Legal and regulatory update

ReedSmith

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This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied upon, specific advice should be sought. Please contact:

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Journal of Commercial Biotechnology (2006) **13,** 52–63. doi:10.1057/palgrave.jcb.3050030

NOTES FROM THE EU

ECJ decides against SPC for combination of active ingredient and excipient

The European Court of Justice (ECJ) has rejected an interpretation that would have meant an extension in the availability of Supplementary Protection Certificates (SPCs) throughout the European Union (EU). In Case C-431/04 *Massachusetts Institute of Technology* (unreported judgment of 4th May, 2006),[1] the Advocate-General had proposed a broad interpretation of the definition of the products for which an SPC could be obtained, arguing that a 'combination medicinal product' comprising an active ingredient and an excipient could be considered as a product attracting SPC protection.[2] The ECJ, unusually, departed from this proposal in giving its judgment.

Council Regulation 1768/92 (the 'SPC Regulation') provides for the grant of up to five years' additional patent protection for a medicinal product where that product is covered by a basic patent and a marketing authorisation in the country where the SPC is sought. The period of protection is the period between the basic patent filing date and the date of grant of the first market authorisation minus five years, subject to a maximum period of additional protection of five years.

In the SPC Regulation, a product for which an SPC may be granted is defined as the 'active ingredient or combination of active ingredients of a medicinal product'. In this case, an application was made for a product consisting of an active ingredient, carmustine, and an excipient, polifeprosan. It had been found that this excipient increased the efficacy and reduced the toxicity of the active substance by controlling the release of the (cytotoxic) active ingredient from an intra-cranial implant. The German Patent Office refused to grant an SPC on the grounds that there was not a combination of active ingredients and also refused an SPC for the active ingredient alone since this had already been known for a considerable period of time. Two questions were referred to the ECJ regarding the interpretation of the definition of product used in the SPC Regulation.

The Advocate-General had taken the view that the SPC Regulation is intended to extend the protection conferred by the basic patent. It follows that if the basic patent covers the combination of active ingredient and excipient in the first place, then this coverage must be capable of being extended by the SPC. Furthermore, the objective of the SPC Regulation to improve public health requires sufficient legal protection to be granted to innovations that allow the therapeutic efficacy of active substances to be increased. He argued that protection should also cover new applications of existing active substances, including as in this case where used in conjunction with a particularly effective excipient.

In reaching its decision, the court adopted a very literal interpretation of the SPC Regulation, finding that the excipient had no therapeutic effect of its own and therefore could form part of a combination of active substances. The court was concerned by the legal uncertainty that could be caused by the Advocate-General's proposal that one should look at the technical merit of the combination and assess whether it was sufficient to justify extension of protection in the particular case. This was an exercise that national patent offices were not equipped to undertake.

Conditional marketing authorisations

On 29th March, the EC adopted Commission Regulation No 507/2006 (the 'Regulation'). The Regulation establishes rules that allow medicinal products to be granted conditional (or so-called compassionate use) marketing authorisations. Such conditional authorisation

is valid for renewable periods of one year and subject to specific obligations.

The Regulation is a departure from the usual procedure in Directive 2001/83/EC and Regulation No 726/2004 that lay down the rules and procedures for obtaining market authorisation. Before a medicinal product for humans is authorised to be placed on the market of one or more Member States, it undergoes extensive studies to ensure that it is safe, of defined quality, and effective for use in its target population.

The Regulation allows the Committee for Medicinal Products for Human Use (the 'Committee') to authorise products for marketing where comprehensive clinical data referring to the safety and efficacy of the product required by under Directive 2001/83/EC and Regulation No 726/2004 has not been supplied. The provisions of Regulation No 726/2004 continue to apply to the conditional marketing authorisations unless expressly stated otherwise by the Regulation.

Categories of products

Article 2 specifies that only products both listed in the Annexe to Regulation No 726/2004 and falling in any one of the following categories may benefit from conditional authorisation:

- medicinal products that are aimed at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;
- medicinal products to be used in emergency situations, in response to public health threats duly recognised by either the World Health Organisation or the Community in the framework Decision No 2119/98/EC; or
- medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation No 141/2000.

Application requirements

Article 4 provides that the Committee may only grant conditional authorisation where:

- the risk–benefit balance of the product is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data required for a full marketing authorisation;
- unmet medical needs will be fulfilled;
- the benefit to public health of the immediate availability on the market of the product outweighs the risk inherent in the fact that the additional data are still required.

An applicant may request the advice of the European Agency for the Evaluation of Medicinal Products (EMEA) on whether a specific product being developed falls within the categories in Article 2 and fulfils the requirement of fulfilling unmet medical needs.

Making an application

Article 3 sets out that a request for conditional marketing authorisation must be accompanied by details showing that the product satisfies the requirements contained in Article 2 and 4(1) of the Regulation. A request for conditional marketing authorisation may be presented by the applicant together with a full application under Article 6 of Regulation No 726/2004.

Where an application for authorisation is received under Article 6 of Regulation No 726/2004, the Committee may on its own initiative propose a conditional marketing authorisation after consultation with the applicant.

Specific obligations

The holder of a conditional marketing authorisation is subject to the specific obligations set out in Article 5. The holder is required to complete ongoing studies, or conduct new studies to confirm that the risk–benefit balance of the product is positive and to provide the additional information required by Article 4. The authorisation will clearly specify the time period for the completion of the specific obligations.

Article 9 imposes an obligation on the applicant to provide the EMEA and Member States with periodic safety reports provided for under Article 24(3) of Regulation 726/2004 at least every six months or immediately upon request.

Validity and renewal

The conditional marketing authorisation may be renewed annually. An application for renewal must be submitted at least six months before the authorisation expires together with an interim report on the fulfilment of the specific obligations to which it is subject. The Committee will assess the application on the basis that the risk–benefit balance is to be confirmed, taking into account the specific obligations contained in the authorisation and their time-frame for completion.

Where the specific obligations have been fulfilled, the Committee may at any time adopt an opinion in favour of granting a market authorisation under Article 14(1) of Regulation No 726/2004.

Conditions on marketing

A product marketed under a conditional authorisation must, in accordance with Article 8, include in the summary of the product's characteristics and packaging leaflet a clear mention that the product is only conditionally authorised and the date for renewal of that authorisation.

Proposal for EU paediatric medicines regime making good progress

The proposed EU Regulation on medicinal products for paediatric use cleared another hurdle on the route to adoption on 1st June, 2006 with completion of the proposal's second reading by the European Parliament. The text approved by the European Parliament was the result of negotiations with representatives of the European Commission and the Council of Ministers and contains few amendments over the text of the Common Position of the Council in March, 2006. In view of the agreement reached between the institutions at this stage, it is likely that the final stage in the legislative process – approval by the Council – will be a formality with the result that the Regulation may even become law before the end of 2006. The principal provisions are summarised below.

It will be recalled that the proposed Regulation is intended to address problems caused by difficulties in recruiting children for the clinical trials process in turn caused by a lack of a legal framework, which have left pharmaceutical companies reluctant to invest developing medicines designed for the paediatric population. This has forced doctors to prescribe medicines to children 'off label' and it is estimated that more than half of the medicines used to treat children have not been tested for safety and efficacy in paediatric populations.

The regime will be superimposed on the existing procedures established by Directive 2001/83 and Regulation (EC) No 726/2004 and will apply to all medicinal products required by children whether currently authorised in the EU or not. However, the proposed Regulation will treat products differently depending on which of the following categories the product falls into:

- product still in development;
- product authorised and still covered by patent/SPC; and
- product authorised and no longer covered by patent/SPC.

Products in development

The proposal requires that any application for a marketing authorisation for a medicinal product not authorised in the EU at the date of entry into force of the Regulation must now include the results of all studies undertaken, and information collected, in compliance with a Paediatric Investigation Plan (PIP). A PIP is a defined research and development programme to be conducted in children, which will ensure that the necessary data are produced to determine the conditions in which the medicinal product may be authorised to treat the paediatric population.

The draft Regulation sets out that a PIP is not required where the marketing authorisation is sought for:

- generics and biosimilar medicinal products;
- medicinal products using the well-established use procedure;
- homeopathic and traditional herbal medicinal products; and

- a medicinal product for which the applicant has otherwise obtained a waiver from the European Medicines Agency (EMEA).

Article 12 provides the EMEA may grant a wavier where:

- evidence shows that the specific medicine or class of medicines is likely to be unsafe or ineffective in part or all of the paediatric population;
- the disease or condition for which the medicinal product or class is intended occurs only in adults; or
- the specific medicinal product does not represent a significant therapeutic benefit over existing treatments available for paediatric patients.

The EMEA will publish a list of products and classes of products that benefit from a waiver.

It is also proposed that an applicant may temporarily defer all or some of the measures set out in the PIP. A deferral must, however, be justified on scientific and technical grounds or be related to public health.

By way of reward for undertaking the PIP, the SPC holder or patent holder who qualifies for the granting of an SPC will be entitled to a six-month extension of the SPC period of protection where tests are conducted in accordance with a PIP. This applies whether or not the tests lead to authorisation for the paediatric population.

Importantly, however, the extension will only be available if the medicine is authorised in all 25 Member States of the EU. This had proved controversial during previous discussions at the Parliament, but has now been accepted in principle. Arguments that the extension should only be limited to those states where the product is authorised were rejected. Compromise was reached between the Commission and the Parliament on the question of how far in advance of SPC expiry the six-month extension should be sought. It was agreed that for five years from commencement of the regime, the period would be six months and thereafter it would be two years.

The six-month SPC extension will not, however, be available to an applicant who obtains an additional year of market protection for the medicinal product concerned for a new therapeutic indication of significant benefit pursuant to the existing data protection rules. In addition, orphan drugs will not benefit from any SPC extension. Instead, the market exclusivity period granted by Regulation (EC) No 141/2000 will be extended to 12 years in respect of orphan drugs.

Products already authorised and still covered by patent/SPC

Results and data arising from a PIP are proposed to be required in support of applications for a line extension to an existing marketing authorisation such as an application for a new indication, pharmaceutical form or new route of administration. However, the same rules regarding waiver and deferral would apply to these products as to products still in development.

In the event that the extension to the marketing authorisation is granted, then the rewards described above with respect to products still in development would apply subject to the requirement that where a previously marketed product is then authorised for a paediatric indication the marketing authorisation holder must, within two years of the date the paediatric indication is authorised, place the product on the market taking into account the paediatric indication. Furthermore, the authorisation holder must transfer the marketing authorisation to a third party or let a third party use the marketing authorisation if the holder removes the authorised product from the market after benefiting from an extension to the period of protection.

Product authorised and no longer covered by patent/SPC

For off-patent medicines, medicines which have no patent protection or for which the patent has expired, the Regulation will provide for a new type of marketing authorisation, the Paediatric Use of Marketing Authorisation ('PUMA'). A PUMA is specifically for medicinal products developed exclusively for use in children. An application for a PUMA is made using the existing

authorisation procedures and requires data collected in accordance with a PIP.

An application for a PUMA may refer to data (in accordance with the usual rules) contained in the dossier of a medicinal product which is or has been authorised in the Community. The paediatric data submitted will benefit from a full period regulatory data protection applying the 8 + 2 + 1 formula.

European Commission issues guidance on data exclusivity for over-the-counter switches

Article 74a of Directive 2001/83 as amended provides that,

> 'Where a change of classification [from prescription only to over-the-counter (OTC)] of a medicinal product has been authorised on the basis of significant preclinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.'

The European Commission has now issued guidance on how this provision operates in practice.[3]

The Commission has given examples of where preclinical test and/or clinical trials are to be considered significant, namely:

- new strength or posology (particularly to confirm that efficacy remains);
- new route of administration;
- new pharmaceutical form; and
- new indication (particularly one not previously authorised for an OTC medicinal product or for certain sub-populations).

In addition, new data are likely to be eligible for protection where these confirm the safety/efficacy profile of a product either within the prescription setting or in the proposed non-prescription setting. Finally, the guideline emphasises that the data must be relevant and necessary to the change in classification.

The guideline notes that the exclusivity period is a standalone period of protection covering only the data that substantiates the change in classification. It follows that the data exclusivity may be granted independently, and after the expiry of, the eight-year data and two-year market exclusivity granted following an original marketing authorisation in respect of the medicinal product in question.

In terms of procedure, it should be noted that it is for the applicant filing the data obtained from significant preclinical tests or clinical trials to claim the additional period of data exclusivity and this claim must be supported by a report justifying this. The competent authority to which the application has been made must then include a clear statement as to whether the change in classification has taken place based on significant preclinical tests or clinical trials.

MHRA issues final report on TGN1412 serious adverse events

The Medicines and Healthcare Products Regulatory Agency (the 'MHRA') has released its final report[4] following investigations into the serious adverse events that occurred during the Phase I study of the monoclonal antibody, TGN1412 at Northwick Park Hospital in March, 2006. The objective of the MHRA investigation was to determine whether an error in the conduct of the trial had caused the serious adverse events that subsequently occurred.

The trial

TGN1412, a CD28-agonist, is a member of a novel class of monoclonal antibody that has a stimulatory action affecting regulatory T cells in the immune system. TeGenero proposed that TGN1412 could be useful in treating both autoimmune conditions such as rheumatoid arthritis, and diseases characterised by a weak immune response such as cancer.

On 13th March Parexel Pharmacology Research Unit ('Parexel'), a research organisation contracted by TeGenero, the sponsor of the study, commenced a Phase I trial of TGN1412. The trial was designed to administer escalating doses of the TGN1412 antibody to six healthy male volunteers and a

placebo to two others. The trial was terminated immediately when the six participants who received the active TGN1412 were left in intensive care after suffering a severe immune reaction. Parexel reported that the participants experienced 'life-threatening Cytokine Release Syndrome.'

Investigation

Premises at TeGenero, Parexel, Boehringer Ingelheim, the drug's manufacturer and the Northwick Park Hospital in Harrow were inspected for compliance with the principles of Good Clinical Practice and Good Manufacturing Practice. Tests were undertaken to establish whether the products used met their batch release specification. The toxicology study that was instrumental in supporting the progression of TGN1412 into human trials was also audited.

Findings

The MHRA found that all the preclinical trial work performed by TeGenero prior to the first human study complied with the appropriate standards. The toxicology report, based on a four-week intravenous toxicity study in cynomolgus monkeys with a six-week observation period, had been conducted in accordance with the principles of Good Laboratory Practice.

No irregularities were found in Parexel's facilities, equipment, quality systems, or documentation and records associated with the storage, preparation, and release of the TGN1412. However, the MHRA uncovered a number of discrepancies in the actions taken by the Parexel:

- There was no formal system in place to provide 24 h medical cover.
- The volunteers given the placebo were permitted to leave the trial before appropriate checks were undertaken to confirm they had in fact taken the placebo.
- Parexel failed to complete a full written medical background of a participant in writing.
- MHRA inspectors were not satisfied that the screening physician had adequate training and experience for their role.
- The Principal Investigator failed to authorise, in their log, the full work remit for the bank screening physician at the start of their employment.
- Parexel failed in their duty to review TeGenero's insurance policy to ensure one was in place and that there were no exclusion categories within it that might impact upon the participants in this study. No such exclusions did in fact exist.

Conclusions

The MHRA concluded that the most likely cause of the severe reactions is an 'unpredicted biological action of the drug in humans' and that 'the resulting activity seen in humans was not predicted from the apparently adequate preclinical testing'.

The report highlights that this is a complex scientific issue that raises important scientific and medical questions about the potential risks associated with this type of drug and how to make the transition from preclinical testing to trials in humans.

It should be noted that the report focused on the execution of the trial rather than its design. The Department of Health has now set up an independent working group lead by Professor Gordon Duff to consider how to make the transition from preclinical trials to testing in humans; particular consideration will be given to drugs that have immune system targets and those with novel mechanisms.

Relaxation of guidelines on pre-emption hoped to ease fundraising

On 15th May, 2006, the Pre-Emption Group[5] published a Statement of Principles giving new guidelines on the disapplication of pre-emption rights on the new issue of equity securities. The Statement of Principles replaces the Pre-Emption Guidelines that have been in place since 1987. The change has been widely welcomed by the UK biotech industry as the new guidelines should give more certainty and make it easier for emerging companies to raise additional finance through the new issue of equity securities. This note takes a brief look at the law on pre-emption rights and

summarises the main changes introduced by the new guidelines.

Background to pre-emption rights

Pre-emption rights give protection to existing shareholders against dilution of their investment by requiring companies that want to issue any new equity securities for cash consideration to first offer such new securities to existing shareholders pro-rata to their existing holding. The pre-emption rights and the offer process are enshrined in the Companies Act 1985[6] and for listed companies also within the UK Listing Authority Rules.[7] The Companies Act in particular sets out detailed procedures with which a pre-emption offer must comply, including the form the offer should take and the length of time during which it may be accepted (21 clear days from the date the offer is made). Only when this date has expired or when the company has received a reply from every shareholder accepting or refusing the offer may the company then allot the security freely to a new investor.

It is possible to disapply the operation of these statutory pre-emption rights, and this must be done by passing a special resolution at a general meeting of the company's shareholders.[8] Most listed companies disapply pre-emption rights on an annual basis at the same time as they take their authority to allot shares. It is this ability to disapply pre-emption rights that is the subject of guidelines from the Pre-Emption Group.

The statement of principles

The original guidelines (referred to as the Pre-Emption Guidelines) were published in 1987. Broadly, these guidelines contained a threshold limitation that only permitted a maximum annual disapplication of statutory pre-emption rights of 5 per cent of the issued ordinary share capital, with a cumulative limit of 7.5 per cent over a three-year period (the 'Threshold Limit'). A common complaint from companies seeking to raise quick finance was that institutions applied the Threshold Limit too rigidly, with requests beyond the Threshold Limit automatically being viewed as negative. Companies within the biotech industry often need to raise finance quickly and cheaply for a specific project in hand or with a specific investment partner. However, too often, shareholders would simply reject requests that were above the Threshold Limit without giving due consideration to the merits or reasons for the request.

On 10th February, 2005, the Department of Trade and Industry published a report by Paul Myners on the application on pre-emption rights. The report acknowledged that the Pre-Emption Guidelines were being viewed too rigidly by shareholders. It recommended that the Pre-Emption Guidelines be replaced with new guidance that allowed more flexibility for companies. These recommendations have been adopted in the Statement of Principles that replaces the Pre-Emption Guidelines.

The Statement of Principles still retains the same Threshold Limit for disapplication requests, despite some strong lobbying from some quarters to increase this limit. However, for requests by companies to disapply pre-emption rights beyond the Threshold Limit (non-routine requests), the Statement of Principles states that such requests must be looked at on a case by case basis to give the company more flexibility and urges substantive dialogue and discussion between the company and its shareholders. Requests within the Threshold Limit are seen as routine requests that should not be controversial. The Statement of Principles provides helpful guidance to companies making a request to shareholders for the disapplication of pre-emption rights and also to shareholders in considering such requests, including the following:

- companies should be open and transparent and seek to communicate their intention to make a non-pre-emptive issue at the earliest opportunity and establish dialogue with shareholders. Companies are encouraged not to leave non-routine requests to the company's general meeting;
- shareholders should review the case made by the company on its merits and decide on each case individually, giving careful thought to the reasons for refusal if a request is not acceptable;

- it also sets out a list of general considerations that are likely to be relevant to the shareholders review of the request, including looking at: (i) the strength of the business case (shareholders should be given a clear explanation of the purpose to which the capital raised will be put and the benefits to be gained); (ii) the size of company (shareholders might be expected to be more sympathetic to a request from a small company with high growth potential than one from a larger more established company); (iii) other financing options and why they have been rejected by the company.

The Statement of Principles applies to companies listed on the Main Market of the London Stock Exchange, but companies quoted on AIM are encouraged to also apply these guidelines, although it is acknowledged greater flexibility is likely to be justified for such companies.

The new position as set out in the Statement of Principles is expected to be welcomed with open arms by the biotech industry. Equity funding can be a quick and cheap method of raising finance and is the option that emerging biotech companies frequently turn to when raising additional funds for developing new drugs. The changes are an important step forward in redressing the imbalance between Britain and the United States, where US biotech companies are typically thought to have had a much freer rein when raising cash through the issue of new equity securities.

NOTES FROM THE US

Omnitrope® finally approved in the US

Following from the decision (reported in the previous issue[9]) of a federal court ordering the Food and Drug administration (FDA) to act on Sandoz's July, 2003 new drug application (NDA) in respect of Omnitrope® somatropin human growth hormone, the FDA has accepted this application, making this the first follow-on version of a recombinant protein to be approved by FDA.

Sandoz was found to have demonstrated preclinical and clinical comparability of Omnitrope® to Genotropin® from Pfizer, but Omnitrope® will not be labelled as therapeutically equivalent to Genotropin®. Sandoz had conducted Phase III studies for the long-term treatment of paediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone and Phase I studies to demonstrate safety in adults; the FDA concluded that indication-specific studies were not needed to support use of the drug in long-term replacement therapy in adults with growth hormone deficiency.

The FDA approved Omnitrope® under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the so-called 'paper NDA'), but stated that the approval does not create a pathway for follow-on versions of products that are marketed under Biologies Licensing Applications (BLAs), which are considered under separate legislation. Pfizer, Genentech and the US Biotechnology Industry Organization had petitioned the FDA challenging its competence to approve a follow-on biologic. This action was rejected at the same time as the decision approving Sandoz's application.

US Supreme Court declines to hear authorised generics dispute

The US Supreme Court dealt a blow to the US competition law authorities on 26th June by refusing to review a pharma settlement agreement that the authorities considered to be anti-competitive.

The settlement was a 'reverse payment' settlement between Schering-Plough (the drug patent holder) and two generics, Upsher-Smith and ESI under which Schering-Plough made large cash payments to the generics and delayed their market entry. These payments are controversial as competition authorities consider that they are illegal agreements entered into by innovative pharma companies to keep competitors out of the market while champions of intellectual property rights consider that the settlements constitute legitimate action by a patent holder to protect its patent rights.

The Supreme Court decision not to review the Schering-Plough case is therefore significant as it means that innovative and generics pharma companies are likely to continue to enter into these kinds of settlement agreements in the absence of a finding that they are anti-competitive.

Background

These pharma settlements have arisen in the context of the US Hatch–Waxman Act which was introduced in the US in the 1980s in order to make it easier for generics to enter the market on expiry of an innovative pharma patent. Generics could essentially obtain approval to sell the generic drug if they could show that it was the bio-equivalent of the innovative pharma product and did not infringe the patents relating to the original drug.

However, if the innovative pharma brings a patent infringement action against the generics company, approval of the generics is suspended for 30 months and no other generic can enter the market (for a more detailed explanation of the Hatch–Waxman Act you should refer to our earlier article '*Possible US Supreme Court Ruling on Pharma Settlement Agreement*'[2]).

The patent settlements which have increasingly resulted from these disputes have involved very substantial cash payments by the innovative pharma to the generics with agreement that the generics would delay entry to the market. These have attracted the attention of competition law authorities (such as the Federal Trade Commission in the US (FTC)) that consider that the innovative pharma companies are paying generics not to enter the market for a period of time which, in accordance with competition law rules, is illegal.

Why the controversy?

These settlements raise important issues in the conflict between patent rights and competition law. On the one hand, competition law seeks to protect the interests of the consumer and regulate the competitive environment so that consumers get the best possible deal. In the context of drugs, it is arguably best for the consumer if there is generic competition at the earliest opportunity as prices drop considerably on entry of generics to the relevant market.

On the other hand, there exist the conflicting rights of patent holders to exclude competition within the scope of their patents as well as the general public policy which favours and seeks to encourage settlements rather than litigation.

Adding some 'heat' to this debate is the not insignificant political interest in this argument. In the US, the cost of healthcare is high with consumers unlikely to be interested in complex legal arguments, which prevent a reduction in drug prices at the earliest opportunity. This is reflected no doubt in the considerable concern expressed by a number of US politicians about the acceptability of these settlement agreements following the U. S. Supreme Court's refusal to review the Schering–Plough case.

Conclusion

All of this raises the question as to what will happen next in relation to pharma settlement agreements. It is likely that pharma and generics companies will continue to enter into these kinds of settlements, particularly given that the US Court of Appeals for the Eleventh Circuit approved the settlement in the Schering–Plough case.

It would also seem likely that the FTC will seek further opportunities to investigate and challenge these patent settlement agreements, particularly if their number increases going forwards. Therefore, although innovative and generic drug companies are likely to have welcomed the US Supreme Court refusal, in entering into further settlement agreements they should proceed with some caution bearing in mind that these agreements may be subject to further scrutiny by the FTC.

FDA issues compliance policy guide for biologics manufacturing inspections

FDA recently issued a revised Compliance Policy Guide (CPG) for the Inspection of Biological Drug Products (CPG 7345.848, posted on 10th March, 2006).[10] This CPG combines and replaces the compliance programmes for licensed allergenics

(7345.001), licensed vaccines (7345.002), plasma derivatives (7342.006) and therapeutic drugs (7341.001). It provides inspectional guidance to investigators assigned to inspect manufacturers of biological drug products, as well as administrative/regulatory guidance for FDA compliance officers and investigators.

Firms affected by this CPG include: licensed manufacturers of vaccines, including source material manufacturers and licensed bulk manufacturers; licensed manufacturers of allergenic products (but not allergenic patch test manufacturers); unlicensed source material suppliers; licensed manufacturers of fractionated products, certain recombinant products, and certain human cell, tissue, and cellular and tissue-based products (HCT/Ps) regulated as drugs, and/or biological products.

This revised CPG incorporates a systems-based, risk management approach to conducting inspections, and identifies six key systems and three critical elements within each system for inspection.

The six key systems are:

1. Quality System
2. Facilities and Equipment System
3. Materials System
4. Production System
5. Packaging and Labelling System
6. Laboratory Control System.

The three critical elements are:

1. standard operating procedures (SOPs)
2. training
3. records

Inspections of biologics manufacturers generally take one of two forms:

1. Level I Inspections: an in-depth audit of the three critical elements in each of the six systems, and provides a comprehensive evaluation of the establishment's compliance with cGMP.
2. Level II Inspections: a streamlined evaluation of an establishment's compliance with cGMP, covering all three critical elements in two mandatory systems (Quality System and Production System), plus at least one additional system on a rotating basis during successive biennial inspections.

Inspections are conducted using a team approach, with a Team Biologics Core Team investigator leading, and Center for Biologics Evaluation and Research product specialists participating. FDA will pay special attention to manufacturing arrangements to ensure that the conditions of an approved BLA are being met. The CPG describes a few of the manufacturing arrangements commonly utilised in the industry, and FDA's inspectional approach to each.

Shared manufacturing

In a shared manufacturing arrangement, each manufacturer is licensed to perform part of the manufacturing of a product. The manufacturer who prepares the product in its final form will be held responsible for any post-approval obligations, such as reporting biological product deviations and adverse events, unless (1) the manufacturers agree and (2) the approved application says otherwise. Investigators will review the agreements to determine if the conditions of the applications are being met.

Divided manufacturing

In a divided manufacturing arrangement, each manufacturer is licensed to manufacture the same product in its entirety, but each performs only part of the process. This arrangement is described in supplements submitted to each manufacturer's licence. The record requirements for divided manufacturing arrangements are described in 21 CFR 600.12(e). Each manufacturer must have documentation of its responsibility for manufacturing the product. FDA will pay particular attention to the conditions under which intermediate product is shipped between the facilities.

Contract manufacturing

A licence holder is responsible for compliance with product and establishment standards, but may contract out part or all of the manufacturing to another facility. Although both the manufacturer and contractor share responsibility for product quality; the

manufacturer remains ultimately responsible; the contractor is responsible for complying with applicable cGMP.

The FDA inspector will review and determine:

- extent of services provided;
- each party's responsibility for the product or operations performed;
- who prepared the SOPs used by the contractor, and
- who performed product quality control tests.

If inspecting the contract manufacturer, FDA will verify that the licence holder is notified of any manufacturing deviations and any manufacturing changes for its licensed product(s).

Component manufacturers

Manufacturers who purchase components from outside sources are required to establish adequate specifications for such components. The FDA inspector will verify that: (1) the firm has written, approved specifications for the component(s); (2) the firm evaluates and selects suppliers based on their ability to meet specified requirements, and (3) the type and extent of control needed over the component and suppliers has been defined and is based on the manufacturer's evaluation of the supplier. FDA will pay particular attention to animal source material, which must meet the applicable requirements of 21 CFR 600.11, and determine if tests and specifications for animal materials that may potentially be contaminated with adventitious agents (eg, mycoplasma, Bovine Spongiform Encephalopathy, and others) are performed as described in the BLA. For example, FDA will verify that the manufacturer has defined methods, for example, inspections, tests, and other verification tools (certificates of analysis and/or supplier audits), to ensure that components conform to all specifications prior to release and are documented in the batch record.

State of control

FDA inspectors will look to determine whether a biologics manufacturer is operating in a 'state-of-control'. A firm is considered to be operating in a state-of-control when it employs conditions and practices that ensure compliance with applicable cGMP regulations. A firm is considered to be in a state of control if there is an adequate level of assurance of the product's quality, strength, identity, purity, and potency. A firm with serious or repeated cGMP deficiencies, or firm's that exhibit a continuing pattern of non-compliance, fail to correct significant deficiencies, or have any deficiency that poses a serious threat to the public health may be considered not in a state-of-control and subject to enforcement action.

The CPG offers a useful tool for biologics manufacturers to understand FDA's approach to manufacturing compliance and how and when it will decide to initiate enforcement actions. It also provides an important reminder of the serious nature of these requirements. Manufacturers should review the CPG carefully, and consider their own operations in light of the expectations that FDA has set out.

References

1. Available from http://www.curia.eu.int.
2. ReedSmith (2006). US and EU legal and regulatory update. *J.Comm. Biotech.* **12**(4), 242–252.
3. See 'A Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use, (available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-**2**/c/switchguide_160106.pdf).
4. The MHRA Report can be found at http://www.mhra.gov.uk/home.
5. The Pre-Emption Group represents listed companies, investors and intermediaries and advises the Department of Trade and Industry.
6. Sections 89–96.
7. LR 9.3.11–LR 9.3.12.
8. It is possible for a private company to permanently disapply statutory pre-emption rights by including such disapplication in its memorandum and articles of association. Such a disapplication is unlikely to be acceptable to an investor without some other assurances to protect against the dilution risk.
9. ReedSmith (2006). US and EU legal and regulatory update. *J. Comm. Biotechnol.* **12**(3), 299–311.
10. The CPG can be found on FDA's webpage at: http://www.fda.gov/cber/cpg/7345848.htm#I.