

Special edition

InFocus

A new framework for approval of medicinal products in Europe



In this special edition of InFocus we review some of the key changes to the European regulatory framework for medicinal products for human use which are set out in Directive 2004/27, Regulation 726/2004 and Directive 2004/24. Member States were required to implement the directives by 30 October 2005. The Regulation came into effect on 20 November 2005.

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Striking the balance - The need for change

In 2001 the European Commission began its overhaul of the legislation covering pharmaceutical products. Its first step was to consolidate the myriad of European Directives into one text, the 'Community Code relating to medicinal products for human use' (Directive 2001/83). Whilst a consolidated text certainly assisted as a point of reference, it did not tackle the key problems with the existing legislation identified following a detailed consultation carried out between 1995-2000.

Areas which the consultation process identified as needing improvement included:

- The applicability of the mutual recognition procedure in an enlarged Europe
- The facilitation of generic product entry into the market balanced against the need to maintain innovative development
- Post-marketing pharmacovigilance and market surveillance, and
- The rules governing packaging and product advertisement.

In April 2004, after a legislative process which had begun on publication of the Commission's original proposal for reform in 2001, the European Parliament and Council published their agreed amendments to the Community Code in Directive 2004/27 (the new Community Code). The changes to the existing Community Code had to be implemented by Member States by no later than 30 October 2005.

The consultation process also identified necessary adaptations to legislation covering the centralised procedure specifically and the workings of the European Medicines Evaluation Agency (EMA), Regulation 2309/93. This has now been replaced by Regulation 726/2004.

Regulation 726/2004 requires no implementation by Member States and had immediate effect from 20 November 2005. The new Regulation cross-refers to the provisions of the new Community Code which as a consequence will also apply to applications made under the centralised procedure.

Finally as part of the pharma package review, it was thought to be necessary to harmonise the disparities between Member States' regulation of herbal medicinal products. Whilst most of such products fall within the definition of medicinal product and therefore required a marketing authorisation, the stringent requirements necessary to obtain such authorisation, could not be satisfied by a number of such products. To ensure that they were able to remain on the market, Directive 2004/24 amended the Community Code as regards herbal medicinal products. These changes also come into effect following implementation that was required to take place no later than 30 October 2005.

The Commission has issued guidance on the application of the new legislation in its November 2005 Notice to Applicants. Further Guidance from the Commission is expected. Although all guidance included in the Notice to Applicants is not legally binding, it is intended by the Commission to facilitate the interpretation and application of the new legislation. As regards the UK, the MHRA has issued its own interpretation in its consultation on the new legislation earlier this year.

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New procedure for marketing authorisations

With the inclusion of the new decentralised procedure there are now four routes for obtaining marketing authorisations in Europe: national, mutual recognition, centralised and decentralised procedures.

National and Mutual Recognition Procedure (MRP)

The general principles of national and mutual recognition procedures have not changed under the new Community Code and companies can still make a first national application and use the MRP sequentially in other member states to expand cover as and when required.

Centralised Procedure

The scope of centralised procedure has changed and it is now mandatory for all new active substances for the treatment of HIV/AIDs, cancer, diabetes and neurodegenerative disorders and for orphan designated substances. Other new active substances can use the procedure, as can medicinal products that constitute a significant therapeutic, technical or scientific advance. However, the definition of "significant ... advance" is not entirely clear.

As before, the timelines for the centralised application procedure are strict and the procedure is designed to be a fast and effective way of obtaining a marketing authorisation throughout the Community. Despite this it remains possible that issues, which arise surrounding the authorisation, may cause delay for the entire authorisation i.e. in every member state.

Decentralised Procedure (DCP)

The decentralised procedure creates a streamlined application and assessment procedure that has the potential for significantly shortened approval times compared to the MRP. It should be used where a medicinal product has not yet received a marketing authorisation in any Member State. It allows simultaneous parallel applications to selected, so called "concerned" member states using one "reference" member state to drive the process forward. It might be advantageous for companies who do not require marketing authorisations in all Member States or who do not have a presence in every Member State or who cannot or do not wish to take advantage of the centralised procedure.

The decentralised procedure can be used across all Member States. As with the MRP, the precise procedure followed depends upon whether it is the Member State or the applicant initiating the procedure. It can end at different stages depending on the degree of harmonisation of the original summary of product characteristics, the quality of the dossier and the assessment report. If consensus is reached between the Member States it would be possible to end the procedure and recommend marketing authorisation at day 105.

The general principles and time line for the procedure involves:

- A pre-procedural step including a 14 day period for validation
- A first assessment step whereby the reference member state has 120 days to prepare the draft assessment report, draft SmPC, patient leaflet and labelling
- A second assessment step with up to day 90 to reach final agreement
- An assessment process with a maximum of 210 days net of clock off periods
- If consensus not reached, discussion at the coordination group
- Following consensus, the national grant must be determined within 30 days

The options for obtaining marketing authorisations give rise to tactical choices and careful regulatory strategic decisions which take into account many factors including, professional endorsement and prescribing 'culture' of the local market and the local prescription reimbursement policies.

Further details on the above procedures are in the recently updated chapters of the Notice to Applicants.

Data exclusivity and the introduction of market exclusivity

The data exclusivity period is the period of protection awarded to data filed by an innovator company in support of its application for a marketing authorisation during which period a regulatory authority cannot make reference to such data to process a generic application.

Up until the new Community Code, the data exclusivity periods in Europe were either six years or 10 years (depending on the national legislation in the country in question) from the date of first authorisation of the innovator product in any Member State. Data provided to the EMEA in support of a centralised application was awarded a data exclusivity period of ten years.

Harmonisation of periods

The new Community Code has harmonised the data exclusivity periods across the EU. It provides the innovator data with a period of eight years exclusivity from the date of first authorisation in a Member State and the eight year period applies irrespective of the application route chosen. Furthermore, the concept of 'marketing exclusivity' is introduced for the first time into EU legislation (Article 10.1 of Community Code as amended). Although a generic company can rely on an innovator's data after the expiry of eight years, no generic product can be placed on the market until a further two years (i.e. ten years) after initial authorisation. The MHRA has indicated that in those cases where a marketing authorisation is issued before the expiry of the ten year period of data and market exclusivity for a reference product, the authorisation document issued by the MHRA will indicate the earliest date on which that product can be placed on the market. Arguably therefore, any product placed on the market before that date could be deemed to be a product marketed without a valid marketing authorisation.

The transitional provisions in the new Community Code make it clear that the new periods of 8+2 years data and marketing exclusivity will be available only to those products for which an application is received on or after the new Community Code and Regulation come into effect.

Extra year for new indications

The new Community Code allows for an additional period of one year's exclusivity where new therapeutic indications are made during the first eight years of the ten years exclusivity that are held to bring a significant clinical benefit in comparison with existing therapy (Article 10.1). The interpretation of this provision in the UK and Germany is that the extra year of data exclusivity is not restricted to the new indication but applies to all indications. The Commissions' Notice to Applicants confirms this stating that generic products, with or without the new therapeutic indication, may not be placed on the market until expiry of the eleventh year. In Germany the extension of the data exclusivity period is automatic in the sense that the regulatory authority has to consider whether the extension is granted on application of the marketing authorisation for the new indication. It is then a question for the German Courts if either the innovator or generic company challenges the decision. This approach appears to be consistent with the Notice to Applicants, which, states that every application for a new indication must be assessed by the competent authority to determine whether the new therapeutic indication brings a significant clinical benefit in comparison with existing therapies. The MHRA have not given guidance on whether the extension also applies automatically in the UK or whether some form of application for an extension is required although in the light of what the Commission say in the Notice to Applicants we consider the latter unlikely.

The MHRA has indicated that in their view the meaning of "significant clinical benefit" is that the indication has not previously been authorised in relation to any other product containing the same active substance and/or extended to new categories of patients. The MHRA has stated that the interpretation of "significant clinical benefit" and "comparison with existing therapies" will emerge in the Notice to Applicants guidance produced by the Commission. No guidance on the meaning of "significant clinical benefit" has been issued in Germany.

As in the case of the new 8+2 periods referred to above, the additional year will only apply in respect of applications made after the new Community Code and the Regulations come into effect.

Extra year for new indications of well-established substances

A 'non-cumulative' period of one year's exclusivity is also given for data in support of an application for a new indication for a well-established substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. In order to satisfy the requirement of significant studies, the MHRA has indicated that

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it 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. No guidance has yet been issued by the Commission.

The meaning of "a non-cumulative period of one year of data exclusivity" is not entirely clear. The MHRA position is that the period can be awarded whether or not the original product had already benefited from the additional one year of market exclusivity awarded for new indications under Article 10.1. The Commission has stated in its Notice to Applicants that the period refers exclusively to the data covering the new indication.

The MHRA has indicated that the extra year data exclusivity will apply to all products, not just those for which a new marketing authorisation has been applied for after 30 October 2005, provided in each case the active substance satisfies the criteria of this provision. The position is the same in Germany. The Notice to Applicants states that the extra year applies in respect of new indications submitted after the new rules start to apply confirming the view that the 'well-established' substance can have been authorised prior to the introduction of the new Community Code and the Regulation.

Extra year for change of classification

A change of classification of a medicinal product authorised on the basis of significant pre-clinical tests or clinical trials will award the applicant a one year period of data exclusivity in respect of the results of those tests or trials from the date of the initial change in authorisation.

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'Global Marketing Authorisation; 'Generic Medicinal Product' and 'European Reference Product'

Global Marketing Authorisation

The new Community Code introduces a definition of 'reference medicinal product' and incorporated within that definition is the introduction of the concept of a 'Global Marketing Authorisation'. Any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions to the initial marketing authorisation shall belong to the same 'Global Marketing Authorisation'. The practical effect of this is that any authorisation falling within the global marketing authorisation is not entitled to a further period of data/market exclusivity over and above the data/market exclusivity granted to the initial marketing authorisation of 8+2(+1) years.

The absence of any such definition in the old Community Code resulted in a number of referrals to the European Court of Justice on the issue of whether a particular type of line extension for example a new indication or a new dosage form was entitled to its own additional data exclusivity period. In each of these referrals the ECJ had held that they did not. This was consistent with the Notice to Applicants and therefore the new Community Code is effectively codifying what was carried out in practice. However, there is still room for uncertainty in respect of certain line extensions which are not expressly covered in the definition.

As regards combination products the Commission's Notice to Applicants states that a new combination product will have an independent period of exclusivity from the data exclusivity period of its individual components i.e. the combination product does not fall within the scope of the Global Marketing Authorisations for the individual components.

European Reference Product

The European Court of Justice had interpreted the old Community Code such that it required a reference medicinal product to have a valid authorisation in the Member State in which the application for the generic medicinal product was made at the time of the generic application although it was not an additional requirement that the authorisation be valid at the time of the generic grant (*Astra Zeneca/Laegemiddelstyrelsen* case). The new Community Code expressly states that the generic application can still be made in a Member State where the reference product has no authorisation. In this case, the applicant has to indicate the name of the Member State in which the reference medicinal product is or has been authorised and the competent authority of the Member State in which the application is submitted shall obtain the relevant documentation from the Member State in which there has been an authorisation. The other Member State must supply all relevant documentation requested for the so-called "European Reference Product".

A current issue arising from the fact that different Member States have a different period of exclusivity is whether in the case of European Reference Product, the applicable exclusivity period would be by reference to the period available in the country in which the reference product is authorised or the country in which the generic application is made. At present the MHRA's position is that the generic authorising state determines the applicable period of exclusivity because this is where the data would be used to authorise the generic product. The German authority has adopted a similar position. However, the MHRA has stated that its view is not universal throughout Europe and has indicated that it will consider a proposal that the longer data exclusivity period as between the two countries should apply. It would appear from what is stated by the Commission in the Notice to Applicants that the data exclusivity period in both the generic authorising state and the reference state has to have expired before an application can be made.

'Generic Medicinal Product'

The new Community Code introduces a definition for "Generic Medicinal Product": "a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies." As this wording is taken from the European Court of Justice Judgment in the case of Generics and has been used in practice since that decision, the presence of this additional wording in the legislation is not going to have an effect to current practice. However, the definition goes on to state "the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active, unless they differ significantly in properties with regard to safety and/or efficacy." Whilst the ECJ had already ruled that a different salt of an active should be considered to be the same active for the purposes of a generic application (*SKB* case), the other variations to an active had not been contained in the legislation or case-law.

Approval of biosimilars

In the case of chemical pharmaceuticals, it is common practice for generic versions to come on the market immediately upon expiry of the patent of the reference product. The same is not true for generics of biological medicinal products (biosimilars, biogenerics, follow-on biologics).

There are three possible approaches to getting approval of a biosimilar drug in Europe:

- Submit a full dossier of pre-clinical and clinical data as would be required for any new drug
- Demonstrate that the product already has well established medical use within the European Community
- Abridged procedure

The first is not generally a viable option due to the time and expense involved. The second was the route followed by Sandoz in its failed attempt to get approval for Omnitrop. Sandoz are currently appealing the decision at the European Court Justice. The third route is the one most favoured by generic companies.

Prior to amendment by Directive 2004/27/EC the legislative basis for authorisation of any generic product (not expressly biosimilars) under the abridged procedure was set out in Article 10 of Directive 2001/83/EC. An applicant under the abridged procedure was required to show that its product was "essentially similar" to the original medicinal product. Annex 1 of Directive 2001/83/EC anticipated that additional data might be required to demonstrate the similar nature of two biologic products. To date no biosimilar product has been approved in any of the Member States. Difficulties have arisen in establishing the data needed to show sufficient similarity with the reference product.

Have these difficulties been resolved under the new Community Code?

The simple answer is no, not yet.

The new Community Code anticipates that data over and above the standard tests required for chemical generics will be required and specifically provides for this in Article 10.4 of the main text. However, the legislation is unclear on exactly how much data will be required to secure approval of a biosimilar.

The EMEA has published guidance on the supplementary data envisaged and draft product specific guidelines on medicinal products containing specific biopharmaceuticals, namely to date recombinant human insulin, human granulocyte- colony stimulating factor, recombinant human growth factor and erythropoetin (EPO) which are intended to be annexed to the more general guideline. In its guidance the EMEA encourages companies to contact the agency to obtain further guidance on their particular products.

The EMEA has indicated that while product specific guidelines will be appropriate for some classes of products, for others, review standards and data requirements will be developed on an ad hoc case-by-case basis. In some cases the abridged procedure may not be appropriate and full preclinical and clinical studies may be required.

Efforts to clarify requirements for biosimilars have recently become more urgent, as at least two applications are now under review at the EMEA. Swiss based, BioPartners has filed dossiers with the EMEA for Valtropin (somatropin) for the treatment of paediatric and adult growth hormone deficiency and for recombinant interferon alpha for the treatment of hepatitis C.

Although no biosimilar products have yet been approved in the EU, the Croatian pharmaceutical Company Pilva recently won approval for generic EPO in its home market of Croatia. Pilva's approval is not a test of the European approval process for biosimilars as Croatia currently lies outside the European Union.

New "Bolar Provision" in Europe

The new Community Code introduces a Bolar provision into EU law for the first time. See Table 1]

Table 1

The Bolar Provision in the new Community Code
<p>Article 10(6) of the Community Code as amended states:</p> <p>"Conducting the necessary studies and trials with a view to the application of paragraph 1, 2, 3 and 4 [of Article 10] and the practical requirements shall not be regarded as contrary to patent rights or supplementary protection certificates for medicinal products."</p>
<p>Paragraph 1 of Article 10 sets out the requirements for a generic application for a marketing authorisation based on a reference product;</p> <p>"By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the production of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.</p>
<p>A generic medicinal product authorised pursuant to this provision shall not be placed on the market until 10 years have elapsed from the initial authorisation of the reference product."</p> <p>Paragraph 2 of Article 10 sets out the definitions of 'generic medicinal product' and 'reference medicinal product'. Article 10(3) sets out the procedure where pre-clinical tests or clinical trials are required and Article 10(4) covers the requirements to be met by biosimilar medicinal products.</p>

Implementation of Bolar provision into UK law

The Bolar Provision has been implemented into UK law by way of an amendment to section 60(5) of the Patents Act 1977 which lists the defences to patent infringement. [See Table 2]

Table 2

<p>"An act which, apart from this subsection, would constitute an infringement of a patent for an invention shall not do so if -</p> <p>(i) it consists of -</p>
<p>(i) an act done in conducting a study, test or trial which is necessary for and is conducted with a view to the application of paragraphs 1 to 5 of article 13 of Directive 2001/82/EC or paragraphs 1 to 4 of article 10 of Directive 2001/83/EC, or</p>
<p>(ii) any other act for the purpose of the application of those paragraphs."</p>

Scope of the Bolar provision in the UK

The MHRA and Patent Office has issued guidance on what activities they perceive as falling within the scope of the Bolar provision. In summary, these are stated to be:

- Manufacture or import of active substances and validation of manufacturing processes
- Manufacture or import of finished product and validation of manufacturing process
- Development/testing/use of analytical techniques associated with manufacture of the active and the finished product

- Conducting pre-clinical tests, clinical and bioavailability trials and stability studies on the medicinal product (although there is some ambiguity in the wording here)
- Compilation and submission of a marketing authorisation and samples of products to regulatory authorities.

The MHRA has made it clear that the list of exempted activities would be included in guidance notes rather than the legislation. As such they will have no legal force. In practice any dispute as to the scope of the Bolar provision is most likely to arise in the context of a patent infringement action where the company conducting the activities prior to patent expiry would rely on Section 60(5) (i) as a defence to a claim of infringement brought by the patentee. Such a dispute would have to be resolved by the UK Patents Court and as with the interpretation of other European derived legislation, the UK Court might consider it necessary to make a referral to the European Court of Justice for clarification on the correct interpretation of this section.

Although the Patent Office/MHRA's views are not legally binding, it is likely that a UK Court would agree, in principle, that the broad classes of activities listed above fall within the Bolar defence as its whole intended purpose is to permit generic companies to carry out the type of tests necessary for obtaining authorisation prior to patent expiry so as to permit them to launch on patent expiry.

Furthermore, given the wording chosen for the UK implementing legislation it appears unlikely that companies conducting tests or trials on patented products other than for the purpose of obtaining a generic authorisation would be able to rely on this defence. This could be relevant, for example, where an innovator company carries out tests for the purposes of developing a new drug on the basis that the development data may ultimately be used for an application for a marketing authorisation for that new drug.

What is less clear is whether the Bolar provision would include activities such as the following:

- Tests carried out for foreign marketing authorisations
- Type and scale of validation runs and sale of products produced from such runs
- Tests/trials later abandoned and not leading to an application for authorisation

Disparities between Member States as regards scope of Bolar provision

Whilst European Community Directives are binding on Member States as to the results to be achieved, the way in which they are implemented is determined by individual Member States. What this means in practice is that the implementation of Directives will not necessarily be identical in every Member State. Accordingly the scope of the Bolar provision will depend on the national implementation legislation and may be different as between Member States.

There is a disparity between Member States as regards the interpretation of the wording of Directive. For example countries such as Germany and Italy have opted for a broader interpretation than the UK.

Table 3

Germany:	Italy:
'The right granted by the patent does not extend to Studies and trials and the resulting practical requirements which are necessary in order to obtain an authorisation to market a medicinal product in the European Union or to obtain authorisation for a medicinal product in one of the Member States of the European Union or in a Third Country.'	'Regardless of the subject of the invention, the exclusive right granted by the patent does not extend to (a) acts performed privately and for non-commercial purposes, or for commercial purposes, even if aimed at obtaining an authorisation to market a medicinal product in any country, and subsequent practical requirements, including the preparation and the use of the active pharmaceutical ingredients if they are absolutely necessary.'

It therefore would appear that one of the fundamental aims behind the new Community Code in achieving a level playing field throughout Europe has not been achieved, at least, in respect of the Bolar provision.

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Insofar as innovator companies are concerned it remains to be seen the extent to which the disparities will lead them to carry out comparative tests in countries such as Germany and Italy in preference to the UK. Although it may be that any such companies carrying out comparative tests in the UK could circumvent the narrower Bolar provision in the UK by arguing before the national Court that a wider interpretation should be given to the existing defence under patent law for acts carried out for experimental purposes.

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SmPCs and second medical use patents

A general requirement for applications under Article 10 of the new Community Code (i.e. under the generic procedure) is that they follow the wording of the Summary of Product Characteristics (SmPC) of the reference medicinal product. This gives rise to tension between the requirement to fulfil regulatory obligations and avoiding patent infringement where, although the basic patent covering the product had expired, additional patents exist covering the use of that product for a previously unpatented indication. Article 11 allows for a deviation, which seeks to alleviate that tension. It states "indications and dosage forms which were still covered by patent law at the time when a generic medicine is marketed need not be included [i.e. in the SmPC]".

The practical problem which arises for applications under the de-centralised and mutual recognition procedures is that the patent position for those indications and dosage forms will not be consistent in all countries where a marketing authorisation is sought.

The practical solution suggested by the Mutual Recognition Facilitation Group (MRFG) is that to enable MRP or DCP to be available for such generic applications a highest common denominator approach will be taken i.e. the dossier for the procedure will be completed without regard to the patent position. Once the marketing authorisation has been obtained using this procedure, in those countries in which patent protection exists, it is the marketing authorisation holder's responsibility to then provide the SPC, labelling and Patient Information Leaflet (PIL) to the competent authority with the relevant sections (i.e. those which relate to the patented indication and dosages) removed. Once the patent has expired the SPC, labelling and PIL must be realigned. Recognising that such inconsistency is not ideal, the MRFG has consulted on some agreed wording for the PIL where differences arise for this reason. It will be a national decision as to whether or not it will be necessary to include such a statement in a "blue box" type format. The proposed wording is:

"[Active substance] which is contained in (product)[may also be/is also] authorised to treat other illnesses which are not mentioned in this leaflet. Ask your doctor, pharmacist or other healthcare professional if you have any further questions and always follow their instructions."

The consultation on this wording closed on 10 November and the results should be published shortly.

As a matter of public policy the MHRA have stated that it will require all contraindications (whether or not they might arise from a patented use) to be included.

For centrally authorised products, guidance is limited but it would seem that Article 11 applies equally and patented indications and dosages need not be included. However, it is possible that for centrally authorised products a lowest common denominator might be used and the broadest patent position be taken into account so that the SmPC (whilst potentially different from the originator product) is consistent throughout Europe. We are awaiting confirmation that this is the position.

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The "Sunset Clause"

There is now an obligation (Article 23 new Community Code) on companies to inform the competent authorities of dates of cessation of marketing and interruption to supply. It is also an obligation to inform when the product is temporarily or permanently off the market. However, the terms temporarily and permanently are unhelpfully not defined.

Article 24 creates the so-called Sunset clause. This places an obligation on companies to place an authorised product on the market within three years of obtaining the marketing authorisation otherwise the marketing authorisation ceases to be valid. The Notice to Applicants defines "placed on the market" as the date of release of the product into the distribution chain. It is the date when the product comes out of the control of the MA holder.

In addition if a medicinal product previously on the market ceases to be marketed for three consecutive years its marketing authority shall also cease to be valid. The Notice to Applicants states that in order for the marketing authorisation to remain valid, at least one presentation of the authorised product must be placed on the market and at least one pack size for that presentation marketed.

For national authorised products "placed on the market in the authorising Member State" means that the medicinal product is on the market of the Member State which has granted the marketing authorisation. It is irrelevant if the nationally authorised product obtained its authorisation through the MRP or DCP routes, to avoid the Sunset Clause taking effect the product must be marketed in each country of authorisation.

For centrally authorised products marketing in one country is enough to prevent the sunset clause taking effect.

The "Sunset Clause" will apply to medicinal products authorised before the new rules applied, however the three year period shall commence for

- Centrally authorised products, from 20 November
- Nationally authorised products, from 30 October unless the legislation was implemented before in which case it is the date that the legislation was implemented in that country

Issues may arise here if companies become involved in patent litigation which prevents them commencing or continuing to market a medicinal product after a marketing authorisation has been granted. What happens if the litigation does not conclude before the sunset clause takes effect? The Commission and the MHRA have indicated that in certain circumstances exceptions will be considered.

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Patient information leaflets and labelling

The new Community Code contains changes to the provisions relating to patient information leaflets (PILs) and also relating to labelling. These were implemented in UK for national authorisations on 1 July 2005 [SI 2004/3224] with a three year transitional period for compliance for national authorisations.

One key change includes the requirement for consultation with patient groups to ensure that the PIL is clear and easy to use. Also there are changes on, information in PILs which now has to be included in a more logical order, a blank section on the packaging should be left so that the sticker applied by the pharmacist upon prescription does not obliterate key pieces of information and it is also a requirement to include the product name in Braille on the label and make the PIL available in Braille. The main effect of these changes is that more time and money may need to be spent on the preparation of PILs and labels. It is anticipated that as the provisions are put into practice further guidance will be developed on the absolute requirements and on best practice for ensuring compliance.

Perhaps one of the most expensive and time consuming changes is the consultation process required with patient groups for the patient information leaflets. This is the subject of transitional provisions. With the exception of centrally authorised products for which the key date is 20 November, the new legislation will only apply to authorisations after 30 October (although in the UK implementation took place in July of this year) but consultation with user groups may well be required for future major variations of authorisations existing at 30 October 2005. For applications under the MRP consultations will be required for those applications already at day 90 of the procedure on 30 October. Some flexibility has been indicated within this but will depend on the extent that the authorisation applicant may seek to provide justification for not providing test results.

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Renewals and PSURs

There have been some significant changes to the procedure and timing for renewals. The most significant of these is that renewal now takes place after five years on the basis of a re-evaluation of the "risk benefit" balance and a renewal submission which, consists of a shortened version of the file for quality, safety and efficacy which has to be submitted six months before expiry. Once renewed the marketing authorisation shall be valid for an unlimited period unless the competent authority decides otherwise.

The MHRA has recently issued guidance on national marketing authorisation renewals. The UK will not be requesting submission of further renewal applications for nationally authorised products that have been renewed at least once before 30 October 2005. This will apply to marketing authorisations (MAs) which are due to expire on 30 January 2006 onwards (i.e. those for which renewal applications are not required under the current legislation).

However, periodic safety update reports (PSUR) are now required every three years after the first renewal and every six months up until the first renewal.

The MHRA has said that it will give more information on the transition of the five to three-year PSUR cycle once the European position has been finalised as it is the intention of the MHRA to be consistent with this advice. However, as an interim measure the MHRA guidance is that the next five-year PSUR data should be submitted when due. The data should be submitted within 60 days of the data-lock point which should be set so that submission is at least three months prior to the date when the marketing authorisation would have expired.

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Simplified registration procedure for traditional herbal medicines

The Traditional Herbal Medicines Directive 2004/24/EC ('The Herbal Medicines Directive') was implemented in the UK by the Medicines (Traditional Herbal Medicinal Products for Human use) Regulations 2005. It came into force on 30 October 2005 except for two sections in Schedule 7. These came into force on 20 November 2005. The Herbal Medicines Directive changes the regulatory framework for herbal medicines in the UK.

Under the old regulatory regime herbal medicines could be approved for sale in either of two ways:

- Licensed as a herbal medicine, or
- Exempt from licensing as a herbal remedy

Companies often had difficulty satisfying the efficacy criteria required to obtain approval as a herbal medicine. The problem with remedies sold under the exemption is that there were no specific safeguards on quality and safety and there was often not enough information for the public on their safe use

The aim of the Herbal Medicines Directive was to overcome these difficulties and to establish higher levels of safety and quality for traditional herbal medicines by the introduction of a product registration scheme. The registration scheme covers manufactured, finished and over the counter traditional herbal remedies. Significantly, instead of the normal requirement for medicines to demonstrate efficacy, there is a requirement to show traditional use.

The following key requirements have to be met for a product to be registered:

- The product must be a 'herbal medicinal product', as defined
- The product must have indications exclusively appropriate to traditional herbal medicinal products
- It must be designed for use without supervision of a medical practitioner
- It must be administered at a specified strength and posology and either orally, externally and/or by inhalation
- Provide a bibliographic review of safety data supported by an expert report
- In order to establish 'traditional use' the application to register must be accompanied by bibliographical or expert evidence proving that the product or a corresponding one has been in medicinal use for the last 30 years preceding the application. Fifteen years of use must have been within the European Union, and
- The product must not be capable of fulfilling the criteria for obtaining a marketing authorisation.

The overriding concern amongst companies in the herbal industry is the cost of complying with the new legislation. The MHRA has recently published proposed fees which can reach as high as £4,500 for herbal products containing new herbal actives. However, for unlicensed herbal medicines legally on the market on 30 April 2004, the UK implementing legislation grants a seven-year transitional period giving companies time to adapt to the new requirements. All unlicensed herbal medicines will need to comply with the scheme by April 2011.

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Implementation and transitional provisions

Whilst the Directive stated that national implementation of the new Community Code was to have taken place by 30 October 2005, it seems that the complete implementation has not happened in most Member States. The UK, German and Italy seem to be ahead of the game. Germany and Italy implemented earlier in the year and the UK implemented just in time. Other countries have implemented some but not all of the provisions. A good example of where this has happened is in France where a few of the concepts of the new Community code were incorporated into the national legislation earlier this year but it is anticipated that full implementation will not take place until the beginning of 2006.

It is worth noting that, whether or not a country has actually implemented the Directive into their national legislation in good time, there has been a general agreement that all countries will follow new procedures in practice from this date. This has been confirmed by the Mutual Recognition Facilitation Group. In addition a general principle has been agreed that beneficial or positive legislation will be available from the implementation date and anything with negative implication will not apply retroactively.

Of course, once implementation has taken place some of the changes are so significant (particularly those of a procedural nature) that it is necessary to have transitional provisions to help companies with the change. We have discussed some of the transitional provisions throughout this document. They have been the subject of much discussion between the Member States and centrally as to how the new provisions will work in practice. Guidance has been provided; much of this appears on the EMEA website:

www.emea.eu.int/htms/general/direct/legislation/legislationhuman.htm

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