Legal and regulatory update

KIRIN-AMGEN INC. *v* TRANSKARYOTIC THERAPIES INC.

The year 2004 saw the end game of what was probably the largest and most significant patent infringement case in the English Courts of the past 10 years. Bird & Bird acted for TKT throughout. Kirin-Amgen and Transkaryotic Therapies Inc. (TKT) crossed swords for the final time in the House of Lords during an eight day appeal hearing in July 2004. The case is significant for the number of patent law issues at stake: novelty of product-by-process claims, three types of pleaded insufficiency, and most importantly the issues of purposive construction and infringement under the Protocol to Article 69 of the European Patent Convention. This section focuses mainly on the first and last of these issues. Indeed, the TKT case is actually the first case dealing with 'protocol infringement' to reach the House of Lords under the 1977 Patents Act. The appellate committee comprised Lords Hoffmann, Hope, Rodger, Walker and Brown.

The case concerned the 1983 Kirin-Amgen patent relating to recombinant erythropoietin (EPO). EPO in its natural state is a hormone produced in tiny quantities in kidney cells of healthy individuals. The hormone stimulates the bone marrow to produce red blood cells, for example in low oxygen conditions such as where the individual is at altitude. The natural product can be isolated from urine. Recombinant EPO is useful for treating various kinds of anaemia.

The Kirin-Amgen patent described the work in collecting vast quantities of human urine, isolating and purifying the natural EPO protein, obtaining its amino acid sequence, fishing out the EPO gene from a human genomic library and finally cloning the gene into a cell for commercial production of EPO. The key battleground of the case centred on Table VI of the patent which set out the full DNA sequence of the EPO gene.

The TKT technology, known as 'gene activation' and developed in the mid- to late 1990s, was not foreshadowed in the Kirin Amgen patent – simply because it was a more advanced technology in a rapidly developing field. TKT recognised that practically every cell in the human body contains the full complement of genes even though not all of those genes may be active in any particular cell. For example, the EPO gene exists in all human cells but it is switched off in all of those cells except for some cells in the kidney where EPO is produced. TKT identified the precise location of the native EPO gene in a human cell that did not make EPO and by means of a process known as homologous recombination, inserted far upstream of the gene a promoter, essentially a genetic on-switch. When the cells were cultivated, they were found to produce EPO.

The key claims of the patent were claim 26, which can be paraphrased as 'A product of the expression in a host cell of a DNA sequence according to claim 1', and Claim 1: 'A DNA sequence for use in securing expression in a eukaryotic host cell of EPO. . .where the DNA sequence was that of Table VI or related thereto'.

Infringement

Kirin-Amgen's case was that the EPO gene in the TKT cells was a DNA sequence of claim 1 and accordingly the TKT EPO product (so-called 'gene-activated' EPO or GA-EPO) was therefore a product within claim 26. TKT's case was that the wording of the claims, particularly the words 'host cell', required that the EPO gene actually be introduced into that cell – ie that it be exogenous to that cell. The Kirin-Amgen cloned EPO gene was indeed exogenous

to the production host cells. Conversely, the TKT EPO gene was endogenous – the gene had always been in that cell, albeit in an inactive form. By merely introducing the promoter 'on-switch', TKT had not made that cell into a host to the EPO gene and therefore the gene could not fall within the claim.

Kirin-Amgen placed great stock in the argument that as TKT had begun its research programme to locate the native EPO gene by relying on the sequence information first published in the Kirin-Amgen patent, it had hijacked the patent's 'contribution', its inventive concept. Consequently, even though TKT might not have fallen within the precise wording of the claims, it would be unfair to the patentee for TKT to be held not to infringe.

This argument found favour at trial before Neuberger J (as he then was). Despite his finding that the relevant claims ought to be construed so that 'host cell' implied use of the exogenous gene (as was TKT's case), the Judge nevertheless held that TKT had appropriated Kirin-Amgen's 'contribution'. But for its utilisation of the Table VI information, the judge said, TKT could not have developed its own process. The Judge also applied the three 'protocol questions' and found TKT to have used an obviously immaterial variant of the patented technique. This was on the basis that the patent 'was getting at the production of EPO' and both processes resulted in production of EPO. Therefore the Judge concluded that TKT infringed.

In the Court of Appeal, the Judges reversed this finding of infringement. They agreed with the trial Judge's construction of the claims (re: the exogenous DNA point). In considering the Protocol questions, they then decided that at the level of generality of the claims, TKT's process was in fact a material variant. Endogenous DNA simply could not be an immaterial variant to exogenous DNA. By generalising the claims to the mere production of EPO, the Trial Judge had over-generalised.

Interestingly the House of Lords agreed with the construction placed by both the Trial Judge and the Court of Appeal on the claim. Indeed, Lord Hoffmann observed that although the Trial Judge had described his exercise as one of 'literal construction', he had, by construing the claim in context, actually conducted a purposive construction of the claim. The Catnic principle, according to Lord Hoffmann, required a consideration of what the person skilled in the art would have understood the patentee to be claiming. The Trial Judge had in fact done precisely this.

Furthermore, Lord Hoffman indicated that this Catnic principle was precisely in accordance with the Protocol to Article 69. The principle was 'a bedrock of patent construction, universally applicable'. This was to be distinguished from the protocol questions which Lord Hoffmann said were 'only guidelines, more useful in some cases than in others'. The key passage of Lord Hoffmann's speech states:

> The determination of the extent of protection conferred by a European Patent is an examination in which there is only one compulsory question, namely that set by Article 69 and its Protocol: what would a person skilled in the art have understood the patentee to have used the language of the claim to mean? Everything else, including the Protocol questions, is only guidance to a judge trying to answer that question. But there is no point in going through the motions of answering the Protocol questions when you cannot sensibly do so until you have construed the claim. In such a case – and the present is in my opinion such a case – they simply provide a formal justification for a conclusion which has already been reached on other grounds.

Lord Hoffmann noted that there were likely to be patent lawyers who would 'feel cast away on a sea of interpretative uncertainty', 'dismayed at the notion that the Protocol questions did not provide an

answer in every case'. However, this was, he said, 'the fate of all who have to understand what people mean by using language'.

Novelty of product-by-process claims

The product-by-process issue will be one familiar to practitioners before the European Patent Office (EPO), where the principle from the *IFF/Claim Categories* case is well established. The principle, however, may appear counter-intuitive to those who litigate solely in the English courts. For a product-by-process claim (ie product X made by process Y) such as claim 26 of the Kirin-Amgen patent to be valid, the product per se must be novel and inventive. Product-by-process claims are allowed as a matter of practice by the EPO only where there is no way precisely to describe the characteristics of the product save by the process by which it is made. Once the patentee has been permitted to claim in this fashion, the EPO rule of law from IFF/Claim Categories is that the claim is purely a product claim – the process element is *not* a claim limitation and cannot be relied upon to give novelty to the product.

Consequently, despite the claim stating 'product X obtained from process Y', under EPO law (and this is the counter-intuitive part), this claim is to product X however it is made. If, then, product X is indistinguishable from a prior art product, then the product-by-process claim will be bad for lack of novelty.

In Kirin-Amgen's case, it was demonstrated by experiment that the product of claim 26 was indistinguishable from prior art EPO isolated from urine samples.

This EPO principle is one that is also applied by the major European jurisdictions. TKT pressed the English courts to apply the same principle, thereby ensuring harmonisation with Europe (all European Patent Convention members are, after all, supposed to be applying the same law). However, neither the Trial Judge nor the Court of Appeal saw fit to follow the EPO principle, merely noting that they were not bound by decisions of the Office.

The House of Lords overturned the Court of Appeal, noting that it was important that the UK should apply the same law as the EPO and other member states when deciding what counts as new for the purposes of the EPC. Lord Hoffmann observed that it 'would be most unfortunate if [the UK courts] were to uphold the validity of a patent which would on identical facts have been revoked in opposition proceedings before the EPO.'

Insufficiency

Of the insufficiency arguments, the most significant concerned the test described in claim 19. The claim referred to products having 'higher molecular weight by SDS-PAGE [sodium dodecyl sulphate polyacrylamide gel electrophoresis] from erythropoietin isolated from urinary sources.' This was essentially the test for infringement of claim 19. If a worker's recombinant EPO had a higher molecular weight by this test, it would infringe the claim; if it did not have a higher molecular weight, it would not infringe. The difficulty stemmed from the 'urinary sources' comparator. The Trial Judge heard days of evidence on experiments to determine the molecular weight of various kinds of uEPO. He concluded from this evidence that there were considerable variations in molecular weight between different batches of uEPO. It was also clear that many recombinant EPOs did not themselves satisfy the test. Accordingly, the Trial Judge found that the skilled person trying to find out whether their product fell within claim 19, would be put in an impossible position. The Judge therefore held that this lack of clarity not only made the claim impossible to infringe but also rendered it insufficient.

The Court of Appeal disagreed. They said that it was merely lack of clarity that was 'dressed up to look like insufficiency'. Lack of clarity was not a ground for

revoking patent under section 72. It was sufficient that some uEPO could be tested aginst rEPO by SDS-PAGE. SDS-PAGE was a standard well-known procedure. It could readily be performed on a given uEPO without undue effort. They continued saying 'we can see no reason to stretch 72(1)(c) to seek to cover issues of lack of clarity of claiming as patentees will not be able to establish infringement of unclear claims.'

The House of Lords overturned the Court of Appeal on this point. Lord Hoffmann disagreed that such an unworkable test merely produced lack of clarity; it was, he said, clearly an issue of insufficiency. He continued

> the lack of clarity does not merely create a fuzzy boundary between that which will work and that which will not. It makes it impossible to work the invention at all until one has found out what ingredient is needed. . .All the skilled man can do is try to guess which uEPO the patentee had in mind and if the specification does not tell him, then it is insufficient.

Conclusion

Lord Hoffmann may be correct in his assessment that many patent lawyers will be dismayed at the perceived uncertainty in applying his 'Catnic principle'. The Protocol questions are generally considered to be useful canons of construction in patent law; just as the fields of contractual and statutory interpretation have their own guidelines, which assist the Courts and the reader. The difficulties identified by Lord Hoffmann were that litigants tended to treat the Protocol questions as legal rules rather than guides and also that the questions had limitations and tended to break down when applied to higher technology.

The 'Catnic principle' does have the attraction of simplicity. It boils down to a single question – what would the person skilled in the art have understood the patentee to be using the language of the claim to mean? It also has the attraction of making it entirely clear that the question of infringement is to be decided from an analysis of the claims, albeit in the context of the rest of the patent document rather than involving an extension of protection outside the claims as seen in the US doctrine of equivalents.

It remains to be seen whether workers and their legal advisers are placed in a position of greater or lesser certainty as to whether or not they are infringing a patent by the step back to a single-question Catnic principle from the three Protocol questions. Lord Hoffmann did state that he envisaged the continued application of the Protocol questions as a guide to applying the Catnic principle. It is far from clear, however, whether the two 'tests' can co-exist except in cases involving the most straightforward mechanical patents – the original *Catnic* case, for example. It is also arguable that the Catnic principle is merely a reworking of Protocol question 3. What is certain, however, is that an infringement analysis must proceed by way of a construction of the claims rather than assessing nebulous concepts such as appropriation of the patentee's contribution to the art or use of information contained in a patent.

CELLTECH R&D LTD *v* MEDIMMUNE INC [2004] EWCA Civ 1331

This case was an appeal from a decision by Laddie J in the Chancery Division (Patents Court). Bird & Bird acted for Celltech. The facts are that Celltech and Medimmune had entered into a licence agreement under which Medimmune was to pay royalties for products sold or manufactured that would, but for the licence granted, infringe Celltech's 'Adair' patents. Celltech alleged that Medimmune's product 'Synagis' manufactured and sold in the USA infringed Celltech's American 'Adair 2' patent and that consequently Medimmune was liable to pay royalties under the licence agreement.

The terms of the agreement provided

that questions of liability would be dealt with by the English courts. However, Medimmune commenced proceedings in America for declarations that the American Adair 2 patent was invalid and that Synagis did not infringe it. Celltech applied to the American court to decline jurisdiction over the claim for a declaration of non-infringement, and brought proceedings against Medimmune in England. Then, Medimmune applied for a stay of the English proceedings.

In the proceedings in the English court Laddie J found for Celltech in that he held that the licence agreement conferred jurisdiction on the English courts, and he declined to stay the English proceedings pending the outcome of the action in the American courts. Medimmune appealed to the Court of Appeal to overturn the refusal to stay the proceedings.

The Court of Appeal in its judgment (given by Jacob LJ and with Potter and Buxton LLJ agreeing) deduced that there were two questions to be determined. First, does the agreement confer jurisdiction on the English courts to decide whether Synagis is covered by the claims of the American Adair 2 patent? Secondly, if so, should the court nonetheless in its discretion decline jurisdiction?

Medimmune argued that the agreement did not confer jurisdiction on the English courts to decide whether Synagis was covered by the claims of the patent. The Court of Appeal held that the agreement did confer jurisdiction on the English courts to determine any issues relating to the performance of the agreement and that an English court would have no difficulty in determining whether any royalties were payable.

The Court also dismissed Medimmune's argument that jurisdiction should be declined because the correct forum in which to construe an American patent was the USA and, if it did not decline jurisdiction, there was a risk of inconsistency between the decisions of the English court and the US court. The Court of Appeal held that English courts were able to apply the appropriate foreign law in respect of the scope of a foreign patent and there was only a very remote possibility of different constructions of the claims. The parties had the power to negotiate jurisdiction and were fully aware of the fact that the validity of the patents could be tried only in the courts of the relevant countries of the patents. The commercial sense of the licence agreement was to select a jurisdiction with a specialist, experienced court that could determine all issues of infringement in relation to patents from many different jurisdictions.

The Court of Appeal held that Laddie J had taken into account all the relevant matters and had correctly exercised his discretion with respect to hearing the matter.

CASE C-31/03 – APPEAL PROCEEDINGS BROUGHT BY PHARMACIA & UPJOHN SPA (2004)

Having received the opinion of the Advocate General, the European Court of Justice (ECJ) gave a preliminary ruling in response to a referral by the German court. The question to be determined was whether a distinction should be drawn for the purposes of granting a supplementary protection certificate (SPC) between market authorisations for medicinal products for human use and for veterinary use. Would the grant of an SPC in a member state on the basis of a medicinal product for human beings authorised in that member state be precluded by an earlier authorisation to place the same product on the market as a veterinary medicinal product granted in another member state? The applicant claimed that where an SPC is sought for a medicinal product for human use, it is the date of the first authorisation to place the product on the market for human use which is relevant for the purpose of grant of an SPC in accordance with Article 19(1) of Council Regulation No. 1768/92.

The ECJ determined that the grant of an SPC in a member state of the

Community on the basis of a medicinal product for human use authorised in that member state was precluded by an earlier authorisation to place the product on the market as a veterinary medicinal product granted in the Community before the date specified in Article 19(1) Council Regulation No. 1768/92 concerning the creation of an SPC for medicinal products.

COMMISSION PROPOSES TO ALLOW EXPORT OF GENERIC MEDICINES TO POOR COUNTRIES

The Commission has proposed a Regulation to allow manufacturers of generic pharmaceuticals to produce patented medicines for export to countries in need and without sufficient capacity to produce them. The Regulation would implement a World Trade Organization (WTO) decision of 30th August, 2003,[1] under which national authorities can grant compulsory licences for the production of generic products if certain criteria are met, including that the destination country must have notified the WTO that it seeks the medicine covered by the patent. According to the Trade Commissioner Pascal Lamy, the adoption of this proposal means that 'the EU leads the way in ensuring access to affordable medicines for poor countries. It shows that we are delivering on our promises in the Doha Development Agenda.' Under the Regulation, customs authorities will be able to prevent the re-importation into the EU of medicines produced under the system.

CHANGES TO RULES ON GOVERNING LAW

A Commission consultation is ongoing in relation to proposals to change the law throughout the European Union on contractual provisions for the exclusive choice of courts for the resolution of disputes arising under contracts between businesses. This is part of a convention being prepared by the Hague Conference on Private International Law. The deadline for replies to the consultation is 15th November, 2004. The effect on intellectual property is uncertain, despite the fact that Article 2 of the convention excludes all intellectual property other than copyright, but the consultation specifically asks for feedback as to whether this exclusion is sufficient or whether it is too broad. The draft convention[2] and the consultation[3] are available.

LAW COMMISSION PROPOSES CHANGES TO THE LAW ON LIMITATION PERIODS

The Law Commission has recommended changes to the English law on limitation periods, ie the time period within which a claimant can bring an action. The indication is that the recommendations are for a core regime of a primary limitation period of three years, which would run from the date on which the claimant knows, or ought reasonably to know, the facts giving rise to the cause of action, the identity of the defendant and that any injury, loss or damage was significant. There would be a longstop period of ten years within which the court would have discretion to allow a claim. This would run from the date of the cause of action.

However, the Patent Office believes that the new (and old) limitation regime does not apply to circumstances where legislation expressly provides for limitation periods such as the Patents Act and other intellectual property legislation. At the time of writing the new statute has yet to be drafted so we do not know how the provisions will operate, but it is expected that parliamentary time will be given to this matter over the next 12 months.

NEW BELGIAN LAW ON EXPERIMENTATION INVOLVING HUMAN SUBJECTS

In Volume 10, Number 3, we reported that the Belgian government had proposed legislation to implement the

provisions of European Parliament and Council Directive 2001/20, better known as the Clinical Trial Directive. This new law was subsequently passed on 7th May, 2004, just after the 1st May, deadline for implementation of the directive. The Belgian Royal Decree of 6th June, 1960, relating to the manufacture, wholesale distribution and dispensing of medicinal products has also been amended. The law largely follows the requirements of the directive as well as the structure described previously, but two areas are worth highlighting in more detail.

First, there is a provision in the implementing law that goes beyond the provisions of the directive as regards insurance and liability which provides as follows:

> Article 29 § 1 The sponsor is liable, even without fault, for damage to the participant and/or his successors connected directly or indirectly to the study; any contractual provision aimed at limiting this liability is void.
>
> § 2 The sponsor must prior to the study obtain insurance covering this liability as well as that of all those involved in the study regardless of the nature of the connection between those involved, the sponsor and the participant.

We believe that it will impose on the trial sponsor a specific (and strict) liability for all events during the trial, whether or not within the control of the sponsor. This would be in addition to liability under the general law, for example under the principles of negligence. Furthermore, 'sponsor' is defined as 'a person, a business, an institution or an entity responsible for the initiation, management and/or financing of a clinical study'. Notwithstanding any agreement with the commercial sponsor, a contract research organisation (CRO) could well fall within this definition. Consequently, a CRO managing a trial in Belgium would be well advised to ensure that it obtains indemnities both from trial centres as regards claims arising from the centre's or the investigator's negligence or misconduct, but moreover from the 'actual' sponsor covering any claims that may be brought against the CRO by study participants on the basis of the above article.

Second, there are some fairly short time limits for both the competent ethics committee and the Directorate General of Medicinal Products (which is the competent authority nominated by the Belgian government) to complete their respective reviews, with a period of 15 days applying in both cases to Phase I trials and 28 days for all other trials. Once the trial is underway, the primary obligation lies with the ethics committee to monitor protocol compliance (the Directive simply requires that this is done by the member state). Unfortunately and contrary to hopes raised during the legislative process, provisions have been introduced to the effect that a clinical study of any product falling within paragraph 1 of the Annexe to Regulation (EC) No. 726/2004 (that is, any medicinal products developed by means of one of the following biotechnological processes: recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells or hybridoma and monoclonal antibody methods) must obtain a positive prior authorisation from the competent authority, rather having the benefit of a presumed authorisation where no objections are raised within the prescribed time-limits.

Finally, there is a circular from the Directorate-General setting out further guidance on the applications for authorisation. All relevant legislation is available (in French) from the website.[4]

RECENT AMENDMENTS TO GERMAN DRUG LAW

On 8 August 2004 the 12th amending law regarding the German Drug Act (*Arzneimittelgesetz*, abbreviated here as 'GDA') came into force after much

political debate. A few days later an administrative order entered into force regulating the implementation of good clinical practice within clinical trials (GCP Administrative Order, abbreviated here as 'GCPAO'). The law and administrative order serve to implement a number of EU directives into national law, among them the EU Clinical Trial Directive (2001/20/EC) and the Community Code Directive (2001/83/EC). The essential changes are as follows:

- The dossiers to be submitted with the applications to ethics committees and to the competent authority have become very extensive (Section 7 GCPAO). In addition the monitoring and disclosure obligations of the investigators, sponsors and authorities during the clinical trials, in particular with regard to adverse effects are prescribed in considerable detail (Sections 12–15 GCPAO).

- Clinical trials now require a positive vote of an ethics committee (Section 40 GDA), and the vote has to be given within 60 days after receipt of the application (Section 42 GDA). The role of the ethics committees, for example with respect to an evaluation of the investigators, have been broadened (Section 42 GDA, Section 2 GCPAO).

- In addition a mere notification of the competent authority is not sufficient but an approval by the authority is needed (Section 40 GDA). The approval is considered given if the applicant does not receive detailed objections within 30 days (Section 42 GDA).

- The requirements for clinical trials involving adults and those involving minors have been harmonised (Section 40 GDA). With regard to minors it now has become possible under a number of conditions to conduct clinical trials even though there may be no individual use for the patient but only a benefit for the patient group. With regard to adults the requirements have become more stringent than they were before in order to protect patients.

- The penalties in cases of production and marketing of counterfeited drugs have become more severe with maximum penalty being increased to three years' imprisonment (Section 95 GDA).

- The duties of continued pharmacovigilance have been extended, in particular with regard to the obligation to document and disclose adverse effects (Section 63b GDA).

In order to be in line with the new requirements, the paperwork required for clinical trials has to be essentially redrafted, and drafting the submission to the relevant ethics committee and to the competent authority has become more time- and money-consuming. On the other hand, the administrative procedure has been streamlined.

NOTES FROM THE USA: DIVVYING-UP THERAPEUTIC INDICATIONS IN BIOTECH DEALS – UNIQUE AND COSTLY CHALLENGES

What is an indication-splitting deal?

When the licensor of a pharmaceutical product grants a licensee the right to market a therapeutic product for a limited number of the indications for which it ultimately may be approved, the parties have entered the tricky world of 'indication splitting'. For example, a biotech licensor might license the right to market a small molecule product for cardiovascular indications, while retaining the rights to market or sublicense the same product for 'all other indications'.

While such a structure sounds simple, without careful legal planning, major commercial problems can result. One problem occurs when physicians (legally) prescribe products 'off-label' for indications that are not yet approved, making it hard to track sales within a particular indication. In addition, once additional indications are approved (through the efforts of the licensor or a different licensee) the commercial substitution of identical products for various approved indications can make it very difficult to match sales by licensees with the indication for which the product is actually used. If royalties are owed to the licensor based on sales for a specific indication, licensor and licensee (or different licensees) can wind up in major disputes about whether the appropriate amount of royalty is being paid.

Why are indication-splitting deals becoming more common?

Despite these difficulties, pharmaceutical companies are favouring indication-splitting deals for several reasons. First, the companies are focusing on 'core indications' for their in-licensed or purchased molecules. The cost of developing pharmaceutical products is so great, and the competition is so intense, that pharmaceutical companies must focus all their efforts to launch a product in the key indication and are forced to ignore other indications. The need to capture market share and provide the maximum financial returns is driving companies away from developing secondary indications on their own. Secondly, many pharmaceutical companies are internally organised into independent functional business units based on therapeutic fields. This provides corporate focus, but makes the development and marketing of cross-functional products more difficult. As a result pharmaceutical companies are more likely to out-license, spin-out or divest the development of secondary indications for their compounds. Also, there has been increased scrutiny from the government with respect to the promotion of 'off-label' uses of pharmaceutical products. To avoid such additional governmental scrutiny, but still capture some sort of income from additional indications, companies are choosing to let another party do the work to get secondary approvals. All of these factors have contributed to the increased trend in partnering deals that rely on indication splitting.

What are the potential risks of adopting such a structure?

Even though the current market conditions seem to favour indication-splitting deals, there are significant risks associated with such arrangements. The problems were exemplified in a highly publicised dispute between Amgen, Inc. and Ortho Pharmaceuticals Corporation. There, Amgen developed a recombinant human erythropoietin as a human therapeutic. Amgen retained the exclusive right to market the erythropoietin in the USA for dialysis patients under the name Epogen®. At the same time, Amgen granted Ortho Pharmaceutical Corporation a licence to commercialise the drug in the USA in all markets other than dialysis under the name Procrit®. Amgen sued Ortho for breach of its licence, claiming that Ortho intentionally sold Procrit® to dialysis patients outside of its licensed field. Multiple arbitrations followed, and Amgen was ultimately awarded US$150m in damages for lost sales of Epogen® in the dialysis market. In addition, Ortho was ordered to reimburse Amgen for all costs and fees, which totalled close to US$100m, a large part of which was incurred to accurately assess lost sales.[5]

What affirmative steps can companies take to avoid such pitfalls?

When deciding on a deal structure, if the potential for indication splitting exists, the parties should consider whether an alternative licensing structure is viable.

For example, it may be possible to license only specific, non-interchangeable formulations, dosages or modes of administration (eg oral *v* topical) for all indications. The parties' interests may also be better aligned through a profit-sharing transaction for all indications, but wherein different marketing rights are allocated between the companies.

If there are no reasonable alternative approaches, and the parties still want to split indications, the parties should negotiate and agree on a methodology to track sales of product in specific indications before signing the deal. There are several product-sales tracking methods available, and the parties will have to balance reliability, accuracy and cost depending on the products involved. Among the more common methods are random sampling, using proxy data, economic modelling and using pre-set ratios based on estimated future sales.

- **Random sampling.** Random sampling uses prescription data from randomly selected physicians, hospitals and pharmacies. Relative contributions of various indications to sales of a particular drug are calculated. This method can produce reasonable data, but the quality and reliability of the data are somewhat questionable given the limited number of sites polled. This method is also not useful for infrequently prescribed drugs or small-market indications.

- **Using proxy data.** Instead of tracking indication-by-indication sales directly, other data can be used as a proxy for indication-specific sales figures. For example, major distribution channels such as hospitals, clinics, mail services or retail stores can be monitored. This method works well when distribution channels correlate with use in a particular indication (eg shipments to nursing homes can help distinguish paediatric from non-paediatric indications).

- **Economic modelling.** Sometimes it is possible to develop a mathematical description of the potential market for a pharmaceutical product. Such a mathematical model would take into account several variables such as the approximate number of patients undergoing a particular treatment, market share of the drug, amount of drug necessary to treat average patients, mortality rates and average selling prices. These mathematical models can become extremely complex since every possible variable must be taken into account, and their ability to accurately capture market share may be difficult.

- **Using pre-set ratios.** For some products, it may be possible to calculate original royalties as a fixed percentage based on estimated future sales for each indication. While this approach seems fairly simple and straightforward, it is not perfect in that it does not account for changes that may occur over time, or the effect of regulatory approval and marketing efforts in additional indications.

Unfortunately, among these options no single method is entirely accurate, and all of the methods are costly. In addition to the advantages and disadvantages discussed here, each method may raise unique regulatory concerns and impact other aspects of the deal, such as dispute resolution. Significant effort should therefore be invested to fully understand the benefits and disadvantages of each method before incorporating any one of these methods into an indication-splitting deal.

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