;
- a description of the pharmacovigilance and risk management systems to be introduced by the applicant;
- an SPC including a mock-up of the outer packaging together with a package leaflet;
- proof of the existence of a pharmacovigilance QP;
- the means to enable the notification of ADRs.

EU discussions

Member States are still discussing the detail of implementing these new provisions and revised guidance in the Notice to Applicants (Volume 2 of the Rules governing medicinal products in the EU) and Volume 9 of the rules governing medicinal products in the EU will be published by the European Commission later this year.

UK implementation

All new MA applications (from 30th October 05) will be required to include an evaluation of the potential environmental risks posed by a medicinal product and, where necessary, a description of the steps taken to limit those risks. The previous legislation required such data only “if applicable”. This amendment therefore represents a change to current practice in which, with few exceptions, only applications for new active substance products needed to include environmental risk assessment data. The type of data and format required will need to be defined by guidelines developed at a European level.

It should be noted that the derogations available under new Articles 10, 10a and 10b from the need to supply certain types of data (see below) concern only the data described in Article 8(3)(i). Therefore there is no such derogation from the need to include the storage, safety and disposal precautionary measures or potential environmental risk evaluation required by the new Article 8(3)(g). Generics applicants must therefore provide the particulars outlined in Article 8(3)(g) with their MA application.
A detailed description of the pharmacovigilance system to be introduced by the applicant must be included in every case, but details of a “risk-management plan” only where appropriate (see the new Article 8(3)(ia). The UK is likely to require details of the risk-management plan from MAHs who are applying with a new active substance, or significant new formulation, route or an expanded patient population for an existing product or if there are safety issues which could impact on the risk benefit post-authorisation or if regulators consider a plan necessary for any other reason.

This provision will apply to all products for which an application for a MA was submitted after 30th October 05.

**Article 26 – grounds for refusing to grant a MA (Article 1(24) of Directive 2004/27/EC)**

**Summary**

The grounds for refusing a MA are amended by Article 1(24) of Directive 2004/27/EC. The new provision requires the competent authority to refuse an application if the risk-benefit balance (i.e. the evaluation the positive therapeutic effects in relation to the risks relating to quality, safety or efficacy of the product as regards patients’ health or public health) of the product is not favourable, if the therapeutic efficacy is insufficiently substantiated, or if its qualitative and quantitative composition is not as declared. The application may also be refused if the documents are not submitted in accordance with the requirements set out in the Directive. The MA holder/applicant is responsible for the accuracy of the data and documentation submitted.

The unfavourable risk-benefit balance is the new ground for refusal and replaces the existing ground that the product is “harmful in the normal conditions of use”. In practice, in considering whether a product met the existing test, the risk of harm had to be considered in relation to the therapeutic benefits of the product (see recital (7) of the 2001 Directive), so in practice the risk-benefit approach was already being applied.

**UK implementation**

The new text will not change MHRA practice. It applies immediately from 30th October 05 to all products on the market.

**Article 10(1) – harmonised periods of data and market exclusivity (Article 1(8) of Directive 2004/27/EC)**

**Summary**

The revised legislation provides for 10 years’ market exclusivity following initial authorisation for innovative products authorised under Articles 6 and 8 of the amending Directive. Second applicants for generic product authorisations based on abridged dossiers may submit applications no earlier than 8 years (the data exclusivity period) from the date of initial authorisation of the innovative reference product and
obtain a MA (a product licence.) However, they may not place their products on the market until the 10 year period has elapsed.

The 10 year period of market exclusivity for innovative products may be extended to a maximum of 11 years if, during the first 8 years from the date of initial authorisation, the MAH obtains an authorisation for one or more new therapeutic indications which are deemed to bring a significant clinical benefit in comparison with existing therapies.

According to Article 2 of the amending Directive, these new periods of data and market exclusivity will only apply to those reference innovative products which have been submitted for authorisation within the Community on or after the date of transposition of these measures into national legislation (that is, from 30th October 05). For products with applications submitted prior to that date, the existing data exclusivity periods apply (6 or 10 years; in the UK 10 years) apply.

Where the reference innovative product has not been authorised in the UK, a generic version can nonetheless be authorised by reference to a MA for the reference product granted in another MS. The other MS must supply all relevant documentation requested for this so-called “European Reference Product”.

**EU interpretation**

The applicable period of data and market exclusivity to apply for ‘European Reference Products’ has been discussed but, at the date of this consultation, has not been agreed. The data and marketing exclusivity periods applicable will be either those which apply in the reference product authorising state or those which apply in the generic authorising state. This is significant for reference products for which applications were submitted prior to 30th October 05, as for those products the existing exclusivity periods apply, which may differ in different MS.

Whether a new indication represents a significant clinical benefit and hence whether the product qualifies for an additional year of market exclusivity, will be evaluated as part of the product assessment and will be included in the assessment report. Where these reports are shared with other MS for purposes of centralised, decentralised or mutual recognition authorisation procedures, there will be an opportunity for the MS to establish an agreement on the significance, or otherwise of the new indication.

**UK implementation**

Amended Article 10(1) replaces the concept of “essential similarity” with that of a “generic” (defined in Article 10(2)(b)) and will be implemented in UK regulations as stated above.

Until implemented the UK would not be able to supply confidential data on so-called European Reference Products to another MS. At present the UK considers that once implemented the applicable periods of data and marketing exclusivity to apply in these cases are those in force in the generic-authorising MS because this is where the data will be used to authorise the generic product, but this view is not universal in Europe.
In relation to the meaning of "significant clinical benefit", our view is that we would expect that the indication had not previously been authorised in relation to any other product containing the same active substance and/or extended to new categories of patients.

In those cases where a MA under Article 10(1) is issued before the expiry of the 10 year or 11 year period of market exclusivity for a reference product, the authorisation document issued by the UK authority will indicate the earliest date on which that product can be placed on the market. This will allow holders of such authorisations to proceed to request their mutual recognition in other MS.

The new periods of data (8) and marketing (10 or 11) exclusivity will be available only to those original products for which an application is received on or after 30th October 2005 (in accordance with Article 2 of the Amending Directive 2004/27/EC).

**Article 10(2)(a) and 10(2)(b) – definition of a reference medicinal product and generic medicinal product (Article 1(8) of Directive 2004/27/EC)**

**Summary**

A reference medicinal product for a generic product application is one which was authorised with data as described in Article 8. A reference medicinal product can be any of the product versions (extensions) included in the ‘global’ authorisation envisaged by Article 6. Since that does not include generic products, as they are authorised under Article 10 with an abridged dossier, generic products cannot themselves be reference products for other abridged applications. Line extension products on the other hand, for example new pharmaceutical forms of an existing product, do fall within the 'global authorisation' envisaged by Article 6.1 and so can be reference products for generics. Note also that Article 10(1) now requires a reference product to be a product that “is or has been authorised”. It is therefore not necessary for that product to be marketed, or for the MA to be current at the time of a generic product application.

The definition of “generic medicinal product” in Article 10(2)(b) initially follows the definition of “essentially similar” provided by The European Court of Justice in 1998. However it also includes broader definitions of qualitative composition (to include different physical and chemical forms of the active substance with the same safety and efficacy) and of pharmaceutical form (all the various oral immediate release forms). This is consistent with the existing guidance in the Notice to Applicants and makes clear that such products with minor differences in the active substance or within that group of pharmaceutical forms will in the future be considered as ‘true generics’.

**UK implementation**

The UK proposes to implement these provisions in line with explanations given above. In addition we consider that products authorised under new Article 10b (and authorised, prior to the implementation of the new provisions, under the existing
Article 10(1)(b) - i.e. new combinations) should continue to be valid reference products for generic product applications.


Summary

This article replaces the final paragraph of Article 10(1)(a)(iii) (the ‘proviso’) which previously provided the legal basis for applications for those products with different uses, different routes of administration or different doses compared to the reference product (often referred to as “hybrid” applications). Our interpretation of the existing provision is that it impliedly covers other differences (e.g. strength). The amended article applies explicitly to products with a different strength, different pharmaceutical form, changes to the active substance or products for which bioequivalence cannot be demonstrated. The list of differences is similar to that already included in the Notice to Applicants guidance document. Since these differences mean a departure from the strict definition of a generic given in Article 10(2)(b), the results of appropriate pre-clinical tests or clinical trials must be submitted in addition to reliance on reference product data.

UK implementation

The legislation will be applied in accordance with the description of the provisions given above. Changes to the active substance envisaged under this Article would be those which meant that it had a significantly different safety and/or efficacy compared to the active substance in a reference product and therefore additional test and trial data would be needed.

Article 10(4) – provisions relating to similar biological products (Article 1(8) of Directive 2004/27/EC)

Summary

This article distinguishes similar biological products from generic chemical products by requiring the former to be supported by their own appropriate additional test or trial data where they cannot be precisely and reliably defined as meeting all of the three criteria in the definition of a “generic”.

UK implementation

The legislation will be applied in accordance with the description of the provisions given above. Guidance on the requirements for additional test or trial data will be developed at the European level.

Article 10(5)– data exclusivity for new indications of well-established substances (Article 1(8) of Directive 2004/27/EC)

Summary
This new provision gives a “non-cumulative” one year period of data exclusivity for an application for a new indication for a well-established substance, where the applicant can demonstrate that significant clinical or pre-clinical studies were carried out in relation to the new indication. This means that no other applicant may refer to the first applicant’s data for one year after authorisation of the new indication.

**EU discussions**

The “non-cumulative period” is considered to mean no more than one additional year of data exclusivity can be awarded for a particular authorisation. This additional year of data exclusivity can however be awarded whether or not the original product had already benefited from an additional one year of market exclusivity under the 4th paragraph of Article 10(1).

**UK implementation**

The requirement for the new indication to be supported by, in particular, significant clinical studies will require the submission of the results of controlled clinical trials in the target patient population. Summary results, for example using published papers, would not be considered sufficient evidence.

For the purposes of the application of this measure we consider that “well-established substance” has the same meaning in Article 10(5) as in Article 10a and elaborated in Annex I to the Directive.

We do not consider this provision to be only ‘prospective’ for products authorised after 30th October 05 and the additional 1 year period of data exclusivity will be available to already-granted as well as new products if their active substance satisfies the ‘well-established use’ test.


*Please note that the following provisions and proposals for implementation apply to equivalent provisions for both human and veterinary medicines*

**Summary**

This new provisions will allow manufacturers of generic versions of products to undertake within the EU certain preparatory studies and trials before patent and supplementary protection periods associated with the innovative product have expired. They also state that the “consequential practical requirements” of conducting such tests and trials shall likewise not constitute infringement of patent rights.

**EU discussion**

The type of studies and trials which would not be contrary to patent rights have been discussed but no list agreed at a EU level.
Activities associated with the development of any of the products supported by ‘abridged’ dossiers relying on data for reference products without consent, and submitted under new Articles 10(1) to 10(4) of the 2001 Directive (or new Article 13 of Directive 2001/82/EC) would qualify for this exemption where otherwise patent rights or supplementary protection certificates are in force in the UK. We propose to implement the provision by amending the relevant UK patent law; for example by amending section 60(5) of the Patents Act 1977. Section 60(5) lists circumstances in which certain acts which would otherwise constitute an infringement of a patent are deemed not to be. The amendment would provide an exemption for acts which consist of conducting the tests and trials referred to in the Directives’ provisions and the “consequential practical requirements”, but which would otherwise constitute an infringement of the patent for the original product.

The exemption would in our view cover the following activities:

i.) the carrying out of chemical and biological synthetic processes suitable for the making, disposal or keeping of the active substance(s) including the manufacture or the import of batches in quantities sufficient to provide material for preparing investigative batches of the medicinal product and to validate the processes to the satisfaction of the competent authorities.

ii.) the development, testing and use of the associated analytical techniques for the above.

iii.) the development of the final pharmaceutical composition and manufacturing processes for the medicinal product to be marketed including the making, disposal or keeping or import of product batches in quantities sufficient to conduct the necessary pre-clinical tests, clinical and bioavailability trials and stability studies of the medicinal product and to validate the processes to the satisfaction of the competent authorities.

iv.) the development, testing and use of the associated analytical techniques for the above.

v.) the manufacture and supply to the competent authorities of samples of active substances, their precursors, intermediates or impurities and of finished product samples.

vi.) the compilation and submission of a MA or Variation application and application for a MA.

The ‘necessary studies and trials’ and the ‘consequential practical requirements’ covered by the exemption would not however include:

viii) The manufacture, packaging and testing of the active substance or finished product not required for conducting the tests and trials necessary for gaining authorisation or for providing small quantities as samples.
It is our view that the non-infringing study and trial activities could be carried out as from the dates of the proposed amendment to patent legislation in the UK (30th October 05) as long as those activities are for the purposes of submitting an application under Article 10 paragraphs 1, 2, 3 and 4 of the 2001 Directive (or Article 13, paragraphs 1 to 4 of Directive 2001/82/EC) and regardless of whether the reference products were submitted for authorisation before, or after 30th October 05, and are protected by old or new periods of data and market exclusivity.

**Article 10a – authorisation applications for well-established substances (Article 1(9) of Directive 2004/27/EC)**

**Summary**

This provision is equivalent to the existing Article 10(1)(a)(ii) and in our view has the same effect. It provides that the applicant will not be required to provide the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substances have been in well-established use in the EU for at least 10 years. Recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I are required. Test and trial results would be replaced by appropriate scientific literature.

**Article 10b – New Combination Products (Article 1(9) of Directive 2004/27/EC)**

**Summary**

The results of new pre-clinical tests or new clinical trials for the new combination products must be submitted in accordance with Article 8(3)(i) but the results of tests and trials of the individual substances need not be submitted. This replaces the existing Article 10(1)(a)(ii).

**EU discussion**

In order to maintain the principle that a complete dossier must be available, the need to specify one or more reference product authorisations for single active substance products in the application has been discussed. In principle, the usual periods of data exclusivity would apply to that data unless consent had been given for its use by a second applicant.

EU discussions have also considered whether new combination packs (so called ‘convenience’ packs in which new combinations of active substances are presented in separate dosage forms) should be authorised on this legal basis. At present the majority opinion is that they should not be so authorised.

**UK implementation**

MAs approved under this article will be considered to establish a new and unique global authorisation as described in Article 6 and therefore new periods of data and marketing exclusivity would apply to new combination products. This is the same approach for UK applications as under the existing legislation (Article 10(1)(a)(ii)).
Likewise we anticipate that new combination medicinal products may be reference products for generic or other abridged applications submitted under the new Articles 10(1) to 10(4) on expiry of the new combination data exclusivity period, because their dossier contains new and original data.


**Summary**

This amendment will now allow reference to the pharmaceutical (product quality) data, as well as the pre-clinical and clinical documentation submitted with another product which has been granted a MA and where its authorisation holder has given permission. The new product and the reference product should therefore have the same active substance composition and the same pharmaceutical form but unlike the requirement in Article 10(1)(a)(i) of the present legislation, need not be essentially similar – they must have the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form, but need not be bioequivalent.

**EU discussion**

In order to rely upon an entire dossier of quality, safety and efficacy data, the active composition of the new and reference products should be the same inasmuch as different physical or chemical versions of the active substance will not be permitted. Where consent is given to refer only to pre-clinical and clinical data but a second applicant supplies their own pharmaceutical (quality) data it is considered that the proper legal basis of that submission would be under Article 8, rather than Article 10c.

**UK implementation**

This article would now provide the legal basis for what in the UK are known as ‘piggy-back’ applications for the same or a second applicant.


**Summary**

There is a reordering of the information to be included in the SPC. In addition, the final paragraph of Article 11 states that for authorisations under Article 10, those parts of the SPC of the reference product referring to indications or dosage forms that are still covered by patent law at the time when a generic medicine is marketed need not be included. This provision will allow the authorisation of generic products with indications that vary between MS to take account of usage patents in force on the innovative product in certain MS. Under the current rules, some MS would only accept an authorisation of the generic with those indications that did not have a usage patent anywhere in the EU.

**EU discussion**
European fora have discussed the extent of changes permitted in the SPC of generic and other products relying on the data of a reference product for which certain dosage forms or indications are covered by patent law and the practical implications of this.

**UK implementation**

The UK takes the view that whilst it may be acceptable to omit reference to certain indications and dosage forms it may not be permissible to omit associated warnings or contraindications where those are important for the protection of public health. Therefore the extent of modifications possible for a particular generic product SPC would be judged on a case by case basis. We propose that the reordering of the SPC for existing products would be undertaken when other regulatory action triggered changes to the SPC, minimising any burden of the change.

**Articles 17(2), 17(3) and Article 18 – use of mutual recognition and decentralised procedures (Article 1(16) of Directive 2004/27/EC)**

**Summary**

Applications in two or more MS must be submitted in accordance with the mutual recognition and decentralised procedures (Articles 27 – 39). Whereas previously MS might assess applications submitted in parallel in more than one MS, now they must decline applications where it is apparent that an application has been made or a MA granted for the same product in another MS.

**EU discussions**

The meaning of the description “same product” for the purposes of these articles will be based on the composition of the products and the relationship between their MA applicants or holders but not on a comparison of their dossiers or their SPCs.

**UK implementation**

In accordance with these articles the UK will no longer assess MA application is parallel with other MS unless it can be justified that the products are in fact different. Article 8(3)(l) will continue to require applicants to disclose information on other applications submitted or authorisations granted in the Community and to keep that information up to date. The new Article 17 would to all applications for a MA submitted after 30th October 05.


**Summary**

This article comprises various amendments to cross-references consequential to changes to Articles 10, 111 and 114.

Summary

Where an applicant wishes to market a product in more than one MS, an identical dossier will be sent to all relevant MS. If an authorisation has not been previously granted, one MS will be appointed by the applicant to act as reference MS who will prepare a draft assessment report with a draft SPC and a draft of the labelling and package leaflet. The concerned MS will have the opportunity to review and approve the documents. Disagreements will be referred to the Co-ordination Group for resolution and if unresolved, the CHMP will arbitrate and deliver an opinion.

EU discussions

These have concentrated on the operational rules of the decentralised procedure and of the new Co-ordination Group (which is to replace the MR).

UK implementation

We will implement this as in the Directive, and when appropriate and time permits, UK rapporteur assessments will be referred to the Commission on Human Medicines (which will replace the CSM in autumn 2005) for its opinion.

Articles 21(3) and 21(4) – transparency (Article 1(19) of Directive 2004/27/EC)

Summary

A new provision obliging the competent authorities to make publicly available without delay the MA, SPC, Assessment Report, and reasons for the opinion after deletion of commercially confidential information.

EU discussion

Where mutual recognition or decentralised procedures are used the Reference MS (which may not be the UK) is responsible for the timely preparation and maintenance of the Public Assessment Report. The report will be provided in English.

UK implementation

The MHRA intends to use website publication in order to fulfil these obligations. We propose that the working definition of commercially confidential information (for deletion) would closely follow that used by the EMEA for products authorised in the Centralised Procedure and be consistent with the exemptions set out in the Freedom of Information Act. Applicants would be given the opportunity for pre-publication comment. It is envisaged that this provision would be applied to new product and significant variation applications submitted after 30th October 2005.
Article 126a – authorisation by Member States of medicinal products (Article 1(84) of Directive 2004/27/EC)

Summary

This provision allows a MS to authorise on public health grounds the marketing of a product on its territory even if the MAH has not made an application for an authorisation to that competent authority. It requires, nonetheless, that the authorising MS ensures that the following requirements of the legislation can still be met: titles V (leaflets and labels), VI (classification), VIII (advertising), IX (pharmacovigilance) and XI (supervision and sanctions).

EU discussion

There has been discussion on the operation of this provision if implemented early in MS. There has also been discussion at a European level of the circumstances under which this measure would be used, for example where there was an urgent unmet medical need across a significant number of patients.

UK implementation

The UK proposes to amend the MA Regulations, so as allow the MHRA to grant authorisations under this provision if necessary. Generally, we would not envisage using this provision to grant authorisations. The UK has a well–established national regime that enables supply provision which enables clinicians to supply products not authorised in the UK if a patient needs them (see Schedule 1 of the MA Regulations). But by ensuring the necessary provision is implemented in national law, it would permit the procurement and supply of a large volume of otherwise unavailable medicinal products, than could otherwise be achieved under the existing provisions of Schedule 1, in the event that was ever necessary on public health grounds.

The UK provision would ensure that if an authorisation under Article 126a was granted, the company marketing the product concerned will be responsible for complying with obligations relating to product labelling, patient leaflets, supply, advertising and pharmacovigilance.

Article 22 – conditional authorisations (Article 1(20) of Directive 2004/27/EC)

Summary

The provision permits the competent authority to grant a MA for a product which may not otherwise be authorised, following consultation with the applicant, subject to a requirement for the applicant to comply with certain conditions concerning the safety of the product and pharmacovigilance. The justification for such conditional authorisations must be one of those detailed in Annex I to the Directive (see Section 6 of Part II of the existing Annex). The provision is similar to the existing Article 22, which it replaces. But it now specifies that the conditions may include conditions relating to the safety of the product and action to be taken (not simply the notification of adverse events). It also includes new requirements that the continuation of the MA
must be linked to an annual assessment of these conditions and that the list of conditions (with the relevant deadlines and dates of fulfilment) must be published.

**UK implementation**

Our view is that the new requirement that continuation of such an authorisation would be linked to an annual reassessment of the conditions means that the authorisation would have to be revoked if those conditions were not met, subject to an evaluation of the impact on patient needs.


**Summary**

This provision states that MS shall ensure that appropriate collection systems are in place for unused or expired medicines.

**UK implementation**

This reinforces current Department of Health policy which encourages patients to dispose of medicines appropriately, in particular, by returning them to a pharmacy. Public funding is provided for medicinal products to be collected from pharmacies and disposed of in an appropriate way.

**CHANGES AFFECTING MARKETING AUTHORISATIONS POST-LICENSING**

As indicated above, the MA Regulations provide that MAHs must comply with the obligations set out in the “relevant Community provisions”. In particular, regulation 7 provides that holders of UK MAs must comply with the relevant obligations which apply to them, including those relating to updating information, to pharmacovigilance and to labels and patient information leaflets. Regulation 11 and Schedule 3 then create various criminal offences for breaches of those obligations, and for breaches by centralised MAHs whose products are marketed in the UK. As previously explained, we propose to amend the MA Regulations by adding references to Directive 2004/27/EC and Regulation (EC) No. 726/2004 to the definition of “relevant Community provisions”. This would mean that as from 30th October, the new obligations set out below would apply to UK MAHs. There would also be specific transitional arrangements – see the sections on individual provisions below. Schedule 3 would be amended to create new offences or modify existing ones; see **Annex B**.


**Summary**
This provision was the subject of a public consultation (MLX 309) and was implemented in the UK on 1 January 05.

**Article 23(a) - notifying the competent authority of the date a product is placed on the market (not the date of authorisation), taking account of different presentations and notifying temporary absence or permanent removal from the market (Article 1(22) of Directive 2004/27/EC).**

**Summary**

These new provisions require the MAH to inform the competent authority (the MHRA in the UK) about various activities associated with the availability of the product on the market; in particular the MAH must inform the competent authority of the date the product is actually placed on the market and provide advance notification if the product is to cease to be placed on the market. In addition to providing valuable information on availability of supply, which will be made available to the Department of Health (DH), this information will enable the MHRA to manage the new provisions concerning validity of a MA when a product has not been available on the UK market for 3 years (see the new Article 24(4) and (5)). The provision also requires the MAH, at the request of the MHRA, to supply all data relating to the sales of the medicinal product, and any data in possession relating to the volume of prescriptions.

This provision will bring real benefits in terms of protecting the public health of users of medicinal products in the UK. DH is responsible for overseeing the supply of medicinal products to the UK market for use by patients. DH is also responsible, within the limits of its powers, to ensure that alternative supply routes are available when shortages of a particular product occur. This provision will contribute towards contingency planning to ensure that patients have continuing access to the medication that they need.

This provision has links with the new Article 81 of Directive 2001/83/EC, which includes a new obligation on MAHs and distributors to maintain – within the limits of their responsibilities – appropriate and continued supplies of a medicinal product to pharmacies and persons authorised to supply so that patients’ needs are met.

**UK implementation**

The new obligations on MAHs will apply to holders of UK MAs by virtue of regulation 7 of the Marketing Authorisations Regulations. In relation to requests for data on volume of sales or prescription, the MHRA will be able to specify a time in which a response to a particular request must be provided (regulation 7(5)).

In relation to the second paragraph of Article 23(a) (advance notification of cessation of supply), the MHRA’s view is that the term "ceases to be placed on the market" is to be taken to mean the complete cessation of supply to the UK market of a particular product presentation. In this regard 'presentation' would mean different strengths and pharmaceutical dosage forms. When requested, we would also expect to receive sales data in the categories of presentation listed above. In terms of the interruption in supply, the absence from the market could be short or long term or indefinite, planned or unplanned.
The provision requires MAHs to notify the competent authority no less than 2 months before the interruption in placing on the market, other than in ‘exceptional circumstances’. The UK implementing legislation would not specify what constitutes ‘exceptional circumstances’, but in our view it would cover situations where it would not be reasonable to expect the MAH to provide the required 2 month’s notice. The MAH may have legitimate reasons for failing to provide 2 month’s notice and we would take these reasons into account when judging whether there were “exceptional circumstances” in a particular case. Although the 2 month time limit would not apply in “exceptional circumstances”, the MAH would still be required to notify the MHRA of any cessation and we would expect to receive a formal notification describing the expected shortage as early as possible.

The requirements of Article 23a are linked to the new obligation in Article 81, which requires the MAH or distributor, within the limits of their responsibilities, to ensure appropriate and continued supply of medicinal products to pharmacies and other persons authorised to supply the products. To assist in the timely reporting of interruptions in supply, we intend to establish an electronic reporting scheme.

The decision about which potential interruptions to notify will remain with MAHs, although the MHRA will draw up detailed guidance on how and when to report. For example, temporary problems with manufacture or other difficulties with the supply chain should be reported where there is a likelihood of an interruption in supply in the future, taking into account any existing stocks held by the MAH.

Although the legislation will impose a legal requirement to notify the MHRA not less than 2 months before an interruption of supply, Department of Health proposes to continue the existing voluntary arrangements for notifying product discontinuations; in particular, the Association of the British Pharmaceutical Industry and DH guidelines set out in the May 2001 document ‘Ensuring Best Practice in the notification of Product Discontinuations’ (www.dh.gov.uk/discontinuedmedicines). Those guidelines would be updated to reflect the new legal requirements. The DH is also seeking to negotiate a similar agreement with the British Generics Manufacturing Association, covering both discontinuations and shortages.

Enforcement and sanctions for non-compliance

The MHRA proposes that the Marketing Authorisations Regulations would be amended so to make provision for the enforcement of the new requirements of Article 23a; in particular for the imposition of penalties for failure to comply with those requirements. We recognise that in view of the range of potential difficulties that may arise in maintaining supplies of medicinal products, sanctions for non-compliance would generally only be appropriate where the MAH had not taken all reasonable steps to comply with its obligations.

The primary requirement for any sanction is that it should be effective, proportionate and dissuasive. Health Ministers are particularly concerned to ensure that supplies of medicinal products essential to meet the needs of patients in the UK are maintained. We must therefore ensure that there are effective sanctions available for use if
companies fail reasonably to report impending cessation of supply. We are therefore seeking your views on two possible options for enforcement and their implications:

- **Option 1.** Non-compliance would be a criminal offence, similar to other offences in Schedule 3 of the Marketing Authorisations Regulations. As with those existing offences, the maximum penalty following a conviction in the magistrates’ court, would be £5000 or a term of imprisonment not exceeding 3 months. In more serious cases tried in the Crown Court, the penalty would be a term of imprisonment not exceeding 2 years or a fine determined by the court. We propose that companies would be entitled to rely on a “due diligence” defence – i.e. they would not be guilty if they could demonstrate that they had taken all reasonable steps to avoid commission of the offence.

- **Option 2.** Compliance would be enforced using an administrative penalty scheme. This would enable the Secretary of State for Health to impose a financial penalty, without instituting criminal proceedings, where it appeared to him that the company had failed to comply with its legal obligations. The procedure for imposing penalties, the levels of those penalties, and the system for hearing appeals against decisions by the Secretary of State would be set out in regulations. Such a scheme may enable the imposition of financial penalties higher than those ordinarily imposed by the criminal courts and could serve as a more effective deterrent. But the MAH would not have a criminal conviction. If, subject to the views of consultees, this option was favoured, we would conduct a separate public consultation to seek views on the details of scheme, including the levels of financial penalties and appeal arrangements.

In considering which option we should adopt, it would be important to consider the extent to which the arrangements will be consistent with the existing provisions for enforcement of other medicines regulatory requirements, such as, for example, failure to report information relevant to the evaluation of the risks and benefits of a product (currently a criminal offence under paragraph 10 of Schedule 3 to the Marketing Authorisations Regulations).


**Summary**

Under the revised legislation only a single renewal is required when the product has been authorised for 5 years. A second renewal may take place after a further 5 years if there are justified pharmacovigilance grounds. In addition, any authorisation, which is not followed by placing on the market within 3 years (or which is not present on the market for 3 years) shall cease to be valid. MS may grant exemptions from the 3 year rule, if justified on public health grounds.

**EU discussions**

These have concerned the detailed documentation to be submitted with the renewal application, criteria for a second renewal and transitional arrangements for authorised
products. In particular, there has been discussion about the need for a 2nd renewal for products already renewed under existing legislation. Once final decisions have been taken guidance will be incorporated into the Notice to Applicants.

UK implementation

The amended article will mean that for most MAs an application to renew will only be required once, 5 years after authorisation. The renewal will be granted on the basis of the risk-benefit balance and unless there are reasons to require a second 5-year renewal, the authorisation will thereafter be valid indefinitely. The 5-yearly Periodic Safety Update Report (PSUR) cycle will be replaced by a 3-yearly cycle (Article 104). Requirements regarding documentation to be submitted with renewal applications will be defined in European guidelines, together with details on the timing of submission, specific PSUR data requirements, expert statements and permitted changes to the product information at time of renewal. The situation regarding transitional arrangements for MAs which have already been renewed under existing legislation is still under consideration at the European level. The UK will be consistent with the agreed position but the preferred UK option is that there will not be a requirement for a further renewal for such products.

Articles 55-63 - Patient Information Leaflet and labelling (Articles 1(41) – 1(44) and 1(46) - 1(48) of Directive 2004/27/EC)

Summary

There are changes to the information to be included on the product label and certain provisions relating to the product’s package leaflet. There is also a new requirement for the name of the medicinal product to be expressed in Braille format on the label. For products containing up to three active substances, the legislation specifies that the international non-proprietary name (INN) must also appear on the labelling. The MA holder must ensure that the package leaflet is made available on request from patients’ organisations in formats appropriate for the blind and partially sighted.

EU Discussions

Discussions are still taking place in a number of EU fora including MRFG, Quality Review of Documents group and the European Commission about how best to introduce these new requirements. Particular discussions have taken place on Braille, the definition of the name of the medicinal product, other formats of the package leaflet which would meet the new requirement and, importantly, new guidance for the pharmaceutical industry is being considered.

UK implementation

The amendment to the definition of “relevant Community provisions” in the MA Regulations would ensure that the requirements would be transposed into national legislation as they are written in EU law. This will be underpinned by both European and national guidance. The requirements for Braille on the label and arrangements for an appropriate format of the package leaflet will affect all applications for MAs submitted to the Agency from 30 October 2005. For existing products, the UK
proposes to amend the MA Regulations so as to put in place a 5 year transition period for compliance of products already the subject of an MA. The obligation will be on MAHs to ensure that compliance is achieved within this timescale. The UK also proposes to produce a best practice guidance document dealing with the issues of Braille placement on packaging. This would reflect the European guidance and would additionally address patient safety, technical and practical issues of compliance. It would also include advice to pharmacists on labelling for dispensing purposes.

The new Articles 59 and 61(1) relating to “user testing” of package leaflets and the order of information were the subject of a public consultation (MLX 309) and have already been implemented in the UK.

**Articles 59(3) and 61(1) – user testing of patient information leaflets - Article 1(44) and 1(45) of amending Directive 2004/27/EC**

**Summary**

These provisions were the subject of a public consultation (MLX 309) and will be implemented in the UK on 1 July 05.


**Summary**

Additional text has been added to the first paragraph of Article 63 stating that for orphan medicinal products, the particulars described in Article 54 may, on request, appear in only one of the official languages of the EU. Paragraphs 2 and 3 of Article 63 state that the package leaflet must be clear and understandable and legible in the official language(s) of the MS in which the product is marketed. The information may be printed in several languages of the EU, provided the same information is used. When the product is not intended to be supplied directly to patients, the legislation enables the MHRA to grant an exemption to the obligation that certain particulars must appear on the label and leaflet, and that the leaflet must be available in the language(s) of the MS in which they are marketed.

**UK implementation**

These are minor amendments to existing provisions with little scope for alternative interpretation. The MHRA intends to implement the provisions as set out in the legislation.

**Article 74 - on when a product can be reclassified (Article 1(53) of amending Directive 2004/27/EC)**

**Summary**

New provision that requires a review (using criteria set out in Article 71) of the legal classification of a product when new information comes to light, rather than on renewal.
UK implementation

There will be no change in the UK as in practice we have always considered legal status when new information has become available.

Article 74(a) Provides a year’s data exclusivity for data in support of an application to change legal classification - Article 1(54) of amending Directive 2004/27/EC

Summary

This provision was the subject of a public consultation (MLX 309) and has already been implemented in the UK.

Articles 88 – 91 and 98 – advertising, patient information and co-promotion
Article 1(63) – 1(66) and 1(70) of amending Directive 2004/27/EC

Summary

The new text includes a requirement for the Commission to consult stakeholders with a view to presenting a report to the Council and European Parliament in 3 years' time on current practice with regard to information provision – particularly on the Internet.

Other changes to the advertising provisions will have a limited impact on the regulation of advertising. They include the removal of the prohibition on the mention of the grant of a MA, minor changes to hospitality at sales promotion meetings and the removal of six disease areas where there is currently a prohibition on advertising for non-prescription products. The Directive specifies that co-promotion shall not be prohibited but no such prohibition existed in UK.

The most significant change is the removal of six disease areas on which advertising for non-prescription products is prohibited but very few products have been identified on which the change will impact.

UK implementation

These are minor amendments which will have little impact on UK practice. We intend to implement the provisions as set out in the legislation.

Article 102 and 102a – operation and independence of a pharmacovigilance system - Articles 1(73) and 1(74) of amending Directive 2004/27/EC

Summary

The new Article 102 includes a provision that requires MS to share suitable information collected through their pharmacovigilance system with other MS and the EMEA. The information must be recorded in a database operated by the EMEA, which should be accessible to Member States and to the public. But the provision is otherwise the same as before. Article 102a states that the management of funds used
in connection with pharmacovigilance and other associated activities must be under the control of the MHRA to ensure independence.

EU discussions

The central database “EudraVigilance” has been developed to allow MS and the EMEA to share information on Adverse Drug Reactions (ADRs) once it has been populated by all MS. The database is still being developed and implementation issues are still being resolved. Four MS currently send ADRs to the database.

UK implementation

The UK is currently re-developing the Pharmacovigilance database and one of the requirements built in will enable the UK to send ADR reports electronically to the Agency once issues relating to confidentiality ownership of the data held on Eudravigilance are resolved. The implementation date for electronic ADR reporting by industry and MS is November 2005. The MHRA currently has permanent control of the management of funding allocated to carry out activities in this area. Therefore this provision will not change current practice.

Article 104 – 107 ADR reporting and Periodic Safety Update Reports (PSURs) Article 1(76) of amending Directive 2004/27/EC

Summary

The new Articles 104 to 107 are similar to the existing provisions, but contain a number of new requirements. In particular, a new requirement for the MAH to submit ADR data in electronic format except in exceptional circumstances.

The new provisions also increase the frequency of Periodic Safety Update Reporting (PSURs) from 5 to 3 years. After authorisation, a MAH will be required to submit PSURs on request by the Competent Authority, but at least every 6-monthly from date of the authorisation until the product is marketed, then 6-monthly for 2 years after marketing, yearly for the following 2 years then 3-yearly. The increased frequency of PSURs links with the changes to the renewals procedure and will ensure regular examination of safety issues, undertaken in a co-ordinated manner across the European Union.

New Article 104(9) provides that a MAH may not communicate information relating to pharmacovigilance concerns to the public without giving prior or simultaneous notification to the MHRA and must ensure that such information is presented objectively and is not misleading. MS are required to take necessary measures to ensure that a MAH who fails to comply is subject to effective, proportionate and dissuasive penalties.

EU discussions

EU Guidance is being updated.

UK implementation

28/88
The UK is looking to balance the removal of the requirement for a second and subsequent renewal of marketing authorisations with the increased frequency of PSURs from 5 to 3 yearly. The UK is working with other MS to minimise the regulatory burden of PSURs by harmonising submission dates between MS and undertaking shared assessment.

Requiring ADR data to be communicated in electronic format facilitates the timely exchange of information between competent authorities and the EMEA. The UK aim is to introduce this requirement with the least possible burden to MAHs. This is particularly relevant for small companies (eg those in the herbals sector for whom ADR reporting is new).

The MHRA is therefore proposing that for those companies for whom the cost of introducing an electronic ADR reporting system would be disproportionately expensive, current ADR reporting arrangements would continue. The MHRA would convert the ADR data into electronic format for onward transmission to the EMEA database. MHRA would charge a fee to cover the costs of undertaking this work.

Where registered traditional herbal medicines have distinctive characteristics, the MHRA will seek to ensure that guidance applies appropriately. For example, in EU discussions covering update PSURs the UK will raise the issue of whether the six monthly frequency of reporting following product authorisation would in all cases be necessary for registered traditional herbal medicinal products.

The MHRA's proposed service on converting ADR reports to electronic format would allow small herbal companies with registered products likely to attract limited numbers of ADRs the possibility of meeting the requirement without having to make major IT changes.

In relation to Article 104(9) (the presentation of pharmacovigilance information by MAHs to the public), we propose to implement the requirement to adopt “effective, proportionate and dissuasive penalties” for non-compliance, by making breach of the obligations a criminal offence under Schedule 3 of the MA Regulations. On conviction, MAHs would then be subject to the penalties specified in Schedule 3 – i.e. in the magistrates’ court, a maximum penalty of a £5000 fine or a term of imprisonment not exceeding 3 months; and in the Crown Court, a term of imprisonment not exceeding 2 years or a fine determined by the court.

MANUFACTURE AND IMPORTATION

Articles 46, 46a and 47 – Good manufacturing practice (GMP) for APIs\(^2\) - Article 1(33) – 1(35) of amending Directive 2004/27/EC

Summary

\(^2\) Also known as starting materials. This is a material or ingredient incorporated into the new drug substance as an important structural element, which is then manufactured to produce the end product
These Articles reflect new Community requirements on pharmaceutical companies to adhere to the principles of GMP for the manufacture of active substances used as APIs, as well as for the manufacture of what are termed “certain excipients”. This includes any repackaging or re-labelling activities carried out by a distributor (broker) of APIs. Herb APIs used as active substances for traditional herbal medicinal products as defined in Directive 2004/24/EC will also be required to comply with these Articles.

The principles of GMP for active substances used as APIs have been adopted in the form of detailed guidance from the Commission – as Annex 18 to the GMP guide. The starting point for the application of GMP to chemical, herbal and biotechnology APIs is illustrated in Table 1 of Annex 18 - this is reproduced below. The proposals for GMP inspection should be read in conjunction with the separate RIA (Annex E to this package).

<table>
<thead>
<tr>
<th>Type of manufacturing</th>
<th>Application of this Guide to steps (shown in grey) used in this type of manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical manufacturing</td>
<td>Production of the API starting material</td>
</tr>
<tr>
<td>API derived from animal sources</td>
<td>Collection of organ, fluid or tissue</td>
</tr>
<tr>
<td>API extracted from plant sources</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>Herbal extracts used as API</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>API consisting of comminuted or powdered herbs</td>
<td>Collection of plants and/or cultivation and harvesting</td>
</tr>
<tr>
<td>Biotechnology: fermentation/cell culture</td>
<td>Establishment of master cell bank and working cell bank</td>
</tr>
<tr>
<td>“Classical” fermentation to produce an API</td>
<td>Establishment of cell bank</td>
</tr>
</tbody>
</table>

3 Excipients are substances which are added to a drug formulation, usually to provide stability or bulk. These are essential constituents of virtually every pharmaceutical product and are rarely produced specifically for pharmaceutical purposes - but where they are, must comply with GMP

EU Discussions

The Directive requires GMP to be followed in the manufacturing processes (production and quality control) for active ingredients and “certain excipients”. The Commission will, in due course, define and list the “certain excipients” to which GMP will apply, and will issue a new Directive on the specific conditions of application. The new Directive on excipient manufacture is not, however, expected before the end of 2005.

The EMEA is looking to develop the GMP guide for excipients. The list of “certain excipients” has not yet been published but may for example contain the excipients commonly used for injectable solutions and more generally the so-called “risk-excipients”. An EMEA “Certain Excipients Working Party” comprising European GMP Inspectors is addressing the issue and a questionnaire has been issued to the industry in order to assemble views. From this, a guidance document is planned, which is intended to set out the types of excipient that will be subject to GMP as well as when it is appropriate to conduct inspections at manufacturing sites.

UK implementation

Implementation of GMP for active pharmaceutical ingredients is discussed under Article 111.1.

Although they do not have the therapeutic benefit of active pharmaceutical ingredients, excipients remain essential constituents of virtually every pharmaceutical product. There are many quality considerations to be taken into account in the manufacture of the excipient, its registration and use by the pharmaceutical manufacturer. Appropriate amendments will be made to the Medicines Act and/or the Standard Provisions Regulations, so as to require holders of UK manufacturers’ to comply with requirement to use only starting materials which comply with the new GMP guidelines.

Where excipient supply from third countries is concerned, pharmaceutical manufacturers should work in co-operation with their suppliers to ensure that they have a detailed understanding of the excipient and its application, and to demonstrate control in the manufacture and use of the material. Evidence of suitably effective arrangements will be sought at inspection time.


5 This refers to an EC Opinion on starting materials used in human and veterinary medicinal products, for which there is a consumer health &/or safety concern that needs to be addressed by laying down and enforcing the GMP requirements adopted by the Scientific Committee on Medicinal Products and Medical Devices (on 21 October 1998). This suggested that, in principle, GMP should be applicable to as broad a range of starting materials as possible (including excipients).

Summary

This amendment (duties of the Qualifies Person – QP) extends the need for full batch analysis and testing in a MS to product imported from third countries (i.e. outside the Community) - whether or not the product was originally manufactured in the Community. For medicinal products imported from third countries, retesting of each batch within the EU is required, excluding those instances where a Mutual Recognition Agreement covering GMP is operating between the EU and the country where the medicinal product is manufactured.

UK Implementation

The licensed wholesale importer must ensure that the manufacture and assembly operations conducted outside the European Economic Area (EEA) have been carried out by a duly authorised manufacturer or assembler; that the products have been manufactured and assembled in accordance with standards equivalent to European GMP; and that each production batch has undergone a full qualitative analysis and a quantitative analysis of at least all the active ingredients.

The new requirement concerns the re-testing of products, including traditional herbal medicinal products that have been made in the EEA, left the EEA and are then imported back into the EEA. The QP is the person responsible for ensuring that each production batch of medicinal products coming from third countries has undergone full qualitative analysis, a quantitative analysis and all other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the MA. All associated testing and quality control operations must be in accordance with European GMP and, even where a Mutual Recognition Agreement exists, the QP must still certify all imported batches.

The Government proposes an amendment to the Medicines Act and/or the Standard Provisions for manufacture and wholesale import distribution to reflect this additional function of the QP.

WHOLESALE DISTRIBUTION OF MEDICINAL PRODUCTS


Summary

New Article 76(3) contains a new requirement for distributors that import medicinal products from other MS to notify the MA holder and the competent authority of the MS to which the product is imported of the intention to import.

UK implementation

7 The Member states of the EU, plus Norway, Liechtenstein and Iceland
Companies that distribute products in the UK that have been imported from other MS would be required to inform the MHRA and the MAH of this activity. The obligation to inform MHRA will be regarded as having been met if the distributor holds a UK parallel import licence covering that product. For distributors of other imported including those products covered by a European MA both obligations would apply.


**Summary**

The existing Article 81 of Directive 2001/83/EC is replaced by a new Article 81, which includes a new provision that the MA holder and the relevant distributor of a medicinal product must ensure appropriate and continued supply of the product to pharmacies and other authorised suppliers, in order to meet patients’ needs. It has links 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.

The new Article 81 also contains the same provision as the existing Article 81 under which Member States are prevented from imposing obligations with regard to the supply to pharmacists and others entitled to supply products to the public, particularly public service obligations, on the holder of a distribution authorisation granted by another Member State which are more stringent than those they impose on the holders of their national authorisations (in the UK, holders of wholesale dealers’ licences). The UK will continue to comply with this provision and no changes to UK legislation are required.

**UK implementation**

The new obligation for MA holders will apply to holders of UK MAs by virtue of regulation 7 of the Marketing Authorisations Regulations. In relation to distributors, we propose to amend the Medicines Act 1968 and/or the regulations under that Act relating to wholesale distribution, so as to require the holders of UK wholesale dealer’s licences to comply with the new obligation, where they are responsible for the distribution of medicinal products covered by the Directive.

Our interpretation is that the provision should be applied to all products on the UK market for which a MA has been granted, regardless of whether this is a centralised or national MA. We therefore propose that the Marketing Authorisation Regulations be amended so as to impose the new obligation on holders of centralised MA for products marketed in the UK.

Guidance would be developed in consultation with stakeholders on the meaning of ‘appropriate and continued supply’. In considering whether this obligation is being met by MAHs and distributors, the MHRA would take into consideration the wider availability of the particular product on the market, and any external factors outside the control of MAHs and distributors that might affect their ability to supply to the market. MHRA will also seek to ensure that the arrangements for implementation comply with the requirement in Article 81 that arrangements are justified on grounds
of public health and would be proportionate in relation to the objective of that protection, in compliance with the rules of the EC Treaty, particularly those concerning the free movement of goods and competition.

Enforcement and sanctions for non-compliance

The MHRA proposes that the Marketing Authorisations Regulations would be amended so to make provision for the enforcement of the new requirements of Article 81; in particular for the imposition of penalties for failure to comply with those requirements. In view of the range of potential difficulties that may arise in maintaining `appropriate and continued’ supplies of medicinal products, sanctions for non-compliance would generally only be appropriate where the MAH had not taken all reasonable steps to comply with its obligations.

The primary requirement for any sanction is that it should be effective, proportionate and dissuasive. Health Ministers are particularly concerned to ensure that supplies of medicinal products essential to meet the needs of patients in the UK are maintained. We must therefore ensure there are effective sanctions available against companies that fail reasonably to ensure `continued and appropriate’ supply. As we with the proposals for implementing the new Article 23a, we are seeking your views on two possible options for enforcement and their implications:

- **Option 1.** Non-compliance would be a criminal offence, similar to other offences in Schedule 3 of the Marketing Authorisations Regulations. As with those existing offences, the maximum penalty following a conviction in the magistrates’ court, would be £5000 or a term of imprisonment not exceeding 3 months. In more serious cases tried in the Crown Court, the penalty would be a term of imprisonment not exceeding 2 years or a fine determined by the court. We propose that companies would be entitled to rely on a “due diligence” defence – i.e. they would not be guilty if they could demonstrate that they had taken all reasonable steps to avoid commission of the offence.

- **Option 2.** Compliance would be enforced using an administrative penalty scheme. This would enable the Secretary of State for Health to impose a financial penalty, without instituting criminal proceedings, where it appeared to him that the company had failed to comply with its legal obligations. The procedure for imposing penalties, the levels of those penalties, and the system for hearing appeals against decisions by the Secretary of State would be set out in regulations. Such a scheme may enable the imposition of financial penalties higher than those ordinarily imposed by the criminal courts and could serve as a more effective deterrent. But the MAH would not have a criminal conviction. If, subject to the views of consultees, this option was favoured, we would propose to conduct a separate public consultation needed to seek views on the details of scheme, including the levels of financial penalties and appeal arrangements.

In considering which option we should adopt, it will be important to consider the extent to which the arrangements will be consistent with the existing provisions for enforcement of other medicines regulatory requirements, such as, for example, failure to report information relevant to the evaluation of the risks and benefits of a product.
(currently a criminal offence under paragraph 10 of Schedule 3 to the Marketing Authorisations Regulations).

**Article 111 – Inspection and Good Manufacturing Practice Article 1(77) of amending Directive 2004/27/EC**

**Summary**

The amending Directive sets out the various changes to the general conditions for supervision and sanctions relating to the regulation of medicines. The new rules reflect the fact that the EU intends to step up pharmacovigilance activity and, more generally, market surveillance and sanctions in the event of failure to comply with the legislative provisions.

In particular, this Article gives the competent authority the power to carry out unannounced inspections at the premises of manufacturers of APIs, or at the premises of MAHs or any firms employed by the MA holder where there are grounds for suspecting non-compliance with the GMP principles set out in Article 47 and the activities described in Articles 103 and 104.

**UK implementation**

From 30th October 2005 the requirement is that Active Pharmaceutical Ingredients (APIs) used in the manufacture of medicinal products must be manufactured in accordance with GMP. The obligation to use GMP compliance APIs would be specified in amendments to the Medicines Act and/or the Standard Provisions Regulations. Evidence of suitably effective arrangements for assuring this will be sought at inspection.

Medicinal products whose manufacture commenced before 30 October 2005, may be released to the market after 30 October 2005.

MS may inspect manufacturers and importers of APIs and certain excipients - including brokers who re-package or re-label product, and any laboratories employed by the MA holder. Although not strictly part of the amending Directive, we intend to ensure that API/excipient manufacturers in third countries will also be inspected. These inspections will be conducted by the competent authority, may be unannounced and may be carried out at the request of an API manufacturer, another MS, the Commission or the EMEA.

Such inspections will be carried out by officials representing the competent authority who shall be empowered to inspect premises, take samples and examine documents. A report will be provided to the manufacturer or MAH who has undergone the inspection and, where relevant, a certificate of GMP compliance issued. Certificates will be entered on a central Community database, as will be any failures in compliance.

In light of the new requirements relating to the inspection of manufacturers of APIs and certain excipients, the Government proposes:
(i) to make any necessary amendment to the powers to inspect under the Medicines Act, in order to make clear that inspectors may carry out inspections for this purpose, although our view is that this is unlikely to be necessary;

(ii) to make a further amendment to the provisions of the Act in order to provide an appropriate legal basis for the issue of certificates to the manufacturers who have undergone inspection.

(iii) to permit inspections at the request of another MS, the Commission or the EMEA in order to verify the data submitted to obtain a conformity certificate comply with the monographs of the European pharmacopoeia. This is a new requirement and may require specific amendment of the legislative provisions relating to inspections.

A rolling programme of inspections for API manufacturers will 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). The relevant inspection costs (chargeable by the MHRA) will be set out in the forthcoming Fees Consultation document, due to begin in April/May 2005.

Article 116 & 117 – outlines the circumstances under which competent authorities must suspend, revoke, withdraw or vary a MA.

**Article 122.3 – General provisions (re-inspections of manufacturing sites) Article 1(82) of amending Directive 2004/27/EC**

**Summary**

While the conclusions of Article 111 inspections shall be valid throughout the Community, the amending Directive creates the possibility of re-inspection in exceptional cases – where a MS informs the Commission that it is unable to accept the conclusions reached following an inspection. There is no explanation in the Directive of what an “exceptional case” might be considered to be except that the MS must have “public health reasons” for not accepting the conclusions.

Where this happens, the Commission will effectively be acting as an intermediary and will consult with the MS concerned. If the concerns are unable to be resolved, the Commission may ask the original inspector to perform a new inspection and he/she may be accompanied by two other inspectors from MS which are not parties to the disagreement.

**UK implementation**

This obligation will not result in any changes to the governing medicines legislation in the UK – it is included here simply as a means of alerting the sector to the
possibility of re-inspection. The MHRA, as competent authority for the UK, will not charge a fee for re-inspection in these circumstances.

**CHANGES TO AGENCY PRACTICE**

**Article 126b - transparency and independence** Article 1(85) of amending Directive 2004/27/EC

**Summary**
This is a new provision. It states in the 1st paragraph that members of staff and experts of competent authorities involved in the authorisation and surveillance of medicinal products must not have any financial or other interests in the pharmaceutical industry that could affect their impartiality. All staff must make an annual declaration of financial interests.

It also requires MS to make publicly accessible its rules of procedure and those of committees, agendas and minutes for meetings, decisions taken, details of votes. There is no requirement to actively publicise this information.

**EU discussion**

This provision has been discussed in a range of EU meetings. The Commission’s overriding concern is that there should be consistency in interpretation across the EU and that all MS should adhere to minimum transparency criteria.

**UK implementation**

The MHRA is amending its procedures for declaring and managing financial and other interests of staff and members of its advisory committees. MHRA is currently consulting (MLX316) on proposals that the chairman and members of the committees that advise Ministers should hold no current personal interests in the pharmaceutical industry. Other interests will be subject to a separate Code of Practice. MHRA is also revising its staff Code on holding and declaring interests to bring it into line with the new EU requirements.

The Government’s approach is that the publication of minutes/agendas/details of votes, etc should not prejudice open debate on the merits or otherwise of MA applications. In addition, the publication of this information should not influence decisions made by the competent authorities (i.e in relation to granting a MA or a discussion about safety issues and the possible withdrawal of a product).

Therefore, a distinction will be drawn between making publicly available information relating to medicinal products for which a MA has been granted and, for example, medicines either in development or about which a safety discussion is taking place. The latter should be deemed to have commercial or public health implications, and should not be made publicly available until a final regulatory decision has been made. But such information might be made accessible at a later date, once the concerns about commercial confidentiality or public health no longer applied.
HOMOEOPATHIC PROVISIONS

Articles 13 – 16 Article 1(12) – 1(15) of amending Directive 2004/27/EC

Summary

Under current requirements, setting up a simplified registration procedure for homeopathic medicinal products is not compulsory and Directive 2001/83/EC specifically states that an MS may refrain from establishing such a procedure. Although MS should take account of homeopathic registrations and authorisations previously granted by another MS, there is no mechanism for formal mutual recognition. Strict criteria for admissibility of a homeopathic product into the simplified procedure under Article 14 are listed and there is no scope for deviation from these criteria. Directive 2004/27/EC makes it compulsory for MS to establish a special, simplified scheme for homeopathic medicinal products not authorised under EU provisions or registered under national law before December 1993 and introduces mutual recognition for registered products (under Articles 28 and 29(1) to (3)). In addition, the option is given to the Commission to amend the procedure to be followed to amend the scope of the Simplified Scheme in the future having followed the procedure set out in Article 121(2).

UK implementation

The UK is already operating a simplified scheme, the only change to UK practice is that we will implement a formal mutual recognition procedure.

GENERAL APPLICATION TO SPECIFIC SECTORS

General Application to Traditional Herbal Medicinal Products

The Directive on Traditional Herbal Medicinal Products (Directive 2004/24/EC) requires each MS to put in place a national registration scheme for traditional herbal medicinal products by October 2005. This simplified registration scheme consists of certain regulatory features that are specific to this category of products (eg requirements for evidence of traditional use) while also applying some, but not all, features of regulation that flow from the principal European Directive regulating medicines (Directive 2001/83/EC). Bringing traditional herbal medicines within the scope of a number of provisions of Directive 2001/83/EC in turn has meant that a number of the features of the legislation implementing the 2001 Review also apply to traditional herbal medicines, for example the “user testing” requirement.

In the current consultation changes that will impact on registered traditional herbal medicinal products include principally: renewals and sunset clause (Article 24); patient information leaflets and labelling, including the Braille requirement (Articles 55 – 63); product reclassification (Article 74/74a); advertising (Articles 88-91, 98); pharmacovigilance including ADR reporting and PSURs (Articles 102, 104-107); GMP for APIs (Articles 46, 46a, 47); importation (Article 51); importation and distribution (Article 76); inspection (Article 111(1)) and 122(3).
Where registered traditional herbal medicines have distinctive characteristics, the MHRA will seek to ensure that guidance applies appropriately. For example, in EU discussions covering update PSURs the UK will raise the issue of whether the six monthly frequency of reporting following product authorisation would in all cases be necessary for registered traditional herbal medicinal products.

In addition to changes affecting products to be registered under Directive 2004/24/EC, the removal of the restriction on mention of grant of a MA is likely to be of particular interest to those advertising herbal medicines with a full MA.

**General application to homoeopathic products and products registered under the Simplified Scheme**

Articles 13 to 16 and 53-63 inclusive apply to all homoeopathic medicinal products. Articles 102-108 apply to all homoeopathic medicinal products except those registered under the simplified scheme, covered by Article 14.

For all other homoeopathic products, article 16 applies – this requires homoeopathic products to be authorised in the same way as conventional products, i.e. with a MA. Therefore all the usual provisions of Directive 2001/83/EC would apply to these products.

**General application to products covered by national Parallel Import Licences**

The majority of the proposed changes are not relevant to the national licensing of parallel imports. However, consideration has been given to the application of the following articles:

- **Article 23a** (date of placing on the market and informing the competent authority of interruptions in market supply, and volumes of sales and prescriptions). These requirements will not apply to parallel imports but licence holders will be expected to supply information of this nature on request.
- **Article 24** (renewal of MA & sunset clause). As the conditions linked with indefinite licensing cannot be applied to parallel imports the 5 yearly renewal procedure will continue for these licences
- **Articles 55-63** (Patient Information Leaflet and labelling) will apply to parallel imports
- **Article 76** (importation and distribution of medicinal products) will apply to parallel imports.
ANNEX B

SANCTIONS FOR NON-COMPLIANCE WITH THE OBLIGATIONS SET OUT IN AMENDING DIRECTIVE 2004/27/EC AND REGULATION 726/2004/EC

Directive 2004 27/EC

The following obligations have been identified in the amending Directive as obligations relating to marketing authorisations which specific provision for enforcement and penalties. We are proposing to extend the current schedule of criminal offences (Schedule 3 of the MA Regulations) to cover these new obligations.

a) Duties relating to the provision of information relevant to benefits and risks of products - 3 additional paragraphs in Article 23 of the 2001 Directive;
b) Duties to notify MHRA of actual placing on the market of cessations of supply – 1st and 2nd paragraphs of the new Article 23a of the 2001 Directive
c) Duty to respond to MHRA requests for information re. volume of sales or prescriptions - 3rd paragraph of new Article 23a of the 2001 Directive;
d) Duty to ensure that information submitted with an MA application is complete and accurate – 3rd paragraph of new Article 26
e) Duty to ensure appropriate and continued supplies – new Article 81 of the 2001 Directive;
f) Duties relating to the public communication of information relating to pharmacovigilance - new Article 104(9) of the 2001 Directive

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

An alternative mechanism for introducing sanctions for non-compliance with the first and second paragraphs of Article 23a and Article 81 of the amending Directive is being considered. This would involve the introduction of an administrative penalty scheme – further information can be found under the respective Articles in Annex A.

Failure to ensure that products are labelled and packaged in accordance with the new provisions inserted by Directive 2004/27/EC, or that patient information leaflets are in accordance with those provisions, will be covered by the existing criminal offences in Schedule 3.

In addition to obligations relating to MAs, we propose that it should be a criminal offence for the holder of a UK manufacturer’s licence to use “starting materials” (referred to as APIs in this document) which have not been manufactured in accordance GMP for starting materials; we would welcome your views on whether this should only be an offence if the manufacturer knew, or should reasonable have been aware, that the starting material was not GMP compliant.

Regulation 726/2004/EC

8 See regulation 3(4) of the Medicines (Marketing Authorisations and Miscellaneous Amendments) Regulations 2004 (S.I. 2004/3224).
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) Duty to forward data at the request of the EMEA - Article 16(2);
b) Duty on the QP responsible for pharmacovigilance to provide competent authority with information relevant to risk and benefit - Article 23(d);
c) Duties relating to the public communication of information relating to pharmacovigilance concerns – Article 24(5);
d) Duty to collect information from targeted patient groups at the request of the EMEA – final paragraph of Article 26

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.
ANNEX C

DRAFT PARTIAL REGULATORY IMPACT ASSESSMENT (RIA)

1. Title of proposal


2. Purpose and intended effect of measure

(i) Objectives

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

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 6 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 6 serves to demonstrate the balance achieved by MS.

(iii) Risk assessment

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

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 changes to the requirement that a MA has to be renewed every 5 years, 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. 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. Options for implementation

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.

3(i) Business sectors 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\(^9\).
• 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\(^{10}\).

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\(^{11}\).
• the likely market size of the generics wholesale industry is about £5.4 billion\(^{12}\).

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.

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.

3(ii) Issues 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.

4. 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.

Option 3 – in addition to the technical matters associated with implementation (addressed under Section 3 – ‘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.

\(^{9}\) ABPI website (at 28 January 2004)
\(^{10}\) ABPI website (at 28 January 2004)
\(^{11}\) OXERA Fundamental Review of the Generic Drugs Market p 146
\(^{12}\) OXERA Fundamental Review of the Generic Drugs Market p 159
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 £4.7 billion of the UK’s national income in 1998 (latest available figures) It also attracts significant R&D resource, receiving about 10% 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 Risk Assessment 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 benefit 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.
   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

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13 Competitiveness and Performance Indicators 2001: p.10 PICTF
14 Competitiveness and Performance Indicators 2002: p.47 PICTF
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.

5. Costs

(i) Compliance costs

Option 1 - failure to transpose this legislation would result in infraction proceeding being brought against the UK leading to an economic cost to the UK competent authority. The social costs associate 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.
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. 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of inspections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>1</td>
</tr>
<tr>
<td>1998</td>
<td>2</td>
</tr>
<tr>
<td>1999</td>
<td>4</td>
</tr>
<tr>
<td>2000</td>
<td>6</td>
</tr>
<tr>
<td>2001</td>
<td>11</td>
</tr>
<tr>
<td>2002</td>
<td>14</td>
</tr>
<tr>
<td>2003</td>
<td>13</td>
</tr>
<tr>
<td>2004</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>67</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of manufacturer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>API for Clinical Trials</td>
<td>6</td>
</tr>
<tr>
<td>Biological API for Clinical Trials</td>
<td>10</td>
</tr>
<tr>
<td>Full scale API</td>
<td>40</td>
</tr>
<tr>
<td>Excipient</td>
<td>8</td>
</tr>
<tr>
<td>Specific risk materials</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>66</strong>*</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Description</th>
<th>No. of companies</th>
<th>No. of employees</th>
<th>Inspection cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>5</td>
<td>0-10</td>
<td>2,481</td>
</tr>
<tr>
<td>Medium</td>
<td>18</td>
<td>10-60</td>
<td>4,601</td>
</tr>
<tr>
<td>Large</td>
<td>15</td>
<td>60-250</td>
<td>5,557</td>
</tr>
<tr>
<td>Extra large</td>
<td>3</td>
<td>&gt;250</td>
<td>9,525</td>
</tr>
</tbody>
</table>

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 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. Informal 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. These additional costs will need to be reflected in the fees charged to product licence applicants.

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.

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.

(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 services provided. Proposals to introduce or revise our current fees schedule will be subject to a separate public consultation, which is due to begin in April/May 2005.


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 that all product 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 the 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.

7. Consultation with small businesses: the Small Firsts’ 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 the measures covered by this consultation is additional to the cost this particular sector is facing at the same time as a result of Directive 2004/24/EC. On the measures in this consultation 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, are electronic reporting of ADRs and frequency of PSURs, and GMP for APIs. In ongoing discussions about detailed implementation the MHRA is seeking to ensure that implementation is proportionate and reflects awareness of regulatory impact issues. For example, in EU discussions on guidance covering PSURs the UK will raise 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 is proposing 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.
8. 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.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: In the market(s) affected by the new regulation, does any firm have more than 10% market share?</td>
<td>No, except within the homeopathic products sector.</td>
</tr>
<tr>
<td>Q2: In the market(s) affected by the new regulation, does any firm have more than 20% market share?</td>
<td>No.</td>
</tr>
<tr>
<td>Q3: In the market(s) affected by the new regulation, do the largest three firms together have at least 50% market share?</td>
<td>No, except within the homeopathic products sector</td>
</tr>
<tr>
<td>Q4: Would the costs of the regulation affect some firms substantially more than others?</td>
<td>No, not substantially.</td>
</tr>
<tr>
<td>Q5: Is the regulation likely to affect the market structure, changing the number or size of firms?</td>
<td>No, in general this is considered unlikely. However, in the herbal sector the introduction of systematic regulation (via Directive 2004/24/EC and Directive 2001/83/EC, as amended by Directive 2004/27/EC), could have the cumulative effect of leading to some consolidation in the market.</td>
</tr>
<tr>
<td>Q6: Would the regulation lead to higher setup costs for new or potential firms that existing firms do not have to meet?</td>
<td>No, none anticipated.</td>
</tr>
<tr>
<td>Q7: Would the regulation lead to higher ongoing costs for new or potential firms that existing firms do not have to meet?</td>
<td>No, none anticipated.</td>
</tr>
<tr>
<td>Q8: Is the sector characterised by rapid technological change?</td>
<td>No, technological change is not rapid in comparison with other industries.</td>
</tr>
<tr>
<td>Q9: Would the regulation restrict the ability of firms to choose the price, quality, range or location of their products?</td>
<td>No, such choices would not be affected although there would be a small cost associated with the new provisions on labelling and patient information leaflets.</td>
</tr>
</tbody>
</table>

On the basis of the above 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.

9. 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**

The following obligations have been identified in the amending Directive as obligations relating to marketing authorisations which specific provision for enforcement and penalties. We are proposing to extend the current schedule of criminal offences (Schedule 3 of the MA Regulations) to cover these new obligations.

a) Duties relating to the provision of information relevant to benefits and risks of products - 3 additional paragraphs in Article 23 of the 2001 Directive;
b) Duties to notify MHRA of actual placing on the market of cessations of supply – 1st and 2nd paragraphs of the new Article 23a of the 2001 Directive

c) Duty to respond to MHRA requests for information re. volume of sales or prescriptions - 3rd paragraph of new Article 23a of the 2001 Directive;

d) Duty to ensure that information submitted with an MA application is complete and accurate – 3rd paragraph of new Article 26

e) Duty to ensure appropriate and continued supplies – new Article 81 of the 2001 Directive;

f) Duty to ensure that information submitted with an MA application is complete and accurate – 3rd paragraph of new Article 26

g) Duty to ensure appropriate and continued supplies – new Article 81 of the 2001 Directive;

h) Duties relating to the public communication of information relating to pharmacovigilance - new Article 104(9) of the 2001 Directive

The new obligations in Article 23 have already been implemented and Schedule 3 to the MA Regulations amended accordingly\textsuperscript{15}.

An alternative mechanism for introducing sanctions for non-compliance with the first and second paragraphs of Article 23a and Article 81 of the amending Directive is being considered. This would involve the introduction of an administrative penalty scheme – further information can be found under the respective Articles in Annex A.

Failure to ensure that products are labelled and packaged in accordance with the new provisions inserted by Directive 2004/27/EC, or that patient information leaflets are in accordance with those provisions, will be covered by the existing criminal offences in Schedule 3.

In addition to obligations relating to MAs, we propose that it should be a criminal offence for the holder of a UK manufacturer’s licence to use “starting materials” (referred to as APIs in this document) which have not been manufactured in accordance GMP for starting materials; we would welcome your views on whether this should only be an offence if the manufacturer knew, or should reasonable have been aware, that the starting material was not GMP compliant.

\textbf{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) Duty to forward data at the request of the EMEA - Article 16(2):

b) Duty on the Qualified Person (QP) responsible for pharmacovigilance to provide competent authority with information relevant to risk and benefit - Article 23(d);

c) Duties relating to the public communication of information relating to pharmacovigilance concerns – Article 24(5);

\textsuperscript{15} See regulation 3(4) of the Medicines (Marketing Authorisations and Miscellaneous Amendments) Regulations 2004 (S.I. 2004/3224).
d) Duty to collect information from targeted patient groups at the request of the EMEA – final paragraph of Article 26

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.

10. Monitoring and 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.

11. 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 and DTI. 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 Partial RIA.

(ii) Public Consultation

A formal public consultation exercise on the Commission’s original proposal was concluded in May 2002. 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. This RIA will be attached to a formal public
consultation letter seeking formal views from a wide range of stakeholders and will subsequently be updated following consideration of those views.

12. Summary and recommendation

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.

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ANNEX D

Other changes to legislation

Introduction

In addition to the transposition of Directive 2004/27/EC into UK legislation, there has been a careful, and much wider examination of how the existing UK legislation implements the Community obligations relating to manufacture, import and distribution of medicines for human use.

Accordingly, we intend to use the process of implementing Directive 2004/27/EC to address areas where we can improve or clarify the existing implementation, as part of a complete package of measures.

We would welcome comments on the proposals, and in particular on the degree of difficulty which you envisage in complying with them.

Imports from third countries & wholesale distribution

Good Distribution Practice

We propose to amend the existing legislation relating to wholesale distribution (see, in particular, sections 8 and 47 of the Medicines Act 1968 and Schedule 3 to the Standard Provisions Regulations) to impose a requirement on wholesale dealers and importers to comply with the principles and guidelines of good distribution practice (GDP) - as required by Article 80(g) of Directive 2001/83/EC. We also propose to amend the legislation relating to manufacturing (sections 8 and 47 of the Act and/or Schedule 2 to the Standard Provisions Regulations) to impose a similar requirement on manufacturers to comply with the principles and guidelines of good distribution practice when they distribute medicinal products manufactured under their manufacturing licence (ML).

Imports from third countries

Directive 2001/83/EC treats imports from third countries as being part of the manufacturing framework, but the UK implementation is currently via the wholesale dealer framework. This approach recognises that importation is not actually manufacturing, and so long as the requirements for importers are reflected in the UK wholesale provisions, the UK remains compliant with European requirements. Of more concern is whether the relevant provisions for Wholesale Dealer’s Licences (WDLs) (see sections 8 and 47 of the Act, Schedule 2 to the Applications Regulations and Schedule 3 to the Standard Provisions Regulations), as they apply to importers, adequately implement the Directive’s requirement.

Article 40(3) of the Directive 2001/83/EC provides that importers of products from third countries (i.e. countries outside the European Community) must hold a
manufacturing authorisation. Strictly speaking, however, the Act only requires a WDL for “wholesale dealing” which, as defined in section 131, does not cover the act of import itself (although it does cover the supply of any product which is imported).

Therefore, in relation to imports the Government has identified the following options:

(i) amend the Act to make it explicit that the import is an act of distribution by way of wholesale dealing - and therefore requires a WDL; and

However, an alternative approach is also possible. There is an issue about whether or not to bring UK legislation more into line with the approach adopted in the Directive (also establishing a degree of parity with the Clinical Trials Regulations in the process) by changing the emphasis in the Medicines Act and making the relationship between manufacturing and import much clearer. Accordingly, the Government’s preferred approach is to:

(ii) seek an amendment to the Medicines Act so as to provide that import from a third country requires a manufacturer’s licence (ML) for import. This would move the issue from the provisions relating to WDL to those relating to MLs, consistent with the approach in the 2001 Directive.

Option (ii) above would not result in any additional burden on licence holders as we intend “rolling over” existing licenses into MLs and absorbing any related costs.

In addition, regulation 3(1)(b) of the MA Regulations states that no person shall distribute an unauthorised product by way of wholesale dealing, yet there is no criminal offence in Schedule 3 for breach of this obligation. Accordingly, we intend making it an 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).

We welcome views on this approach.

Application requirements

Article 41 of Directive 2001/83/EC sets out the application requirements for manufacturing authorisations (which, as stated, includes importers of products from third countries). To obtain a manufacturing authorisation, the products proposed for import must be specified. In relation to Article 41(b), certain other conditions are also required to be met - the applicant is required to give details of the premises, facilities and equipment he has to carry out controls (as well as to store & distribute the products).

Articles 46 and 46(a) then impose a number of requirements on holders of manufacturing authorisations. The authorisation holder is required to have at his disposal the services of staff who comply with the MS legal requirements. In the UK, Schedule 3 of the Standard Provisions Regulations deals with the different aspects of

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16 The Medicines for Human Use (Clinical Trials) Regulations 2004 – S.I. 2004 No. 1031
importation as relating to the storage and distribution of the product, and quality assurance of the imported product, but does not, at present, mention the control activity which must be carried out by importers.

As indicated above, we are consulting on whether the requirements relating to imports from third countries should be applied by the UK’s provisions relating to manufacturing rather than wholesale dealing. If, however, the requirements remain part of the wholesale dealing framework, amendments are required to the Standard Provisions, or the provisions of the Act, affecting WDLs relating to imports from third countries, as follows:

(i) to require applicants to give details of the premises, facilities and equipment at which he carries out controls; and

(ii) to require the holders of such WDLs to comply with all the requirements of Article 46, in particular the requirement to comply with GMP, in so far as it relates to the import of products from third countries.

**Time limits for licence applications**

Articles 43-45 and 78 of Directive 2001/83/EC concern the examination of licence applications and the time limits for granting a manufacturing or wholesale distribution authorization. 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. The Medicines Act does not currently specify the time limits for considering applications for no equivalent provisions for MLs or WDLs; although in practice the MHRA has an obligation to comply with the European limits.

We propose an amendment to the Medicines Act to reflect the time limits set out in the Directive.

**Manufacturing and Wholesaling**

**Good Manufacturing Practice**

Article 46 of the 2001 Directive sets out the obligations which MS must impose on holders of manufacturing authorisations; in particular, under Article 46(f) the holder must comply with the principles and guidelines of GMP as laid down by Community law. The relevant principles and guidelines are currently laid down in Commission Directive 2003/94/EC\(^\text{17}\) (the “GMP” Directive). We are seeking to use the 2001 Review process to clarify and improve the current provisions in UK domestic legislation so that they more closely match European requirements in this area.

At present, the UK complies with its obligations by including relevant requirements in the standard provisions of MLs, in accordance with section 47 of the Act and the Standard Provisions Regulations. Consideration has been given to whether the terms

\(^{17}\) Laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. OJ L262/22
of the Standard Provisions are sufficient to transpose the obligations of the 2001 Directive. In general terms there are many areas where, although the UK can demonstrate that it is compliant, the wording of the provision is different from Article 46(f) and the GMP Directive. This leads to areas where there may be doubt as to whether certain obligations may not be adequately implemented, or at least where the precise match between the two is unclear.

The Government therefore proposes to modify the present UK legislation relating to standard provisions for MLs, so that there is a general requirement to comply with the principles of GMP set out in Commission Directive 2003/94/EC. The existing standard provisions which replicate, overlap or are potentially inconsistent with those principles would then be removed to avoid confusion.

It is important to bear in mind that UK manufacturers already rely on the GMP guidelines and the relevant European guidance, so this would mean no change in practice. Indeed, the planned modifications to domestic legislation will make things easier, since, in relation to GMP, manufacturers would no longer need to consult both the SPs and the relevant principles for the detail of the obligations, but would refer primarily to the GMP documents.

**Minimum requirements for Manufacturing Licence (ML)/WDL holders**

Articles 46 and 80 of Directive 2001/83/EC place particular obligations on the holders of manufacturing licence and WDLs; as indicated above, Article 46 includes the requirement to comply with GMP. The standard provisions which apply to most licences are set out in the Standard Provisions Regulations, which, as we indicated above, are relied on for compliance. However, according to the existing legislation, the licensing authority (in practice the MHRA) can choose whether to include individual standard provisions or not (see sections 20(1)(a) and 47(2) of the Act). In practice, to ensure compliance with our Community obligations, the necessary provision are included. But in order to ensure the UK’s position is entirely clear, we propose to amend the legislation so that the relevant provisions apply to all MLs (which relate to products subject to the Directive), plus WDLs - and remove the (largely theoretical) licensing authority discretion.

Thus, the Government intends amending the relevant sections of the Act to ensure that the relevant provisions are binding. The preferred option is to adopt an approach similar to that used for the Clinical Trials Regulations - i.e. ensure that all manufacturing authorisation holders must comply with the obligations specified in Articles 46 and 80 (including compliance with GMP and/or GDP – see above) and then have additional standard provisions which the licensing authority may chose to incorporate in the licence. It is intended that the compulsory provisions are listed in the legislation itself, so that there are those which the licensing authority must apply and those for which it has a discretion.

Consideration would need to be given to the position of the limited number of MLs for products falling outside the scope of the Directive. Should the obligations in Article 46 be applied to them, or should there be a difference in the provisions which apply? We would welcome comments on this point. Please also note that there will no
longer be a requirement for 5-yearly renewals of licences for manufacturers, importers and distributors.

Disposal of product

Article 46(b) of the Directive 2001/83/EC provides that ML holders shall be obliged “to dispose of the authorized medicinal products only in accordance with the legislation of the MS concerned”. This relates to the safe disposal and destruction of unwanted relevant medicinal products, yet there is nothing directly equivalent in the Standard Provisions Regulations.

The Government therefore proposes to introduce an additional obligation in the legislation which requires ML holders to dispose of unwanted or expired drugs safely and for this to be verified on a case by case basis during the course of an inspection.

“Specials”

Article 5 of the 2001 Directive allows MS to exclude certain medicinal products from the provisions of the directive. It provides that “A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.” This is commonly known as the “Specials” exclusion.

This provision has not changed in the review and has been transposed into UK legislation by Schedule 1 to the MA Regulations. However, the provisions of paragraph 1 of Schedule 1 to the Regulations do not accurately reflect the limitations in Article 5 of the Directive. In particular, there is no requirement in the Regulations that the product in question is needed to “fulfil special needs”. This principle has, however, always been present in guidance and is accepted as an important condition which must be fulfilled for the supply of unlicensed relevant medicinal products for individual patients.

The Government intends taking the opportunity presented by the Review to amend the MA Regulations in order to ensure that there is an express requirement in Schedule 1 that the product must be needed to “fulfil special needs”.

“Specials” licenses

The MHRA (as licensing authority) grants “specials” manufacturing licences in the same way as for licensed products. These “specials” licences have the same provisions as other licences, except that a QP is not required for release of a finished unlicensed product.

These licences are not intended to be manufacturing authorisations for the purposes of Directive 2001/83/EC (i.e. an Article 40 authorisation), yet the UK domestic

18 Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 (S.I. 1994 No. 3144), as amended
legislation (see paragraph 2(e) of Schedule 1 to the MA Regulations) purports to provide that “specials” must be manufactured, assembled or imported by the holder of an authorization under Article 40.

Accordingly, an amendment is required to paragraph 2(e) of Schedule 1 of the MA Regulations, in order to clarify that the “specials” ML is not intended to be an Article 40 authorisation.

**Export to EC/EEA countries**

The existing WDL provisions are consistent with Directive 2001/83/EC, which has the effect that export to another MS is a form of wholesale distribution. Export from the UK to another MS of the European Community requires a WDL, by virtue of section 49A of the Medicines Act. But 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.

Therefore, sections 14(2) and 49A require a small amendment to clarify that a WDL is required for export to all EEA States - not just MS of the EC.

**Sanctions**

**Possession**

The Medicines Act currently provides that only pharmacists may sell or supply POMs to the public, in accordance with a prescription written by an “appropriate practitioner” (sections 58(2) & 67). The Government wishes to use the power to make regulations under section 2(2) of the European Communities Act 1972 to strengthen further existing legislation by creating an offence for possession of a POM with intent to supply contrary to the Act. The creation of such an offence would greatly assist the MHRA in dealing with individuals found in possession of large quantities of a (possibly impure, counterfeit or unlicensed) medicinal product with a view to selling or supplying to the public. Thus, the offence would be formulated as possession with intent to supply and the competent authority would have the power to search, seize the quantities of product found and to take appropriate action. The competent authority would look to prove intent by saying that an individual could not legitimately have more than a certain amount in his/her possession for personal use.

The potential risk to public health posed by unlicensed or counterfeit drugs entering the legitimate supply chain is clear. This sanction is aimed at tackling the growing problem of trafficking of medicinal products.

The proposed offence would be included in Part 3 of the Medicines Act, as amended using regulations under section 2(2) of the European Communities Act 1972. Criminal offences created under section 2(2) 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.

**APIs**
APIs are “starting materials” in EC parlance and, as outlined above, some control will occur from October 2005. Under the new manufacturing provisions of Directive 2001/83/EC (inserted by the amending Directive 2004/27/EC), manufacturers will be obliged to use only APIs which have been manufactured in accordance with good manufacturing practice.

The Directive does not require licensing as such of manufacturers of APIs/excipients – as has already been stated, inspections will result in the issue of GMP certificates (which the API/excipient manufacturer could then produce to the manufacturer of the medicinal product as evidence of GMP compliance) and results of inspections shall be posted to a central Commission database.

The Government intends strengthening this position by making it a criminal offence for an API manufacturer to supply an active ingredient or listed excipient which does not comply with the principles of GMP, knowing or having reasonable cause to believe that such an active ingredient or listed excipient is intended to be used in the manufacture of a medicinal product.

The proposed offence needs to be limited in this way due to the fact that active ingredients and excipients have non-medicinal uses. The offence needs to link to the supply rather than the manufacture of these products to catch intermediate dealers and to exempt from liability any manufacturer who did not comply with GMP, sold their product to a wholesaler for another use and that wholesaler sold on for use in the manufacture of medicinal products.

In addition, due to the increased importance and value of GMP inspection certificates, via the new measures set out at Articles 46, 47 and 111 of the amending Directive, an additional sanction is planned. It is proposed that the deliberate alteration or falsification of a GMP certificate (other than by the licensing authority) should constitute a criminal offence.

We would welcome comments on these points.
PARTIAL REGULATORY IMPACT ASSESSMENT

Title of regulatory proposal
Implementing the 2001 Review – other changes to UK medicines legislation

1. Purpose and intended effect of measure

Policy objective

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

1.1 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.

1.2 In addition to the main 2001 Review provisions, which are discussed elsewhere in this consultation package, 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 completely or precisely implemented the European Community obligations relating to the manufacture, import and distribution of medicinal products for human use.

1.3 The changes identified for action within this 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.

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

Risk Assessment

1.5 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 with other UK policy goals, including minimising the burdens on business.

1.6 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.

1.7 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

1.8 The detail of the regulatory proposals can be found at Annex D and this regulatory impact assessment should be read in conjunction with that. Briefly, there are new requirements relating to Good Manufacturing Practice, as follows, around:

- Training;
- Record-keeping;
- Premises and equipment;
- Production;
- Quality control;
- Inspection

1.9 In addition, 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 and wholesaling;
- Unlicensed medicines;
- Disposal of medicinal products;
- New sanctions

1.10 The proposed changes will result in amendments to the Medicines Act 1968, the Standard Provisions Regulations (to be updated as a single consolidated Statutory Instrument) and the MA Regulations.

2. Options
2.1 The UK is obliged to implement European legislative requirements. Commission Directive 2003/94/EC on good manufacturing practice (GMP) of medicinal products for human use was transposed into UK domestic legislation during 2004\(^{19}\). During transposition, it was felt that a number of obligations relating to GMP required further clarification within domestic legislation, in order to achieve compliance with European requirements. This is explained at annex D of the consultation package. Accordingly, they are being included within 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 compliance with European requirements.

2.2 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.

### 3. Benefits

3.1 **Option 1** - 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) if they were unable to demonstrate compliance with European requirements and there would be continuing problems for enforcement. This option would also risk infraction proceedings from the Commission.

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

3.3 The GMP proposals will result in amendments to the Standard Provisions Regulations, which will be updated as a single consolidated Statutory Instrument – making it easier for companies and licence holders to operate through a framework of clearer and simplified legislation.

\(^{19}\) The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 2004 – S.I. 2004 No. 1678
4. **Costs**

4.1 The new regulatory requirements around manufacture, import and wholesale dealing simply establish in legislation that which should already be happening as good practice within the pharmaceutical sector. As such, there are no implementation or compliance costs identified – other than the creation of the new fees for inspections of API/excipient suppliers, which are set out within the separate Fees Consultation.

4.2 Although the new fees are an extra cost burden on API/excipient suppliers there are benefits to affected companies. A report will be provided to the manufacturer or manufacturing authorisation holder (MAH) who has undergone the inspection and, where relevant, a certificate of GMP compliance issued. Holders of GMP certificates will therefore hold a competitive advantage and the costs arising from this are not expected to be sufficiently high to affect competition or entry to the market.

4.3 The new fees are discussed in full within the context of the 2001 Review provisions as well as within the separate fees consultation document.

5. **Issues of equity and fairness**

5.1 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. **Impact on small businesses**

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 Whilst there are additional inspection requirements, as well as some small changes to manufacturing processes the Government believes that these should be accommodated relatively easily by good manufacturers.

6.3 The Government wishes to test these assumptions with consultees and across interested Government Departments (including the Small Business Service), and welcomes views.

7. **Competition assessment**

**The market**

7.1 It is necessary to consider the impact on competition within UK markets and to analyse the impacts of the proposed Regulations on UK businesses in the relevant markets and on importers into the UK.
Restrictions on businesses?

7.2 It is important to consider whether the regulatory proposals will have any detrimental impact on new businesses. The Government’s view is that there is unlikely to be any change in the number or size of businesses within the market, and no 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 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. Views are sought on these points.

8. Enforcement and sanctions

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 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 – i.e. not punishable with imprisonment for more than two years or punishable on summary conviction with imprisonment for more than three months or with a fine of more than £400 (if not calculated on a daily basis) or with a fine of more than £5 a day.

9. Monitoring and review

9.1 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.

10. **Consultation**

10.1 The Agency is committed to seeking views from as many interested parties as possible. In particular, we would like your opinion on whether:

- The benefits and costs look reasonable;
- The assessment of competition effects looks reasonable;
- The enforcement issues are reasonable and fair;
- There are any unintended consequences.

10.2 Please ensure that responses concerning the potential costs of the proposals are accompanied by evidence to support respondents’ claims.

11. **Summary and recommendation**

11.1 It is recommended that option 2 be supported and implemented. There are clear benefits for industry and the end user from harmonising UK legislation with European requirements. The regulatory proposals will result in clearer, more accurate and more consistent information about the standards met by pharmaceutical manufacturers, importers and wholesalers and will provide a level playing field for industry. This comes at modest cost. Manufacturers may also benefit from the security that providing accurate information and observing quality processes will not lead to competitive disadvantage.

11.2 These regulatory proposals allow the UK to fulfil its Community obligation to implement the provisions of European legislation and ensure delivery of the intended consumer protection and trade benefits. Subject to the outcome of consultation, the Government plans to implement the changes by November 2005.

12. **Declaration**

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

Date

Minister’s name, title, department

Contact Point

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# GLOSSARY OF TERMS

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<td>EU</td>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>QP</td>
<td>Qualified Person</td>
</tr>
</tbody>
</table>
ANNEX G

To: Andrew Kaye  
Review of EU Medicines Legislation – MLX 317  
MHRA  
Rm. 16-157  
Market Towers  
1 Nine Elms Lane  
London SW8 5NQ  
e-mail: andrew.kaye@mhra.gsi.gov.uk

From: _________________________  
_________________________  
_________________________  
_________________________  
_________________________  

CONSULTATION LETTER MLX 317  
Title: IMPLEMENTATION OF REVISED EU MEDICINES LEGISLATION

*1. We do not propose to comment on the proposals in MLX 317  
*2. Our comments on the proposals in MLX 317 are below/overleaf/attached

Confidentiality Declaration  
Please note that it will be assumed that your reply can be made publicly available unless you indicate that you wish all or part of it to be treated as confidential and excluded from this arrangement.

*Our reply may be made freely available  
*Our reply is confidential  
*Our reply is partially confidential (indicate clearly in the text of the reply the material to be regarded as confidential)

*Delete as appropriate

Signed: ______________________________

Date: __________________________
Consultation list

Advertising Association
Advertising Standards Authority
Ainworths
All-Party Pharmacy Group
Alliance for Natural Health
Andean Medicine Centre Ltd
Animal Medicines Training Regulatory Authority
Anthroposophical Association
Aqueous II (NHS Information Authority)
Aromatherapy Trade Council
Arthritis Care
Association of Anaesthetists of Great Britain and Northern Ireland
Association of Ayurvedic Practitioners (TAPASI)
Association of British Cardiac Nurses
Association of British Health Care Industries
Association of British Neurologists
Association of Chinese Medicine Practitioners (ACMP)
Association of Clinical Research in the Pharmaceutical Industry
Association of Community Health Councils of England & Wales
Association of Contact Lens Manufacturers
Association of Chief Police Officers
Association of Chief Police Officers Scotland
Association of Dispensing Opticians
Association of Head Teachers
Association of Hospice Management
Association of Independent Clinical Research Contractors
Association of Independent Multiple Pharmacies
Association of Medical Microbiologists
Association of Medical Research Charities
Association of Optometrists
Association of Paediatric Anaesthesia
Association of Palliative Medicine
Association of Pharmaceutical Importers
Association of British Pharmaceutical Industries
Association of Professional Ambulance Personnel
Association of Respiratory Specialists
Association of Scottish Trusts
Association of Surgeons in GB and Ireland
Association of Traditional Chinese Medicine UK
Association of Veterinarians in Industry
Association for Nurse Prescribing
Association for Residential Care
Association for Sick Children
Aston Trelford Consultants Ltd
Aromatherapy Trade Council (ATC)
Ayurvedic Medical Association UK
Ayurvedic Trade Association
Asthma & Allergy Research
Back Care
Bayer Diagnostics Manufacturing Ltd
Biotechnology and Biological Sciences Research Council (BBSRC)
Besselaar Clinical Research Unit
Biohealth Ltd
Bioindustry Association
Birth control Trust
Boots Company, The
Breakthrough Breast Cancer
Breast Cancer Care
British Acupuncture Council
British Agrochemicals Associations
British Associations for A&E Medicine
British Association for Nursing in Cardiac Care
British Association for Nutritional Therapists
British Association of Chemical Specialities
British Association of Accredited Ayurvedic Practitioners (BAAAP)
British Association of Dermatologists
British Association of European Distributors
British Association of European Pharmaceutical Distributors
British Association of Feed Suppliers and Add Manufacturers
British Association of Feed Supplements and Additive Manufacturers (BASFAM)
British Association of Flowers Essence Producers
British Association of Homoeopathic Manufacturers
British Association of Nutritional Therapies (BANT)
British Association of Pharmaceutical Physicians
British Association of Pharmaceutical Wholesalers
British Association of Research Quality Assurance
British Ayurvedic Medical Council, The
British Cardiac Patients Association
British Chambers of Commerce
British Chiropody and Podiatry Association
British College of Optometrists
British Complementary Medicines Association
British Contact Dermatitis Group
British Dental Association
British Dental Association (Northern Ireland)
British Dental Association (Scotland)
British Dental Association (Wales)
British Dental Trade Association
British Diabetic Association
British Dietetic Association
British Epilepsy Association
British Flower & Vibrational Essence Association
British Generic Manufacturers Association
British Geriatric Association
British Geriatric Society

80/88
British Heart Foundation
British Herb Trade Association
British Herbal Medicines Association
British Homoeopathic Association
British Horse Society
British Institute of Regulatory Affairs
British International Doctors’ Association
British Medical Association
British Medical Association (Northern Ireland)
British Medical Association (Scottish Branch)
British Medical Association (Welsh Office)
British Medical Journal (BMJ)
British Menopause Society
British Nuclear Medicine Society
British Oncological Association
British Osteopathic Association
British Pharmacological Society
British Plastics Federation
British Pregnancy Advisory Service
British Printing Industries Federation
British Retail Consortium
British Society for Allergy and Clinical Immunology
British Society for Allergy, Environment and Nutritional Medicine
British Society of Chinese Medicine
British Society for Rheumatology
British Society of Gastroenterology
British Standards Institute
British Thoracic Society
British Toxicology Society
British Veterinary Association
Broadcast Advertising Clearance Centre
British Advisory Centres
Brittle Bone Society, The
Burford Research Consultants
CA Medica
Cancer BACUP
Cancer Research Campaign
Cancer Research UK
CARE
Careers National Association
Central Committee for Community and Public Health Dentistry (CCCPH)
Centre for Pharmacognosy and Phytotherapy, University of London
Council of Ethnic Minority Voluntary Sector Organisation (CEMVO)
Central Medical Advisory Committee
Central Office for Research Ethics Committee
Commission for Healthcare Audit and Inspection (CHAI)
Chemical Industries Association
Chemist & Druggist
Child Safe Packaging Group
Chinese Competent Authority
Chinese Medical Institute & Register
Chinese Medicine Association of Suppliers
Clinical Contract Research Association
CMAS (unable to find)
Co-operative Pharmacy Technical Panel
Co-operative Union Ltd Parliamentary Committee
College of Health
College of Optometrists
College of Pharmacy Practice
Commission for Racial Equality
Committee on Advertising Practice
Common Services Agency
Commonwealth Working Group on Traditional and Complementary Health
Community Pharmacy Magazine
Community Pharmacy Wales
Community Practitioners and Health Visitors Association
Community Services Pharmacists Group
Company Chemist Association Ltd
Confederation of British Industry
Consolidated Communications
Consumers Association
Consumers in Europe
Consumers for Health Choice
Council for the Professions Supplementary to Medicine
Council for Responsible Nutrition
Council of Heads of Medical Schools
Court Service
Community Practitioners and Health Visitors Association (CPHVA)
Committee on Safety of Medicines – Sub Committee on Pharmacovigilance (CSM SCOP)
CTPA Ltd
CTS Dental Supplies
Dental Defence Union
Dental Formulary Subcommittee of the JFC
Dental Protection
Department of Agriculture
Department of Health
Department of Health and Social Services (NI)
Dept of Trade and Industry (DTI)
Diabetes UK
Dr China
Dispensing Doctors Association
Doctor Magazine
Drug & Therapeutics Bulletin
Drug Information Pharmacists Group
Drug Safety Research Unit
English Board for Nursing, Midwifery & Health Visiting
Holland and Barrett
Human Genetics Commission
Icon Regulatory Division
International Federation of Aromatherapists (IFA)
Independent Hospice Representative Committee (IHRC)
Imperial Cancer Research Fund
Independent Healthcare Association
Independent Healthcare Foundation
Independent Television Commission
Institute of Biology
Institute for Complementary Medicine
Institute of Directors
Institute of Health Food Retailing
Institute of Quality Assurance
Insulin Dependent Diabetes Trust
International Ayurveda Foundation, The
International Society for Pharmaco-epidemiology
International Society of Professional Aromatherapists
Internal Holistic Aromatherapy Foundation
Institute for Optimum Nutrition
International Federation of Aromatherapists
International Research Consultants
International Planned Parenthood Foundation
International Society of Pharmacovigilance
International Society of Professional Aromatherapists
Irish Veterinary Association
Joint Committee on Vaccination and Immunisation (JCVI)
Joint Consultants Committee
Joint Formulary Committee
Joint Royal Colleges Ambulance Service Liaison Committee
Keele University
Kings College Hospital
Lancet (The)
Life (Pro-Life charity)
Limited Liability Partnership
Local Authority Central Office of Trading Standards (LACOTS)
London Port Health Authority
London School of Hygiene and Tropical Medicine
Long-Term Medical Conditions Alliance
Lymphone Association
Macmillan Cancer Charity
Maharishi Ayurveda Products
Medical Defence Union
Medical Defence Union (Scotland)
Medical Protection Society Ltd
Medical Research Council
Medical Women's Federation
Medicines Commission
Milton Keynes PCT
MIMS (Haymarket Medical Publishing Ltd)
MIND (National Association for Mental Health)
Ministry of Defence
National Asthma Campaign
National AIDS Trust
National Assembly for Wales
National Association of GP Co-operatives
National Association of Health Stores
National Association of Primary Care
National Association of Private Ambulance Services
National Association of Women Pharmacists
National Back Pain Association
National Board for Nursing, Midwifery and Health Visiting
National Care Standards Commission
National Consumer Council
National Council for Hospice and Specialist Palliative Care Services (NCHSPCS)
National Council of Women of GB
National Eczema Society
National Farmers Union of England and Wales
National Farmers Union of Scotland
National Federation of Retail Newsagents
National Federation of Women’s Institutes
National HIV Nurses Association
National Institute for Mental Health England
National Institute of Medical Herbalists
National Meningitis Trust
National Patient Safety Agency
National Osteoporosis Society
National Pharmaceutical Association
Natropathic Forum UK
Natural Medicines Manufacturers’ Association UK
Natural Medicines Society
Nelsonbach
Neonatal and Paediatric Pharmacists Group
Neurological Alliance
NHS Alliance
NHS Confederation
NHS Information Authority (Coding & Classification)
NHS Pharmaceutical Quality Control Committee
NICE (National Institute for Clinical Excellence)
NMMA Potters (Herbal Supplies) Ltd
Northern Ireland Consumer Council
Novartis Consumer Health
Nursing and Midwifery Council
Only Natural Products
Ophthalmic Group Committee
Organic Herb Trading Company, The
OTC Bulletin
OTC Business News (Informa Publishing Group Ltd)
OTC News & Market Report
Overseas Doctors Association in the UK Ltd
Paediatric Chief Pharmacists Group
Pain Concern UK
Pain Relief Foundation
Pain Society, The
Pan European federation of TCM Societies
Paramedics Board
Patent Office
Patients Association
Pavilion Healthcare International Ltd
Promoting Excellence in Consumer Medicine Information (PECMI)
Peninsula Medical School
Perrigo (UK) Ltd
Pharmaceutical Contractors Committee (Northern Ireland)
Pharmaceutical Journal
Pharmaceutical Quality Group
Pharmaceutical Services Negotiating Committee
Pharmaceutical Society for Northern Ireland
Pharmacy Insurance Agency
Pharmag
Phytomed Medicinal Herbs Ltd
Potters Herbal Supplies Ltd
Prescription Medicines Code of Practice Authority
Prescription Pricing Authority
Primary and Community Care Pharmacy
Proprietary Association of Great Britain
Prostate Cancer Charity
Public Health Laboratory Service Board
Quality Improvement Scotland (NHS)
Queens University
Radio Advertising Clearance Centre
Reading Scientific Services Ltd
Reckitt Benckiser
Register for Chinese Herbal Medicine
Registered Nursing Home Association
Rethink
Royal Botanic Gardens, Kew
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Nursing (Northern Ireland)
Royal College of Nursing (Scotland)
Royal College of Nursing (Wales)
Royal College of Obstetricians & Gynaecologists
Royal College of Ophthalmologists
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians & Surgeons (Glasgow)
Royal College of Physicians (Edinburgh)
Royal College of Physicians (London)
Royal Colleges of Physicians: Faculty of Pharmaceutical Medicine
Royal Colleges of Physicians: Faculty of Public Health Medicine
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons (Edinburgh)
Royal College of Surgeons (England)
Royal College of Surgeons (Faculty of Dental Surgery)
Royal Pharmaceutical Society of Great Britain
Royal Pharmaceutical Society of Great Britain (Scotland)
Royal Pharmaceutical Society of Great Britain (Welsh Executive)
Royal Society of Chemistry
Royal Society for the Promotion of Health
Royal Welsh Agricultural Society
SANE
Scottish Ambulance Services
Scottish Association of Health Councils
Scottish Biomedical Association
Scottish Consumer Council
Scottish Deans Medical Curriculum Group
Scottish Executive
Scottish Executive Agricultural and Food Department
Scottish General Medical Services Committee
Scottish General Practitioners Committee
Scottish Pharmaceutical Federation
Scottish Pharmaceutical General Council
Scottish Wholesale Druggists Association
Scrip Ltd
Servier Laboratories Ltd
Shadow Health Professionals Council
Sinolink (UK) Ltd
Skin Care Campaign
Small Business Service
Social Audit Unit
Society of Chiropodists and Podiatrists
Society of Homoeopaths
Society of Pharmaceutical Medicine
Society of Radiographers
Society for the Promotion of Nutritional Therapy
Solgar Vitamins Ltd
Specialist Advisory Committee on Antimicrobial Resistance
SSIPH c/o Lanarkshire NHS Board
St Andrews’ Ambulance Service
St. Guy's Hospital
St Johns’ Ambulance Service
Sterilised Suture Manufacturers Association
Surgical Dressings Manufacturers Association
Switch
Traditional Herbal Medicine Producers
Terrance Higgins Trust
Third Sector
Tic-Tac Administration
Tutshells Enterprise IG
UK Central Council for Nursing, Midwifery & Health Visiting
UK Clinical Pharmacy Association
UK Gout Society
UK Homeopathic Medical Association
UK Inter-Professional Group
UK Psychiatric Group
UK-DURG Administrator
Ulster Chemist Review
Ulster Farmers Union
Unified Register of Herbal Practitioners
UNISON
University of Aberdeen
University of London
University of Nottingham
University of Southampton
Veterinary Medicines Directorate (VMD)
Volunteer Development Scotland
Welsh Assembly
Welsh Consumer Council
WNBNMHV
Women in Medicine
Women’s National Commission
Wythenshaw Hospital