Legal and regulatory update

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Legal and regulatory update

NOTES FROM THE EU
Amendments to EC medicines legislation

EC Directive 2001/83/EC (the 'Medicines Directive'), which governs the manufacture, marketing and distribution of medicinal products for human use, is being amended by Directive 2004/27/EC. For ease of reference, a consolidated version of the amended Medicines Directive has been published by the European Commission and is available at the EUDRA website.[1] The deadline for each member state to implement the amendments into national law was 30th October, 2005.

At the time of writing, some amendments have already been implemented into UK law by amending the Medicines for Human Use (Marketing Authorisation Etc) Regulations 1994 (SI No 1994/3144). These amendments concern the marketing authorisation holder's obligation to inform the UK Medicines and Healthcare Products Regulatory Agency (MHRA) of relevant new information, the obligation to ensure that patient information leaflets reflect the results of user testing with target patient groups and the provision of one year's data exclusivity protection for a marketing authorisation holder's test or trial results used for switching the legal status of a medicinal product (such as from prescription only to non-prescription status, for example).

The MHRA is consulting on the implementation of the remaining amendments (MLX 317, available on the MHRA website[2]). Some of the most important amendments which the UK has yet to implement include:

- amending the definition of '**medicinal product**' to cover borderline products;
- introducing a '**European reference product**' for abridged applications for marketing authorisation of 'generic' products;
- harmonising the period of regulatory data protection across all member states to a period of between 8 and 11 years (the so-called '**8 + 2 + 1**' provision);
- the introduction of a so-called '**Bolar**' provision to enable generic companies to conduct certain trials and studies to support 'abridged' applications for marketing authorisations before patent and supplementary protection certificate (SPC) expiry without liability for infringement of the relevant patents and SPCs; and
- amending the marketing authorisation renewal periods and introducing a three year '**sunset clause**' to invalidate marketing authorisations if the product is not placed on the market within three years of authorisation, or for a continuous three year period thereafter.

The UK proposals for implementation of the above amendments to Directive 2001/83/EC are considered in this paper, which also sets out the proposals for implementation of the 'Bolar' provision into the national law of the UK, Sweden, Germany, the Netherlands, France and Belgium.

Amended definition of 'medicinal product'

The definition of 'medicinal product' in the Medicines Directive has been altered so that new types of emerging therapies, such as gene therapy, radiopharmaceutical products and also 'borderline products' are regulated under the stricter regime for medicinal products. 'Borderline products'

are those that fall between the previous definition of a 'medicinal product' and definitions for other regulated sectors, such as medicinal devices, cosmetics, biocides and food supplements. In order to maintain a harmonised position across the EU, the MHRA intends to modify its current guidance on the borderline between medicinal products and medical devices once the outcome of Europe-wide discussions becomes clear.

European reference product for 'abridged' applications for 'generic' products

Directive 2004/27/EC introduced sweeping amendments to Article 10 of the Medicines Directive, including the introduction of a European reference product for 'generic' applications for marketing authorisations. The concept of a 'generic' product replaces the concept of 'essential similarity' in Article 10 of the Medicines Directive. The definition of a 'generic' product follows the European Court of Justice's (ECJ) definition of 'essentially similar' products but goes wider to cover different physical and chemical forms of active substances that have the same safety and efficacy profiles and also, for example, to cover alternative immediate release oral pharmaceutical formulations. Products with minor differences to the authorised product will therefore be treated as generic products and will be able to take advantage of the 'abridged' procedure for submitting marketing authorisation applications.

Introducing a European reference product means that generic manufacturers using the 'abridged' application procedure (and who need not therefore supply a full dossier of preclinical tests and trials for their generic product) may apply for marketing authorisation in *any* member state and rely on the dossier of information already submitted for the European reference product in another member state. The other member state must supply all the relevant documentation requested. Previously, the MHRA would not supply confidential information on UK reference products to other member states, but once this amendment has been implemented into UK law, it will be obliged to do so to support generic abridged applications in other member states.

The '8 + 2 + 1' rule for regulatory data protection

Directive 2004/27/EC amended the period of data protection that is available in respect of innovative medicinal products following the grant of the first marketing authorisation in the EU. Applicants for generic product authorisations under the 'abridged' application procedure set out in Article 10(1) or the 'hybrid abridged' procedure set out in Article 10(3) of the amended Medicines Directive may rely on the dossier of preclinical tests and clinical trials submitted for the reference product (or for a European reference product) provided that the relevant reference product has been authorised for 8 years or more in any member state (data exclusivity). The generic product authorised under the abridged procedure may not be placed on the market until 10 years have elapsed from the date of authorisation of the reference product (market exclusivity), although this result will be obtained only in those member states that grant marketing authorisations which permit marketing only after the full 10 years have elapsed. This ensures that the holders of marketing authorisations for innovative medicinal products obtain at least 8 years of data exclusivity in all member states relating to the full dossier of information and 10 years of market exclusivity (this is the '8 + 2' part of the '8 + 2 + 1' rule). Previously, each member state had a choice of setting its own period of data exclusivity as either 6 or 10 years, and so the period of protection was not harmonised across the EU.

It is worth noting that the effect of the period of market exclusivity is not to prevent generic products being placed on the market within 10 years of the grant of marketing authorisation for the reference

product, but simply to prevent generic products that are authorised under the abridged procedure from coming onto the market within that 10 year time frame. It is still open to the generic product manufacturer to go through the full application procedure for marketing authorisation and submit a comprehensive dossier of data, including results from clinical tests and trials that the generic manufacturer has itself conducted. Providing that there is no infringement of patent or SPC rights, the generic product could hit the market in less than 10 years from the date the innovative product was authorised.

All marketing authorisations for a single active substance are now considered to fall within the same 'global' marketing authorisation for the purposes of the generic abridged application procedure (amended Article 6(1) of the Medicines Directive). This means that a generic applicant will be able to rely on marketing authorisations already submitted for so-called 'line-extension' products (which have the same active ingredient as the initially authorised product but may be in a different pharmaceutical form, a different strength or have a different administration route) even if the line-extension product itself has not already had a marketing authorisation for the requisite 8 year data exclusivity period, so long as the reference product has been authorised for such a period of time. This is in accordance with recent case law from the ECJ (*R (on the application of Novartis)* v *Licensing Authority* (Case C-106/01) and *R (on the application of Approved Prescription Services)* v *Licensing Authority* (Case C-36/03)) and also accords with previous UK policy on data exclusivity.

The '+1' part of the '8 + 2 + 1' rule extends the period before a generic product authorised through the abridged procedure may come onto the market from 10 years to 11 years after the reference product was first authorised. This extension will only apply if, during the first 8 years of authorisation of the reference product, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison with existing therapies. The MHRA has stated that, in its view, 'significant clinical benefit' would require that no product containing the same active substance has previously been authorised in the relevant indication and/or extended to new categories of patients.

The MHRA has stated that, in accordance with Article 2 of Directive 2004/27/EC, the new periods of data and market exclusivity will be available only for innovative reference products for which a marketing authorisation application is received on or after 30th October, 2005 (the deadline for implementation of the amendments to the Medicines Directive). For reference products with applications submitted before that date, the existing data and marketing exclusivity periods will apply (being either 6 or 10 years, depending upon the particular member state).

The consequence of the previous, non-harmonised, periods of data and market exclusivity which applied in different member states will become apparent where an abridged application is made in one member state which relies on a dossier of information submitted for a European reference product in another member state before 30th October, 2005. There are two options for which period of data and market exclusivity should apply in such a situation: (i) the data and market exclusivity periods which apply in the member state where the European reference product was authorised; or (ii) the data and market exclusivity periods which apply in the member state where the generic application has been submitted. At the time of writing, there is no EU-wide agreement on the periods of data and market exclusivity which should apply, so each individual member state will have to make its own decision.

The MHRA has stated that the applicable periods of data and market exclusivity are those in force in the generic

authorising member state, because this is where the data will be used to authorise the generic product. In the UK, the relevant data exclusivity period is 10 years, and so European reference products authorised in a member state which previously had only a 6 year data exclusivity period would obtain an extended period of protection against generic abridged applications made in the UK.

The 'Bolar' provision

The title of this provision comes from the US case of *Roche* v *Bolar* (733 F.2d 858, 221 USPQ 937) in which it was decided that a generic pharmaceutical company was not permitted to conduct tests on a patented compound prior to patent expiry, even though the tests were conducted in order to fulfil the regulatory requirements for obtaining a generic drug marketing authorisation. Following this case, US patent law was amended to include an exemption to permit such activities, hence the name 'Bolar' provision. However, it should be noted that the scope of the US 'Bolar' provision is not the same as that described below.

Directive 2004/27/EC required the introduction into Article 10 of the Medicines Directive of new Article 10(6) which states that:

> Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.

Paragraphs 1, 2, 3 and 4 of Article 10 set out the abridged procedures whereby manufacturers of generic products and products similar to authorised 'reference' products can obtain a marketing authorisation without submitting a full dossier of preclinical tests and clinical trials. This is because the applicant may, without the marketing authorisation holder's consent, rely on the relevant dossier originally submitted for the reference product (the 'abridged' and 'hybrid abridged' application procedures).

The 'hybrid abridged' procedure in Article 10(3) of the amended Medicines Directive is available for applicants with a medicinal product that does not fall within the definition of a 'generic' product (and so cannot use the abridged procedure set out in Article 10(1)). The applicant under the 'hybrid abridged' procedure must supply appropriate preclinical trial or test data, but not a full dossier of information. The situations in which the 'hybrid abridged' procedure is available include medicinal products for which bioequivalence cannot be demonstrated through bioavailability studies and where there is a change in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration compared with the reference medicinal product.

The intended effect of the 'Bolar' provision is to permit applicants for marketing authorisation under the 'abridged' and 'hybrid abridged' procedures, to conduct the necessary studies and trials to submit their marketing authorisation application before expiry of the patents and SPCs covering the reference product.

In many member states, implementing the 'Bolar' provision required amendments to national patent law to introduce an exemption for such studies and trials, which would otherwise constitute infringement of the patent holder's, or SPC holder's, rights. At the time of writing, no definitive list of the type of studies and trials or 'consequential practical requirements' which should fall within this exemption has been agreed at EU level, so there is a risk that each member state might interpret the requirements of Directive 2004/27/EC slightly differently and accordingly implement a different exemption into its national law.

Some member states, including the UK and Sweden, propose to amend their national patent laws by including amendments that either refer expressly to

the exemption in Article 10(6) of the amended Medicines Directive, or use the same wording. This ensures that the national exemption accurately reflects what is required by the Medicines Directive. However, these amendments to national patent laws will not, of themselves, explain the scope of the exemption, or how it dove-tails with the pre-existing research exemption.

The scope of the 'Bolar' provision will therefore be determined over the coming years by the ECJ case law whenever a national court refers a relevant question to it on the interpretation of the exemption and/or the national implementation of the exemption. In the meantime, pharmaceutical and generics manufacturers face a period of uncertainty, although the relevant national authorities are issuing their views on what activities should fall within the exemption under national implementation of Directive 2004/27/EC. However, such views are not binding and will be subject to national legislative implementations and, eventually, ECJ rulings.

It is notable that, under Article 10(6), only generic applicants for marketing authorisation within the EU are able to benefit from this exemption, so the same research conducted for a marketing authorisation outside the EU would not be covered. However, each member state could have implemented a wider exemption had it wished to, as is the case in Germany (see further details below).

There is no limit on the patents and SPCs to which the 'Bolar' exemption will apply, so recent patents covering the relevant product would be included, provided that the acts are conducted for the purposes of making an 'abridged' or 'hybrid abridged' application. However, the exemption probably does not cover patents for research tools used in the relevant research, as these are of general application and would not relate specifically to the relevant product.

The 'Bolar' exemption would not be available to the first marketing authorisation applicant, so they would require a licence from the patent and SPC holders for their preparatory work to submit the application.

The 'Bolar' provision in the UK

In its consultation on the implementation into UK law of the amendments required by Directive 2004/27/EC (MLX 317, available on the MHRA website[2]), the MHRA proposes that section 60(5) of the Patents Act 1977 be amended so that the 'Bolar' exemption is added to the list of exemptions of acts which would otherwise constitute patent infringement. The proposed amendment would incorporate the wording of Article 10(6) of the amended Medicines Directive. UK law would therefore accurately reflect the wording of Directive 2004/27/EC, but there would be no explanation in the statute of the scope of the exemption and so the question of how this will be interpreted by the courts will be left open.

The MHRA has set out its view on how the exemption should be interpreted. The sort of activities which should be covered are directed only to 'abridged' and 'hybrid abridged' applications for marketing authorisation in the EU and include:

- the manufacture and importation of the active substance(s), including in sufficient quantities to conduct trials and validate the manufacturing and other processes (including analytical processes) in accordance with regulatory requirements;
- the development of the final pharmaceutical form of the active substance;
- the conduct of preclinical tests, clinical and bioavailability trials and stability studies;
- the manufacture and supply to the regulatory authorities of samples of active substances, precursors, intermediates, impurities and finished product samples; and

- the compilation and submission of a marketing authorisation application or a variation application.

The MHRA considers that the exemption should *not* cover such activities as the manufacture, packaging and testing of active substances or finished products that are not required for conducting the tests and trials necessary for obtaining a marketing authorisation or for providing small quantities of samples. This would therefore exclude activities carried out before expiry of the relevant patents or SPCs by a potential manufacturer which are not done in order to submit a marketing authorisation application. For example, activities carried out in order to determine whether a manufacturer would, after patent and SPC expiry, be able to produce the active product to the necessary quality standards would not fall within the exemption.

It is not clear whether the subjective intention of the potential manufacturer undertaking relevant activities will be taken into account. For example, a potential manufacturer may undertake relevant activities with the intention of submitting a marketing authorisation but then change its mind and not submit an application. If the activities did not fall within the research exemption set out in section 60(5)(b) of the Patents Act, which permits 'acts done for experimental purposes relating to the subject-matter of the invention', would such activities, if they came to the attention of the patent or SPC holder, fall within the 'Bolar' exemption? One of the respondents to the MHRA consultation raised this question with regard to failed or abandoned work carried out with the initial intention of submitting a generic application ('Analysis of the Responses to MLX 317', available on the MHRA website[2]). The MHRA has stated that it considers that the wording 'with a view to' in the 'Bolar' provision encompasses aborted development where no actual application is subsequently made. The only requirement to fall within the exemption is that the work was done with that aim and there is no need to submit the data generated as a generic application.

The MHRA considers that the exempt activities should be able to be carried out by applicants for marketing authorisations under the 'abridged' and 'hybrid abridged' procedures from 30th October, 2005 (the proposed date for amending the Patents Act 1977). This date should apply equally to reference products submitted for authorisation before 30th October, 2005 and to those authorised after that date and irrespective of whether the reference product is protected by old or new periods of data and market exclusivity.

The 'Bolar' provision in Sweden

At the time of writing, it has been proposed that section 1(3) of the Swedish Patents be amended by direct reference to Article 10(1)–10(4) of the amended Medicines Directive to ensure that the exemption accurately reflects what is required by the amended Medicines Directive. The previous ambit of the Swedish exemptions for acts which would otherwise constitute patent infringement would therefore be increased, since the current exemption is narrower than the activities contemplated by Article 10(6) of the amended Medicines Directive.

The 'Bolar' provision in Germany

All the amendments set out in Directive 2001/27/EC were implemented into German law by the Fourteenth Act Amending the Drug Act, which came into force on 6th September, 2005.

Article 3 of the Act introduced the 'Bolar' provision into German law by adding new paragraph 2b to section 11 of the German Patent Act. The amendment is translated as follows:

> The effect of a patent shall not extend to [. . .]
> 2. Acts done for experimental purposes relating to the subject matter of the patented invention;
> [. . .]
> 2b. Studies and trials and the

> consequential practical requirements which are necessary to obtain an authorisation according to Drug Law for the marketing in the European Union or an authorisation according to Drug Law for the marketing in the Member States of the European Union or in third countries.
> [. . .]

Like the UK proposals, Germany has not amended its research exemption (sub-section 2 above), which exists alongside the 'Bolar' provision. However, the scope of the 'Bolar' provision in Germany is wider than that set out in the amended Medicines Directive. Crucially, the exemption is not limited to activities carried out in order to submit an 'abridged' or 'hybrid abridged' application for a generic marketing authorisation in the EU, as there is no reference to Article 10 of the amended Medicines Directive. Instead, the exemption refers simply to Drug Law and so will apply to all applications, including the first application for an innovative product as well as generic applications. Similarly, the exemption will be available for activities conducted in order to obtain marketing authorisation in countries outside the EU. The scope of the German exemption also extends to marketing authorisations applied for through the centralised procedure as well as to applications in individual member states.

The 'Bolar' provision in the Netherlands

At the time of writing, Article 53 section 3 of the Dutch Patent Act ('Rijksoctrooiwet 1995') contains an exemption that is different from the 'Bolar' provision set out Directive 2004/27/EC:

> The exclusive rights of the patentee do not extend to acts which solely serve to research the patented invention, including research of the product obtained through a patented process.

The Dutch Supreme Court (Hoge Raad) interpreted this article restrictively in *ICI* v *Medicopharma* (BIE 1993/81, 18th December, 1992). The Court decided that certain research activities that would otherwise infringe the patent, nevertheless fall within the exemption when these acts have a legitimate purpose. Such a legitimate purpose exists only where the person who conducts the research can demonstrate that their research is solely *purely scientific*, or only focused on achieving a goal which Dutch patent law intends to achieve, such as further developing the state of the art. Research aimed at the commercial purpose of marketing the product is not covered by the exemption.

On the basis of this interpretation, the Dutch courts were able to grant an injunction that imposed a moratorium on a manufacturer of a generic drug who started clinical trials for obtaining a marketing approval before the patent or SPC had expired. The European Court of Justice confirmed that such an injunction was allowed in *Generics* v *Smith, Kline & French* (C-316/95, 9th July, 1997).

It has been proposed that the text of the 'Bolar' provision of Directive 2004/27/EC be implemented literally into the new Medicinal Products Act (Geneesmiddelenwet) as article 42 section 10. At the time of writing, this proposal is pending before the Second Chamber of Parliament. If adopted, it would still have to be approved by the First Chamber of Parliament before it can come into force. No change to the Dutch Patent Act itself is foreseen, however, as the Dutch Patent Act is a so-called 'Rijkswet', which also applies in the Dutch Antilles and Aruba, which are not part of the European Union.

At the time of writing, it is thought to be extremely unlikely that the new law would come into force before the implementation date of Directive 2004/27/EC, which was 30th October, 2005. However, this need not be a problem. The exemption in the Dutch Patent Act is in such general wording that there should be no problem in construing it in accordance with 'Bolar' provision in Directive 2004/27/EC. The Dutch courts are thought

likely, as of 30th October, 2005, to interpret the Dutch Patent Act so that research for the purpose of Article 10 of Directive 2004/27/EC is excluded from patent or SPC infringement.

The 'Bolar' provision in France

At the time of writing, the Direction Générale de la Santé (General Health Directorate), which is part of the French Health Ministry, has produced a draft Bill to implement the provisions of Directive 2004/27/EC.

France adopted the same approach as the UK, by proposing to introduce the 'Bolar' exemption into patent law alongside the existing research exemption. The Bill proposes to amend Article L.613-5 of the French Intellectual Property Code (CPI) by introducing new paragraph (d):

> The rights afforded by a patent shall not extend to:
> a) acts done privately and for non-commercial purposes;
> b) acts done for experimental purposes relating to the subject matter of the patented invention;
> c) the extemporaneous preparation for individual cases in a pharmacy of a medicine in accordance with a medical prescription or acts concerning the medicine so prepared; or
> d) the studies and trials necessary in order to obtain a marketing authorization for a medicinal product in any Member State of the European Community or any Member State of the European Economic Area, as well as any acts necessary for their performance**.**

The proposed implementation of the 'Bolar' provision under French law is therefore wider than that set out in Article 10(6) of the amended Medicines Directive, as it is not limited to generic applications, although, in contrast to the German implementation, it is limited to applications within the European Economic Area (EEA).

The body that grants marketing authorisations in France is the AFSSAPS. The Bill also proposes that Article L.5121-10 of the French Public Heath Code (CSP) should be amended as shown in bold text below.

> For a generic medicinal product as defined in paragraph 5 of Article L. 5121-1, a marketing authorization can be granted before the expiration of the intellectual property rights related to the reference medicinal product. **The studies and trials necessary in order to obtain such a marketing authorization as well as any acts necessary for their performance do not infringe these rights.** The applicant for such authorization informs the holder of these rights at the moment of the filing of the application.
> When the AFSSAPS grants a marketing authorization for a generic medicinal product, it informs the holder of the marketing authorization of the reference product of this grant. The General Manager of the AFSSAPS proceeds to the inclusion of the generic medicinal product in the directory of generic medicinal products within 60 days from the notification of the grant of the marketing authorization for the generic medicinal product to the holder of the reference product. Nevertheless, the commercialization of this generic medicinal product can only occur after the expiration of the intellectual property rights, except in the case where the right holder consents to such commercialization. For the sole purpose of publicity, the General Manager of the AFSSAPS keeps available to the public the list of intellectual property titles protecting a reference medicinal product if these titles have been communicated to the AFSSAPS by holder of this reference product. The pharmaceutical company is solely responsible for the correctness of the information provided. The

payment conditions for the service provided by the AFSSAPS are fixed by a decision from its Executive Board.

LEEM, the French organisation representing the pharmaceutical industry, has reviewed the Bill, although its opinion is still awaited.

The 'Bolar' provision in Belgium

At the time of writing, the Belgian government has not yet published its proposal for how to implement the 'Bolar' provision in Belgium, but it is understood that a proposal has been adopted and so publication should be expected shortly. It is understood that the draft law under preparation will propose an amendment to the law of 25th March, 1964, on medicinal products, which will reproduce the language of the 'Bolar' provision set out in Article 10(6) of the amended Medicines Directive almost word for word.

It is also worth noting, as previously reported,[3] that the Belgian law of 28th March, 1984, on patents was recently amended to extend the scope of the experimental use exemption to include 'use for scientific purposes on or with the subject-matter of the patented invention' as well as experiments relating to the subject matter of the invention.

Sunset clause

At the time of writing, marketing authorisations are valid for an initial five year period and are renewable for further five year periods. Directive 2004/27/EC amends this so that once the initial five year period has expired, the marketing authorisation need only be renewed once, and this renewal will be valid indefinitely unless the regulatory authority limits this to a further five year period on the basis of pharmacovigilance grounds.

A 'sunset clause' is introduced whereby the marketing authorisation for a product will expire automatically if the medicinal product is not placed on the market in the authorising member state within three years of grant. Similarly, if a medicinal product was previously on the market in the authorising member state, but is subsequently not present on the market for a period of three consecutive years, the marketing authorisation for that product will expire.

At the time of writing, European guidelines are expected, setting out the detail of the documentation that would be required for renewal applications. A European consensus on transitional arrangements for marketing authorisations which have already been renewed under the existing regime is awaited. The MHRA has stated that it would prefer that such products would not require a further renewal, but the UK would adopt the agreed EU position. The MHRA also prefers that the three year period would begin on 30th October, 2005, for all products, even if the relevant product was first granted marketing authorisation, or ceased to be placed on the market, before that date. At the date of going to print, the common position has not been agreed. This is to be contrasted with the agreement on the position under the centralised procedure for marketing authorisations (see below).

Article 14 of Regulation 726/2004 came into force across the EU on 20th November, 2005, and introduced the same initial five year validity period for products granted a marketing authorisation under the centralised procedure. Once renewed, centrally authorised marketing authorisations will be valid indefinitely, unless the regulatory authority limits this to a further five year period on the basis of pharmacovigilance grounds. There is also a three year sunset clause which is the same as the three year sunset clause for nationally authorised medicinal products. The European Commission stated on 4th August, 2005, that for products authorised under the centralised procedure prior to 20th November, 2005 (the date the amendments came into force), the three year sunset period will be calculated from the date the marketing authorisation was granted, or the date the product ceases to

be placed on the market, irrespective of whether this date was prior to 20th November, 2005.

COMP reports on five years of EU orphan medicinal product legislation

The Committee for Orphan Medicinal Products (COMP) reports that, five years on from the implementation of EU orphan medicinal product legislation, over one million patients suffering from rare conditions have benefited. The full text of the report is available on the European Agency for Evaluation of Medicinal Products' website.[4]

The legislation was brought in to stimulate the development of medicinal products for rare diseases. To obtain orphan designation, sponsors have to demonstrate that the medicinal product is intended to diagnose, prevent or treat life-threatening or chronically debilitating conditions that affect fewer than 5 in 10,000 people within the Community or that there would be insufficient return on investment to make development viable. Sponsors must show that the medicinal product is medically plausible and that there is a clinically relevant advantage or major contribution to patient care within the EU (the significant benefit criterion) from the development of the product.

Between April 2000 and April 2005, COMP received over 450 applications for orphan designation. Of those, more than 260 have been designated and 22 have gone on to receive marketing authorisation. The majority of the products designated have been chemical products although approximately 20 per cent are biotechnology products, and this percentage is expected to increase.

COMP identifies that one of the main benefits of orphan designation for sponsors has been protocol assistance. Protocol assistance enables the sponsor to request advice on the conduct of the tests and trials necessary to demonstrate safety, quality and efficacy prior to submission for a marketing authorisation. This is particularly important to small and medium sized enterprises (SMEs) that have limited experience with product development. Sponsors also have access to the EU's centralised procedure for marketing authorisation and can request reductions in the regulatory fees payable to the European Medicines Agency. Additionally, orphan products that receive marketing authorisation benefit from a 10 year period of market exclusivity that protects the medicinal product in the orphan therapeutic indication.

Overall, COMP reports that the legislation has been implemented smoothly and only makes suggestions for minor amendments to clarify and facilitate the practical process of seeking designation. As part of the development of its mandate and to maintain the spirit of the EU's orphan legislation, COMP calls on the Commission to consider a waiver of the significant benefit criterion for those applications that concern 'neglected' diseases in developing countries outside of the EU. COMP also calls on member states to increase national incentives such as fee waivers, research grants, tax deductions etc. for orphan medicinal products.

Although five years is a relatively short period of time, COMP states that public health benefits are already being felt. The orphan medicinal legislation has also stimulated scientific and public awareness of rare diseases and fostered increased research in the area. More importantly, it has given hope and opportunities to patients suffering from rare diseases.

NOTES FROM THE USA

National Institutes of Health Model Organism Sharing Policy and its implications

The National Institutes of Health (NIH), in complying with its mission as a public sponsor of biomedical research, seeks to ensure that research resources developed with NIH funding are made available throughout the research community. To that end, the NIH has implemented the Policy on Sharing of Model Organisms for Biomedical Research.[5] The new policy aims to avoid the duplication of

expensive research efforts so that the NIH can support more investigators and fund development of a greater variety of model organisms. Because the policy applies to all extramural[6] recipients of NIH funds, it is important that recipients of NIH funding, including those in industry, understand the new policy and its implications.

Background

Initially published on 7th May, 2004, in the NIH Guide,[5] the new Model Organism Sharing Policy became effective on 1st October, 2004. The new policy is considered to be an extension of NIH's existing policy on sharing research resources, reaffirming the NIH's commitment to the dissemination of research resources developed with NIH funding.[7]

Support for this broader approach traces back to the Report of the NIH Working Group on Research Tools in June 1998 which recommended that the NIH review its policies with regard to the dissemination of research tools generated under the NIH's intramural and extramural funding programmes.[8] The Working Group was concerned that all research communities, including governmental institutions, academia and industry, were experiencing increasing difficulty in accessing and using newly developed research tools. Without action from the NIH, the Working Group warned that 'current trends pose a serious threat to the best interests of the biomedical research and development community. . .'.[8] The Working Group continued by saying, '[t]he gravity of this threat is sufficient to warrant the participation of all segments of the community in the very difficult task of developing a set of mutually acceptable general principles to guide the community in the transfer of research tools.'[9]

In December of 1999, the NIH published the Final Notice on this issue.[10] The Model Organism Sharing Policy is the implementation of the policy articulated in that notice.

Model Organism Sharing Policy

Beginning on 1st October, 2004, all applications and contract proposals received by the NIH must include either a sharing plan for the distribution of unique model organism research resources (as defined below) *or* request a waiver of the sharing obligation by specifying the reasons such sharing is restricted or impossible. The policy statement applies to all extramural investigators funded by NIH grants, cooperative agreements or contracts (including Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) awards). It is worthwhile to note that the policy also applies to international collaborations and foreign grants so long as the primary grantee is a US institution. In such case, the US institution is responsible for its subgrantee or subcontract arrangements and must ensure that the sharing policy is adequately addressed in the application for NIH funding. Additionally, in contrast to the NIH Data Sharing Policy, the model organism sharing plan is not subject to the cost threshold of US$500,000, but rather is required of all applications where the applicant anticipates the development of a model organism.[11]

Under the new policy, an application for NIH funding must include a plan for sharing new, genetically modified[12] variants of non-human model organisms and related research resources developed pursuant to the investigation so funded. The term 'model organism' includes, without limitation, mammalian models such as mouse and rat and non-mammalian models such as budding yeast, social amoebae, round worm, fruit fly, zebrafish and frog. At least initially after the effectiveness of the new policy, the NIH stated that it did not expect a submission to include a sharing plan for non-eukaryotic organisms.[13] The term 'research resources' includes materials and data necessary for the production and understanding of model organisms, including genetically modified or mutant organisms, sperm, embryos, vectors, non-

human embryonic stem cells, established cell lines, protocols for genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains.

Although the sharing policy specifies certain requirements of the sharing plan, the NIH acknowledges that every plan will vary depending on the organism, the intellectual property issues and the nature of the research resources to be shared. Notwithstanding this, the sharing plan should articulate how the novel strains will be made available to the scientific community and how technology transfer and intellectual property issues will be handled. In describing how novel strains will be made available to the scientific community, the investigator should state in what form the model organisms will be provided (eg adults, embryos, sperm); in what reasonable time-frame periodic deposition of material and associated data will be made; whether a repository will be used; and if relevant, a plan to minimise the risks of infection and/or contamination. With respect to the investigator's handling of technology transfer and intellectual property issues, the sharing plan should specify how the applicant plans to make the organism and resources available to the research community; under what conditions the applicant will exercise its intellectual property rights while continuing to make the organism available to the scientific community; how the applicant will ensure that certain rights or obligations to third parties are consistent with the terms and conditions of the NIH award so as to guarantee appropriate dissemination of the model organisms; and a description of the material transfer agreements (MTA) used for such dissemination.

In addition to the foregoing, the NIH has stated that at a minimum, the sharing plan should clearly and concisely describe three subjects. First, the plan should specify whether the MTAs associated with the transfer of generated model organisms and research resources will contain no more restrictive terms than contained in a Simple Letter Agreement[14] or Uniform Biological Material Transfer Agreement[15] for the transfer. Second, the sharing plan should describe how the technologies will remain widely available and accessible to the research community even in the event that a patent application is filed on a particular technology. Finally, the sharing plan should address how the investigator will handle reach-through requirements, ie provisions requiring a recipient of the transferred materials to grant to the investigator certain rights (eg ownership, licences or payments) under any inventions or products that the recipient makes using the transferred materials.

The adequacy of any sharing plan will be reviewed and considered by the NIH Scientific Review Group, or study section, for the current application and will be considered in future funding decisions for the investigator and the investigator's institution. The reviewers will describe their assessment of the sharing plan in an administrative note but will generally not include their assessment in the overall priority score for the application. Nonetheless, for certain special initiatives, such as Request for Applications and Request for Proposals, where the application is directly related to the development of model organisms, the reviewers may integrate their evaluation of the sharing plan into the overall priority score of the application. The reasonability of a sharing plan will be determined by the reviewers on a case-by-case basis. According to the NIH, any concerns about the sharing plan must be addressed and resolved before an NIH funding award can be made; however, it is unclear whether the NIH would withhold funds if the sharing plan is deemed inadequate by the reviewers.

Implications

Although each recipient of NIH funding should carefully read and consider all elements of the Model Organism Sharing Policy, four issues require particular attention. The first involves intellectual property that may be generated in

connection with the model organism or research resources. The second concerns MTAs for use with non-profit and for-profit entities and an investigator's long-term commercialisation plans. The third issue centres on other third party agreements and how some of them may need to be structured to comply with the new policy. The fourth issue relates to the actual implementation and associated cost of sharing the material with the scientific community.

The NIH has stated that investigators and their institutions are not discouraged from seeking patent protection for the development of a research tool as a potential product for sale and distribution to the research community. Indeed, pursuant to the Bayh–Dole Act,[16] institutions are permitted to retain title to subject inventions developed with federal funding. However, under the sharing policy, such patented resources must still be made reasonably available and accessible to the scientific research community in accordance with NIH's Grant Policy Statement and Research Tools Policy.[17] Although the NIH recognises that there is a legitimate interest in protecting and benefiting from one's own investigations, the sharing policy does not allow an investigator to deliberately delay or extend exclusive use of the model organism or research resource. Accordingly, investigators may decide to file patent applications on their newly developed model organisms and related research resources sooner than normal to protect their rights to such materials. Additionally, the NIH warns if investigators inappropriately enforce their patents to limit use of the model organism, such actions may interfere with the distribution of the material throughout the scientific community and thus such investigator's actions may fail to comply with the sharing policy. To that end, the NIH directs investigators to rely on the NIH Research Tools Policy for guidance on the appropriate implementation and use of intellectual property. It is not clear whether allowing access to a model organism only for certain fields outside the investigator's primary area of interest will meet the policy's requirements.

Although the NIH does not require a particular MTA for the transfer of materials developed with NIH funding, it has specified certain terms that such an MTA should contain depending on whether the transfer is to a not-for-profit entity or to a for-profit entity. This raises a second issue for investigators as they may be forced to re-evaluate their form MTAs to ensure they are compliant with the NIH guidance, or use new forms for transfer of such organisms. Specifically, when an institution is transferring unpatented material to a not-for-profit entity, the terms of the agreement should be no more restrictive than the Uniform Biological Materials Transfer Agreement. For the transfer of related research resources to a not-for-profit entity, a Simple Letter Agreement may be used. Notwithstanding the foregoing, if the materials and/or resources are patented, then the transferring institution may grant an exclusive or non-exclusive patent licence or even sell the material to a not-for-profit entity, provided the institution does not seek any commercialisation option rights or any reach-through rights to either future products or royalties developed by the non-profit entity. When an institution is transferring material to a for-profit entity for internal use, such transfer should be effected with as few encumbrances as possible, but the institution may nevertheless grant a non-exclusive or exclusive patent licence and may even sell the materials for a profit. Additionally, agreements with for-profit entities may include a grant of a non-exclusive, royalty-free right to the transferring institution to use any improvements and/or new uses of the transferred material developed by the recipient that would infringe any patents held by the institution. Notwithstanding such flexibility, an investigator's sharing plan must still ensure the widespread availability and dissemination of the model organism and related research resources.

The implication of these requirements for investigators is not only that they should work closely with their legal counsel to ensure that their form agreements for the transfer of such NIH-funded materials comply with the sharing policy, but also that they should give thought to whether and how they may eventually commercialise the model organism and research resources, and account for such in their sharing plan.

A third issue concerns the need for an investigator to revise any third-party agreements to ensure such agreements are in compliance with the new policy. For example, if an investigator receives funding from the NIH and from an organisation whose sharing policy is inconsistent with the model organism sharing policy, then the pre-existing third party agreement must be revised to provide for sharing of model organisms and related research resources as required by the sharing policy in order for the investigator to remain compliant with the NIH award. For example, such third party agreement must include a provision for any inventions developed with NIH funding to be assigned to the investigator's institution and made available for distribution. Additionally, if the investigator wishes to waive or assign title to the invention to another party, then such investigator must seek approval from the NIH before making such waiver or assignment. The implication to an investigator is that he/she may need to take additional steps to ensure that any third-party agreements are compliant with the new sharing policy. The related issue of how investigators of small commercial companies, whose NIH-funded research and inventions provide the competitive advantage to their firms, should comply with the sharing plan requirements has not been clearly answered by the NIH. The NIH has suggested that some situations (including, perhaps, the foregoing) will present 'compelling reasons why sharing must be restricted or is not possible.'[18] However, the NIH has not provided more explicit discussion of this issue or details as to what may be sufficiently compelling to withhold dissemination of the organism or research resources. As a result, investigators should assume that such compelling reasons will be evaluated on a case-by-case basis, and if they do restrict sharing of model organisms and related research resources to more than a *de minimis* degree, they risk being deemed non-compliant.

The fourth issue involved with this new sharing policy centres on the actual implementation and associated costs of distributing model organisms and research resources to the scientific community. When distributing the organisms and research resources, an NIH-funding recipient may choose to share the material under its own auspices or via repositories or stock centres. An investigator may find it less burdensome to share the materials through a repository, stock centre or vendor rather than by way of his/her own lab because of the cost of maintaining such materials for distribution. In order to cover the costs of such dissemination (either performed by the investigator him/herself or through a third party) an investigator may request funds from the NIH to pay for the costs of stock maintenance and distribution.[19] Investigators may also recoup the costs of sharing the materials by charging the recipient for shipping and related expenses; however, any charges in excess of such costs must be reported as programme income by the investigator.[19]

Conclusion

The effectiveness of the NIH Model Organism Sharing Policy will depend on NIH-funded investigators' abilities to facilitate the widespread and timely dissemination of model organisms and related research resources. Current and future applicants of NIH funds must carefully consider the requirements of the new policy and understand the implications of such plan for their research and commercialisation plans. As a consequence of the new policy, some investigators may need to incorporate

new policies and practices in their institutions in order to comply with the NIH policy while still protecting the results of their research. They may need to file patent applications more promptly, may need to review and revise their material transfer agreements and other third-party arrangements, may need to consider their commercialisation plans for inventions arising from model organism research earlier than otherwise expected, and may need to request additional funding or otherwise modify their processes to ensure the timely dissemination of the materials. Additionally, the ambiguity of 'permitted' restrictions leaves for-profit institutions in the somewhat untenable position of ensuring that they comply with the sharing obligations while also protecting their commercial platform. Future guidance from the NIH will hopefully provide better clarity on these issues.

References and notes

1. URL: http://dg3.eudra.org/F2/eudralex/vol-1/CONSOL_2004/Human%20Code.pdf
2. URL: http://www.mhra.gov.uk/home/rdcplg?ldcService=SS_GET_PAGE4useSecondary=true4ssDocName=CON10043954ssTargetNodeId=373
3. *J. Comm. Biotechnol.* (2005), Vol. 11(4), pp. 381–382.
4. URL: http://www.emea.eu.int/pdfs/human/comp/3521805en.pdf
5. NOT-OD-04-042 (URL: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html); NIH Policy on the Sharing of Model Organisms for Biomedical Research, Pub. No. 04-5776 (URL: http://grants.nih.gov/grants/policy/model_organism/).
6. As used herein, extramural research refers to that research occurring outside the NIH and intramural research is that research occurring inside the NIH.
7. See FAQ #4 (URL: http://grants.nih.gov/grants/policy/model_organism/model_organisms_faqs.htm).
8. Report of the National Institutes of Health (NIH) Working Group on Research Tools, Presented to the Advisory Committee to the Director (4th June, 1998) (available at URL: http://www.nih.gov./news/researchtools/index.htm).
9. Id. As defined by the Working Group, 'research tools' are broadly constructed to include 'cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software.'
10. See NIH Policy on the Sharing of Model Organisms for Biomedical Research Pub. No. 04-5776 (available at URL: http://grants.nih.gov/grants/policy/model_organism/).
11. See NOT-OD-03-032 (URL: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html). Under the Data Sharing Policy, only investigators submitting an NIH application seeking US$500,000 or more to cover direct costs in any single year are required to include a data sharing plan or state why data sharing is not possible.
12. As defined in the policy, the term 'genetically modified organisms' are those organisms in which mutations have been induced by chemicals, irradiation, transposons or transgenesis (eg knock-outs and injection of DNA and blastocysts) or those in which spontaneous mutations have occurred.
13. See FAQ #1 (URL: http://grants.nih.gov/grants/policy/model_organism/model_organisms_faqs.htm).
14. Available at URL: http://ott.od.nih.gov/RTguide_final.html#sla
15. Available at URL: http://ott.od.nih.gov/NewPages/UBMTA.pdf
16. Bayh–Dole Act, P.L. 96-517, Patent and Trademark Act Amendments of 1980.
17. URL: http://ott.od.nih.gov/RTguide_final.html; Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources (URL: http://ott.od.nih.gov/NewPages/64FR72090.pdf).
18. See FAQ #23 (URL: http://grants.nih.gov/grants/policy/model_organism/model_organisms_faqs.htm).
19. See FAQ #22 (URL: http://grants.nih.gov/grants/policy/model_organism/model_organisms_faqs.htm).