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The month in Europe

On or off-side?

The issue of parallel trade is one that never fails to excite. Often, originator companies would have us regard parallel traders as the spawn of Satan, a malign influence in the medicines industry sent to endanger the public and destroy the very foundations of research and innovation. On the other hand, governments are not so quick to adopt this interpretation as they are quick to see that parallel trade can offer a small, albeit welcome, means to cut healthcare spending. And the courts? Well, they really are divided on the issue. On occasion they have slated the profession, yet at other times they have let it flourish. Indeed, even the European Court of Justice is not sure how to deal with issue of parallel trade, preferring to err on the side of caution in recent times. This month, the European Association of Euro-Pharmaceutical Companies (EAEPC) offered *EURALex* a robust defence of its activities, seeming at times to relish its members' position as the underdogs in the pharmaceutical market. According to the association, parallel trade is here to stay, and each attack by the originator companies does not serve to destroy the industry, but simply to gain time ....p 8-9

You only sing when you're winning?

A recent ruling by the European Court of Justice, which ensures that an excipient does not fall within the definition of "a combination of active ingredients" has received a muted response from the research-based pharmaceutical industry. The implications from the judgement for the industry are substantial as this means that companies will not be able to apply for Supplementary Protection Certificates as easily as they had previously hoped, thereby facilitating an earlier entry into the market for generic products. However, the fact that industry has not made an outcry is at best admirable and at worst baffling. Is this simply a stunned silence, an acceptance of the inevitable or the calm before the storm? ....p 14-15

Foul play

Poland is set to introduce certain measures in the pharmaceutical arena that will not comply with EU law. The major bone of contention here is the issue of data protection. The EU term of ten years has been deemed as unacceptable by the Polish government who is simply averse to harmonisation in this particular case. The question is whether the Commission will be forced to draw a yellow or red card on the matter. ....p 17

Advanced Therapies Directive must be balanced, says industry

More clarification is needed in the European Commission's draft Regulation on Advanced Therapies if it is to ensure compliance from hospitals, says the European medical devices industry association, Eucomed. In a recent critique of the Regulation, the association stressed that, although it welcomed the legislation, amendments to the text must require hospitals to fulfil the same obligations as industrial manufacturers of similar products.

Eucomed conceded that if the requirements were to apply to "one-off" products, the system would then become unworkable. However, it said that patients had the right to expect the same level of quality, safety and efficacy from products routinely prepared in a hospital setting. The implementation of the Regulation would then inspire public confidence in an emerging therapeutic field, which would subsequently lead to increased investment, the association claimed.

It is also pressing for more targeted expert representation in the proposed Committee for Advanced Therapies (CAT), which is set to fulfil an advisory role, evaluating new treatments and making recommendations for marketing authorisations. However, the actual decision on recommendations will be made by the Committee for Human Medicinal Products (CHMP). Eucomed views this as a duplication of activities and suggests that, as long as the constituent membership of the CAT is sufficiently qualified, there would be no reason to involve the CHMP.

However, if the finished Regulation still envisaged interaction between the CAT and the CHMP, then Eucomed believes that a mechanism should be introduced to allow the committees to reach agreements. A similar mechanism could also be set up internally within the CAT, it suggests.

Eucomed is uncomfortable with the transition period of two years for the introduction of the Regulation. It argues that this could disrupt treatment with the use of advanced therapies in those countries that have already permitted their use, such as Germany. The association advocates a five-year transition period, in line with the European Medicines Agency's (EMEA) product renewal system, but stresses that new products would have to comply with the Regulation from day one.

Ethical concerns are well addressed with the proposed Regulation, with Member States being permitted to deviate from the Regulation where they have particular issues with types of human or animal cells or tissues, Eucomed says. However, it has called for a tightening of the Regulation to oblige Member States to list these concerns in an open and transparent manner. This would create more confidence and certainty amongst companies in the advanced tissues field, the association says.

The new legal framework behind the Regulation is to be drawn up based on the creation of technical requirements as well as amendments to existing legislation and guidelines. However, for tissue engineered products, it would be insufficient to amend the Clinical Practice Directive, as modifications to the Clinical Trials Directive and the Good Manufacturing Practice Directive would also be required, claims Eucomed. Expertise in the field is scarce and Eucomed says it is ready to offer industry's services to create the best possible legal framework.

The association has expressed concern that certain areas of advanced therapeutic products appear to have "fallen through the net". The Regulation as it stands does not cover products that do not act as medicines, whose principal mode of action is neither pharmaceutical, nor immunologic, nor metabolic. Again, it says that industry has a role to play here and would be keen to lend expertise so that these products can be properly regulated. ❊

EFSA improves transparency procedures

The European Food Safety Authority's Guidance Document published in May 2006. is set to provide procedural guidelines in the area of transparency and risk assessment. The document was created by the members of the Scientific Committee and of several EFSA departments including the Science, Legal, Institutional, International Relations and Communication Departments.

According to the new guidance document, EFSA's risk management procedures can be made more transparent by selecting qualified scientists to participate in EFSA's activities and ensuring their independence. There is also an emphasis on ensuring that all relevant data is made available to the risk assessors handling any given case.

The Document has further laid down guidelines allowing for the exchange of information between the sides involved in a given request for risk assessment, i.e. between EFSA's Scientific Committee, the Panels and the originator of the request. ❊

Device manufacturers to benefit from EU accession to Geneva Act

Following recent votes in the European Parliament firms will find it easier to secure international protection for their industrial designs. MEP's approval of EU accession to the Geneva Act, an international agreement administered by the World Intellectual Property Organisation (WIPO), is likely to be a source of comfort to medical device manufacturers.

...benefits of accession

Accession means that firms will be able to seek protection for their designs in 42 countries worldwide through a single application to Geneva. The UK Patent Office said that the EU move is expected to provide many benefits. "There would no longer be a need to provide translations of the documents, to keep watch on the different deadlines for renewal of a great number of national registrations and to pay a series of national fees and fees to agents in different countries.

Overall there would be savings both in cost and administration," it claimed. The Act tries to make the 1960 Hague Agreement on international protection of industrial designs more compatible with practice in the UK, US, and Japan, where registration of designs is contingent upon examination.

Currently, only 12 of the 25 EU states are parties to the Hague Agreement: Belgium; Estonia; France; Germany; Greece; Hungary; Italy; Latvia; Luxembourg; Netherlands; Slovenia; and Spain. Five are also party to the Geneva Act: Estonia; Hungary; Latvia; Slovenia; and Spain.

On account of their domestic requirements, neither the UK nor the USA, are currently party to the Hague system. However, a working document seen by MEPs suggests that the US now plans to accede in November, while UK designers will get access to the Hague system through the EU's collective ratification. EU accession – together with changes to EU laws on design protection also approved by the European Parliament – will also create a link between the Hague/Geneva regime and the EU's own Community Design registration system managed by the EU trade mark and design registration body, the Office for the Harmonisation in the Internal Market (OHIM) based in Alicante, Spain.

The UK Patent Office comments that EU accession to the Hague/Geneva system will not directly link the UK Registered Designs system to the Hague system. "So it would not be possible to obtain a UK Registered Design, as opposed to a Community Registered Design, through an application under the Geneva Act," the Office's Intellectual Property and Innovation Directorate claimed.

In order for this to happen the UK would need to amend its Registered Designs Act 1949 to establish a link with the Hague system before it can ratify and so become party to the Hague Agreement for the first time. ❊

Pfizer is first to receive an EU conditional marketing authorisation

Pfizer has become the first pharmaceutical company to receive a positive opinion from the European Medicines Agency for a conditional marketing authorisation. The opinion was granted by the Committee for Human Medicinal Products (CHMP) in favour of 12.5mg, 25mg and 50mg hard capsules of the cancer drug Sutent.

Sutent is now set to be authorised by the European Commission to treat metastatic renal cell carcinoma (mRCC) after failure of interferon alpha or interleukin-2-based therapy, and for gastrointestinal stromal tumour (GIST) in patients who are resistant or intolerant to imatinib mesylate. mRCC is a type of kidney cancer that affects more than 37,000 people each year in Europe. In addition, over 6,000 Europeans annually are diagnosed with GIST, a rare type of soft-tissue cancer found in the gastrointestinal tract.

Conditional marketing authorisations may be granted in certain categories of medicinal products in order to treat unmet medical needs of patients and in the interests of public health. As they are awarded on the basis of less complete data than is usually accepted by the EMEA, they are subject to specific obligations.

The products should be targeted at the treatment, prevention or diagnosis of seriously debilitating or life-threatening diseases, or for use in emergency situations in response to public health threats recognised either by the World Health Organisation or by the Community. They may also be orphan medicinal products as designated in accordance with Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999. Sutent – which contains the active ingredient sunitinib malate – received such an EMEA designation on 10 March 2006 for both GIST and mRCC.

The US FDA approved Sutent in less than six months in January 2006 for the treatment of GIST in patients whose disease has progressed or who are unable to tolerate treatment with Gleevec, the current treatment. Approval was also granted for its use in patients with advanced RCC. This was the first time that the FDA had approved a new oncology product for two indications simultaneously.

"approval of this drug for these indications provides compelling evidence that the use of alternative data endpoints allows us to see the benefits of novel therapies earlier in patients"

During the GIST clinical trial, the application submitted to the FDA contained "an early interim analysis" of data. Richard Pazdur, Director of the FDA's office of oncology drug products, said at the time that the "approval of this drug for these indications provides compelling evidence that the use of alternative data endpoints allows us to see the benefits of novel therapies earlier in patients", a sentiment echoed by the EMEA opinion.

A European Public Assessment Report (EPAR) will be available after the conditional marketing authorisation has been officially granted by the Commission. This reflects the scientific conclusion reached by the CHMP at the end of the centralised evaluation process, provides a summary of the grounds for the Opinion, and is designed to be easily understood by patients and the general public.❊

EC to shed light on sunscreen product labelling

Issues of safety concerning sunscreen products have prompted the European Commission (EC) to launch a public consultation with a view to revising labelling requirements for these products. "The current situation is untenable. The best way forward is a recommendation to which industry commits to label sunscreen products properly. This will give consumers clear and coherent information without creating unnecessary red-tape for industry," said Enterprise and Industry Commissioner Günter Verheugen.

The Commission argues that current information provided on sunscreen products makes it difficult for the consumer to understand the level of protection offered. Both UVA and UVB radiation are potentially harmful, it stresses. Whereas UVB radiation is the main cause of sunburn, UVA radiation is responsible for skin ageing, can have a negative effect on the immune system and carries with it a risk of skin cancer. But the "sun protection factor" highlighted on many sunscreen products guards only against UVB radiation.

However, according to Directive 76/768/EEC, cosmetic products placed on the Community market must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking account, in particular, of the product's presentation, its labelling and any instructions for its use.

Furthermore, Member States must ensure activities linked to the labelling, putting up for sale and advertising of cosmetic products, including text, names, trade marks, pictures and figurative or other signs do not imply that these products have properties that are non-existent. Enforcement, however, appears to be failing.

There are numerous spurious and often confusing claims attached to sunscreen products, the Commission notes. Terms such as "broad spectrum", "broad extra UVA, UVB", "100% anti UVA/UVB/IR", "keeps short UVA radiation away", among others, are of little benefit to the average consumer. Furthermore, claims of total protection are unachievable and should therefore disappear from packaging, the Commission maintains. The introduction of approved, similar testing methods that will be derived from the EC's drive to standardise labelling by 2007, should provide clarity and improve safety.

Colipa, the European Cosmetic, Toiletry and Perfumery Association, has welcomed efforts being made towards the better regulation of the €1.3bn sunscreen products industry. It also supports measures to ensure that labelling referring to UVA protection should be linked to a demonstrative minimum efficacy, and has said that it will contribute to their implementation. ❊

EMEA gives the all clear to two hepatitis B vaccines

The European Medicines Agency (EMEA) has moved quickly to allay concerns raised about the efficacy of two centrally-authorised vaccines – HBVAXPRO and Procomvax – used in the treatment of hepatitis B. Following a review of the products by the Committee for Medicinal Products for Human Use (CHMP), started at the request of the European Commission in February 2006, the EMEA declared that the products continued to offer effective protection against hepatitis B.

The vaccines – the marketing authorisation for both is held by Sanofi Pasteur MSD – came under suspicion because they share the same component for combating hepatitis B as Hexavac (Aventis Pasteur). The authorisation for this vaccine is currently suspended due to concerns about a decrease in its long-term protection capabilities that are the possible result of variability in the production process for the product.

HBVAXPRO is used to combat hepatitis B to be used in children – including neonates – adolescents and adults. Procomvax is used in infants aged 6 weeks to 15 months and also protects against disease caused by Haemophilus influenzae type b (HIb). Before the availability of vaccines, this was one of the most common causes of meningitis.

The CHMP requested the marketing authorisation holder to carry out a number of studies in different age groups to provide evidence of the long-term efficacy of HBVAXPRO and Procomvax. Although the review found no indication of a decrease in efficacy of the vaccines, the CHMP has requested changes to the product information for doctors in order to guarantee optimum use. It stresses, however, that the changes are not related to the safety profile of the vaccines.

There are also reinforced recommendations to carry out blood tests and to administer additional doses in high-risk populations

These amendments include a change to administration schedules for HBVAXPRO so that in countries where it is given at 0, 1 and 2 months, a booster is provided at 12 months. There are also reinforced recommendations to carry out blood tests and to administer additional doses in high-risk populations of either vaccine, where necessary.

Finally, the concomitant administration of HBVAXPRO and Prevent (Wyeth Pharmaceuticals) – a pneumococcal saccharide conjugated vaccine for infants and young children, used to prevent invasive pneumococcal disease – is not advised, as insufficient tests have been undertaken in this area. ❊

EMEA accounts for 2004 get Parliament's approval

The European Parliament has granted discharge to the Executive Director of the European Medicines Agency of the EMEA budget for the financial year 2004. It has also approved the closure of the agency's accounts for that year.

The EP's decision follows on from a report submitted by the European Court of Auditors (ECA) on the annual accounts of the EMEA, which stated that the accounts for the financial year ended 31 December 2004 were "in all material respects reliable". It added that the transactions underlying the agency's annual accounts, taken as a whole, were legal and regular.

But the ECA made a number of observations concerning matters that required further clarification. It noted that contracts with certain banks had been in force for over five years, even though rules governing the implementation of the EMEA's Financial Regulation stipulate that there should be a new invitation to tender at least once every five years.

The transgression was the result of the agency's need to implement a wide-ranging reform of the Financial Regulation and Accounting procedures over the last few years, the EMEA said. "It was considered prudent not to seek a change in the main bank at the same time due to an integration of our systems with this bank's electronic payment system," it added.

...transfer costs reduced

As the agency is now in the final stages of implementing the Financial Regulation, a call for tender will be launched in the last quarter of this year.

"However it should be noted that substantial reductions in bank transfer costs have been achieved through direct negotiations with the bank and automation of payments," the agency stressed. It added that the placements of funds are subject to individual bids from up to three banks, based on the market rates on a particular day. ❊

NovoSeven application withdrawn, but trial continues

The European Medicines Agency's Committee for Human Medicinal Products (CHMP) has voiced concern that the data submitted for the authorisation of Novo Nordisk's haemophilia product NovoSeven is too limited to justify its use in the treatment of acute intracerebral haemorrhage (ICH) in adults.

...application withdrawn

As a result, the Danish drug manufacturer has withdrawn its application for a marketing authorisation for the product. The withdrawal of the application has no consequences for NovoSeven's use in the indications for which it is already authorised, including the treatment of haemophilia and Glanzmann's thrombasthenia.

The data provided by Novo Nordisk were aimed to prove that the drug, when used in haemorrhage treatment, would limit bleeding and the spread of the disease. According to the CHMP, the data submitted show that the drug has an effect on the volume of the haemorrhage. It is not clear, however, how this improves the outcome for the patient.

The CHMP also raised questions concerning the thromboembolic side effects for this indication. Having taken into consideration all the points mentioned above, the Committee feels that at the moment the benefits of the drug in haemorrhage treatment are not sufficient and do not outweigh the identified risk.

...trial to continue

Novo Nordisk says that it has no intention to terminate the current clinical trial of NovoSeven in intracerebral haemorrhage and has already informed the CHMP that the research will continue. ❊

Persistence of avian flu prompts EU to extend bans

The European Commission's Standing Committee on the Food Chain and Animal Health (SCFCAH) has given the go-ahead to the extension of provisions introduced to guard against the potential proliferation of avian influenza in the EU.

Biosecurity measures in place to protect domestic flocks, such as keeping or feeding poultry indoors in identified high-risk areas, will now remain in place until 31 December 2006. The SCFCAH also agreed to prolong until 31 July 2006 restrictions on the movement of birds accompanying their owners, and the import ban from third countries on live, captive birds – other than poultry – for use in commercial purposes.

"biosecurity measures in place to protect domestic flocks, such as keeping or feeding poultry indoors in identified high-risk areas, will now remain in place until 31 December 2006"

The committee agreed to extend "regionalised" import bans on poultry and poultry products from Bulgaria and Romania – set for EU accession in 2007 – until 31 December 2006. The region-based prohibitions will now also cover live poultry and hatching eggs, imports of which have hitherto been banned from the whole of Bulgaria and Romania. For Croatia, the regionalised ban on live birds, poultry and poultry products is to be extended to cover the region of Zagreb, following confirmation in April of a case of the virulent H5N1 strain in a wild swan from the area.

Austria has been permitted to begin vaccinating birds in zoos against the virus, based on the avian influenza control Directive 2005/94/EC of 20 December 2005. The SCHCAH also backed Commission proposals to allow France to extend its preventive vaccination programme for ducks and geese.

Member States also gave the go-ahead to extend an understanding with Switzerland, whereby the Swiss authorities would continue to implement the same measures that would be taken within the EU in the event of a highly pathogenic outbreak in a Member State. ❊

EURALEX European national courts round-up

EURALex's monthly national courts round-up is provided by international law firm Freshfields Bruckhaus Deringer

Dutch court disagrees with UK and holds Angiotech's drug eluting stent patent valid

On 3 May 2006, the District Court in The Hague issued judgment in *Angiotech Pharmaceuticals Inc and Boston Scientific Corporation v Sahajanand Medical Technologies Ltd (SMT)* regarding the alleged infringement of Angiotech's European patent 0.706.376 for a taxol eluting stent.

SMT had been involved in delivery of a limited number of stents in the Netherlands for use in an experimental setting. The stents comprised taxol and a polymeric carrier. In addition to a non-infringement defence, SMT argued invalidity of the patent due to lack of inventive step. SMT used similar arguments to those brought by Conor Medsystems Inc in UK proceedings. In Angiotech v Conor [(1)], the UK High Court held the UK part of Angiotech's European patent invalid due to lack of inventive step over the prior art. The UK court looked at the question of whether a person skilled in the art would consider using the drug taxol on a drug eluting stent. In the court's opinion, the answer was that a skilled person would consider trying taxol, and therefore the patent was held invalid.

The Dutch court applied a different standard for assessment of the validity. After determining the closest prior art and the objective problem to be solved, the court evaluated the alleged obviousness of using taxol on a drug eluting stent. On the basis of the prior art, the court concluded that it was known to use a drug eluting stent in which the drug is affixed to the stent through a polymeric carrier to reduce restenosis. Taxol in itself was also known, but not for use against restenosis. In the absence of any specific so called 'pointers' in the prior art, which would lead a person skilled in the art to the use of taxol on a stent for treating restenosis, the patent was held to contain an inventive step.

Unlike in the UK, the Dutch patent was held valid. The court also held it infringed, and issued an injunction.

1 *24 February 2006, Pumfrey J, Case No: HC05C00376, Conor / Angiotech - UBC*Conor Medsystems Inc v Angiotech Pharmaceuticals Inc and another [2006] EWHC 260) 24 February 2006, [Reported in April 2006 issue]

German court prohibits distance selling of veterinary pharmaceuticals

The Higher Administrative Court of Rhineland-Palatinate in Koblenz has held that non-prescription veterinary pharmaceuticals that are classified as pharmacy-only may not be sold by distance selling, such as over the internet (24 January 2006, *6 A 11097/05.OVG*).

The complainant company sold non-prescription veterinary pharmaceuticals over the internet. The competent authority stopped this, referring to the German Pharmaceuticals Act which prohibits distance selling of veterinary, pharmacy-only pharmaceuticals. The complainant claimed this prohibition under the legislation is unconstitutional because the legislation allows distance selling of pharmaceuticals for human use – including prescription-only pharmaceuticals. The Administrative Court had already dismissed this complaint and the Higher Administrative Court has now confirmed that court's decision.

The Higher Administrative Court held that the statutory prohibition of distance selling of veterinary, pharmacy-only pharmaceuticals was compatible with the "freedom to exercise a profession", a basic right guaranteed by the German constitution. The prohibition served to protect both animals and humans consuming those animals treated with pharmaceuticals. It also protected against other potentially harmful animal products. The court said that the fact that distance selling is allowed for human pharmaceuticals but prohibited for veterinary pharmaceuticals was based on the following reasoning. A prudent person who is concerned about his own health would be careful to avoid wrong and dangerous treatment if he decided to consume pharmaceuticals that were not prescribed. In contrast, an irresponsible keeper of animals might administer pharmaceuticals to the animals for economic reasons and not because they were necessary medically, and so create risks for both the animals and humans.

UK Patent Office considers inventiveness and industrial application of a human gene encoding a specified protein

In a recently published decision (*Aeomica Inc's Application* BL 0/286/05), the Patent Office considered the patentability of a human gene expressing a particular protein. The application, filed by Aeomica Inc, was rejected at both the initial hearing and subsequent appeal. This decision was made on the basis that it lacked industrial application – as required under paragraph 6 of Schedule A2 to the UK Patents Act 1977 – since no specific function of the gene or protein (a type of V-ATPase known as ZZAP1) was demonstrated. The application was also held to lack inventive step over the earlier disclosure of the very similar gene and hypothetical protein from a macaque monkey.

In *Chiron Corporation v Murex Diagnostics* the Court of Appeal had considered the requirement of industrial application and said that the Patents Act and the European Patent Convention (EPC) intended that monopoly rights be confined to those having some useful purpose. In *Icos Corporation* the European Patent Office (EPO) said that the requirement is not satisfied where the potential uses of an expressed protein are speculative – i.e. where they are not specific, substantial and credible. The "specific, substantial and credible" test is incorporated into the UK Patent Office guidelines. Applying the test in this case:

a) the proposed utility of the ZZAP1 gene sequence was not specific – V-ATPases are known to have a variety of roles;

b) further research was required to verify the function of the ZZAP1 protein – this failure to define a "real world" use meant the proposed industrial application was not substantial; and

c) without a definitive role for the gene sequence as a probe, there was no credible utility for such use – i.e. the notional skilled person trained in the field of molecular biology, familiar with bioinformatics tools and web-based genomic resources, would not have accepted that the invention could realistically be given such a use.

Applying the *Windsurfer* test, the inventive concept was considered to be the identification of the isolated gene sequence encoding the ZZAP1 protein. The Patent Office decision makes it clear that primate sequence information will usually be a valid starting point for the identification of human genome sequences. This means that applications covering the equivalent human sequences are likely to lack the necessary inventive step. ❊

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Parallel trade: does it offer budget relief whilst preserving safety and competition?

As European health economies look to slash budgets and cut the prices of pharmaceuticals, governments are increasingly focusing on generics. However, these medicines represent only one of the weapons in the existing healthcare budget armoury. Heinz Kobelt, secretary general of the European Association of Euro-Pharmaceutical Companies (EAEPC) and Richard Freudenberg, secretary general of the British association of European pharmaceutical distributors (BAEPD), spoke to *EURALex* about the limited role parallel traders have to play in cutting healthcare spending as well as safety and legal issues affecting the industry.

In terms of potential savings, volumes must be first taken into account, explained Mr Kobelt. Parallel trade amounts to some 4.5-5% of the total pharmaceutical market in Europe. Therefore with this alone it would be inconceivable to cull European healthcare budgets. However, parallel trade provides savings and an element of competition amongst otherwise very rigid European price structures. "There are savings from the various national incentives. Then there are more dynamic savings where a parallel import hits a manufacturer within a domestic market so that he is more likely to reduce his price to retain market share at the expense of the parallel import," said Mr Kobelt.

But the parallel import industry is being perpetually tested by the looming shadows of various ECJ and national court judgements that could potentially hamper certain areas of its activities. Both Mr Freudenberg and Mr Kobelt are confident that no single ECJ decision would seriously threaten the industry. Mr Kobelt points to the opinion of Advocate General Jacobs in the Glaxo/Syfait case, in which he indicated that a dominant company should not be obliged to meet orders that were out of the ordinary. Mr Kobelt believes that the court did accept the arguments of the AG because it would have meant a complete U-turn for its whole history of case-law on the subject. "The ECJ could not rule once and for all because the cases that go up the legal ladder define a specific episode in the trade and it is not always easy to conclude general rules from these, more or less, single cases," Mr Kobelt said.

Furthermore, the series of judgements handed down by the ECJ are essentially too complicated to undo in one single judgement, Mr Freudenberg added. "There have been cases about repackaging, cases about trademark law and cases about patent law," he explained.

Mr Kobelt maintained that by bringing these cases, manufacturers were not so much "wasting time" as "winning time". For example, an EAEPC member filed a complaint against Glaxo in 2001 for introducing dual pricing in Spain. The European Commission delivered a decision in May of that year condemning the manufacturer's activities. "Glaxo launched an appeal and the matter has been hanging around the Court of First Instance since that time. The indications are that it may go forward to a hearing later this year," said Mr Kobelt. However, during the interim period, all pharmaceutical companies, with the exception of Glaxo itself, could actually practice some kind of a dual-pricing system in Spain, with the "tolerated blessing" of the competition authorities. But under normal competition rules – as standard practice – dual-pricing would *per se* be an abuse and ruled out, Mr Kobelt maintained.

He added that Pfizer drew up a similar scheme shortly after the Commission had condemned Glaxo and although the EAEPC lodged a complaint with the EC, action in the matter has yet to be taken. " We also filed a complaint last autumn against Pfizer Spain for mounting a cartel with wholesalers – again essentially a dual-pricing business. The EAEPC believes the Commission views this as "basically the same scheme" as the one it had already condemned with respect to Glaxo in 2001. "We are in discussions with the Commission on how to keep this case alive pending a decision in the Court of First Instance on the dual-pricing issue," Mr Kobelt explained.

But these actions also have a business impact on EAEPC members, often in the form of increasing supply restriction schemes, which at the moment seem to be tolerated following the Adalat ruling of the Court (*Joined Cases C-2/01 P and C-3/01 P: Bundesverband der Arzneimittel-Importeure eV against Commission of the European Communities*).

Mr Freudenberg highlighted an ongoing case in the UK, which has been running since 1999. It has already been to the High Court and questions were then referred to the ECJ in 2001. "When this came back, the decision was in our favour, but Glaxo/Boehringer/Lilly appealed and it went back to the UK court, was then sent back to the ECJ and so on and so forth," he said. Mr Freudenberg explained that each time the court decision is amended it modifies the behaviour of the parallel importer and indeed the behaviour of the trademark owners. "There has, however, never been any single knock-out blow," he stressed. Furthermore, because there are now 25 jurisdictions in terms of national competition authorities, it is unlikely that a single decision could ever be applicable across the board.

And there are still ongoing cases in Greece, Italy and France. "What is lacking is a coherent policy on such issues in the pharmaceutical sector by the European legislators and the European Commission, so that is something that needs to come," said Mr Kobelt.

However, that is not to say that certain "legislation" does not exist on the parallel trade issue in Europe. A communication from the Commission exists that summarises the recent case-law and the practice regarding parallel trade that Member States must follow. There is a series of competition law cases, addressing private restrictions on parallel trade and usually based on Article 81 of the EC Treaty which is concerned with "all agreements between undertakings, decisions by associations of undertakings and concerted practices which may affect trade between Member States and which have as their object or effect the prevention, restriction or distortion of competition within the common market".

In the recent Adalat case the Commission lost its position. "Since that, supply restrictions have increased almost as an industry-wide pattern. This, of course, has an impact on the supply of goods, but it also has an impact on all wholesalers across Europe," explained Mr Kobelt. A new type of thinking has been generated, whereby there is now a consideration that competition issues may be addressed the under Article 82 – the abuse of dominant position. "If you talk to large wholesalers, you will find that even they feel dominated by pharmaceutical manufacturers," said Mr Kobelt. The question is, can competition rules be interpreted in such a way that manufacturers who impose supply restrictions or refuse even to supply their customers could be attacked under these provisions of "abuse of a dominant position"?

However, abuse of a dominant position is a particularly complicated area, because as long as a company, to a certain degree, supports

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competition, or helps to support competition, it should, as a manufacturer, be able to control where its goods are bound. Mr Kobelt conceded that this may well be the case, but added that the only competition to a patented medicine is the parallel import of the same medicine. There is no other price competition to a patent-protected product, he stressed. "There is no substitution either, so if a prescription is written for product X, you cannot supply product Y," Mr Freudenberg added. This means that the market is essentially locked starting with physicians' surgeries. "That explains why all the marketing efforts of manufacturers are more or less targeted at the doctor," said Mr Kobelt.

Mr Freudenberg pointed out that parallel trade prices were not uniform in individual countries. This essentially made the market even more competitive, he said.

. . . liability and responsibility

Once a drug is in the public domain there is certainly a question as to what extent responsibility for the product can be divided between the parallel trader and the manufacturer. "It varies according to jurisdiction. In Germany, a parallel importer is considered a manufacturer and falls under the same regulatory rules and has to fulfil the same conditions as a pharmaceutical manufacturer in terms of good manufacturing practice," said Mr Kobelt. Germany also has rules concerning liability with relation to pharmaceutical manufacturing, he added, and German member companies must subscribe to this. "So they are responsible, because they are putting the product in the market," Mr Kobelt explained.

However, the UK has a different take on the matter, said Mr Freundenberg. "The way it is perceived here is that there is a liability, which derives to the parallel importer, but only to the extent that he alters the product – that is to say, changes the packaging. We never break bulk, or blister packaging. Most underwriters will insure on that basis," he explained. But parallel importers may alter the patient information leaflet (PIL), an element that has been pre-approved by the MHRA. "We are not talking about a translation of the leaflet from, for example, Greek into English, but rather a replacement leaflet, based on the UK leaflet," he stressed. This is what the parallel importer in the UK inserts into the packaging. However, the most significant measure imposed by the regulators is that the name of both the parallel importer and the repackager must be included on the leaflet as well as on the outside packaging. If it is the leaflet that might have misled the patient into taking the wrong dosage, then it is likely that the parallel importer would be liable, Mr Freudenberg conceded. "But when it comes to real product deficiencies or side effects, the manufacturer is responsible," Mr Kobelt concluded.

. . . the repackaging issue

There are two ways to modify a package for a parallel trade product. The simplest is to stick a label on the outside of the box. It shows the name of the importer and it is a requirement of the law that the name of the manufacturer is also clearly shown. "We would also have to remove the foreign language PIL, replace it with an English language PIL and place something on the blister packaging in case the two got separated," explained Mr Freudenberg. This is an additional label containing a minimum amount of information. The practice is known as over-stickering or over-labelling. The alternative procedure involves disposing of the original carton, replacing it and the PIL, whilst also adding a sticker to the blister packaging. "In terms of components, it is cheaper to over-sticker. But whilst the new box would be more expensive, it probably takes you somewhat longer to over sticker," said Mr Freudenberg.

During repackaging, the PIL must be taken out of the original carton and this permits an examination of the external condition of the blister pack to be undertaken. "Very often our members find defective products, such as broken or even empty blister packs. I am not saying that you could discover a counterfeit product by this optical inspection, unless it is very badly copied," claimed Mr Kobelt.

An optical inspection takes place and the experienced pharmacist – the qualified person, whose employment is a condition of the parallel trader's licensing - has to determine whether this product is fit for the market. "We can't say our processes are safer than that of the original manufacturer, but we are adding an additional layer of inspection," Mr Freudenberg maintained.

. . . compliance

The EAEPC is keen to ensure that on a consistent basis the handling of labelling and packaging by its member companies in the individual countries is up to the standards it has set. It is the national regulators that have put in place standards for what Mr Kobelt refers to as a "highly regulated profession". Not only in Germany, but also in the Scandinavian markets, importers are considered manufacturers and are consequently subject to the same routine controls. Standard operating procedures must therefore be in line with national regulations as inspections occur on a regular basis, this being the essential tool for ensuring compliance.

"we can't say our processes are safer than that of the original manufacturer, but we are adding an additional layer of inspection"

"Our guidelines do not serve to recodify what already exists, but rather summarise from a more accessible point of view the essential safety requirements. They make a kind of first attempt at self-regulation to check that our membership complies with these requirements," said Mr Kobelt. The EAEPC asks its members to submit proof that annual inspections have been carried out and the date of inspection so that it can monitor compliance. "Should a member fail to deliver, the general assembly has the right of expulsion," Mr Kobelt explained.

Ejecting members is a deterrent but could create a situation in which these "rogue" parallel traders could then carry on trading and by the nature of their negative performance could do serious harm to the whole concept of parallel trade. "In theory this could happen, but my impression of the trade is that this has evolved out of a niche situation, starting with a group of people that knew each other. This personal knowledge and trust from the past is still there and yet it is nowadays augmented by the principle of 'know your source'," said Mr Kobelt. A wholesaler or parallel distributor looking to maintain its reputation would therefore not default on such fundamental principles and buy from a questionable source, he concluded. ✻

Selected decisions of the European Patent Office Boards of Appeal

Case Number / Date	Applicant / Opponent	Title of Invention	Appeal Keywords	Decision
T 0918/01 3.3.04 06 October 2004	Biogen / Neumann Lydia Ellen	Treatment for inflammatory bowel disease	Main and first auxiliary request: Inventive step (no); Second auxiliary request – not admissible	The decision under appeal is set aside. The patent is revoked
T 0239/01 3.3.4 16 March 2005	Promega Corporation / Roche Diagnostics	Coupled transcription and translation in eukaryotic cell-free extract	Inventive step (no)	The decision under appeal is set aside. The patent is revoked
T 0676/01 3.3.04 09 May 2005	Sonoran Desert Chemicals LLC / ZLB Behring Genzyme Transgenics	Treatment of inflammation	Main request: Right to priority (yes); Added; subject-matter (no) Novelty (yes); Inventive step (yes)	The decision under appeal is set aside. The case is remitted to the first instance with the order to maintain the patent as amended
T 0445/04 3.3.04 24 May 2005	F.Hoffmann La Roche / The Secretary of State for Defence	Homogeneous assay system	Main request: added subject-matter (no); Novelty (yes); Inventive step (yes)	The decision under appeal is set aside. The matter is remitted to the first instance with the order to maintain the patent on the basis of selected claims
T 0606/03 3.3.08 12 January 2006	Artemis Pharmaceuticals / N/A (EPO Examining Division)	Conditional gene trapping construct for the disruption of genes	Main and first auxiliary requests exception to patentability (yes) Second auxiliary request: exception to patentability (no) Novelty and inventive step (yes)	The decision under appeal is set aside. The case is remitted to the first instance with the order to grant a patent on the basis of the second auxiliary request filed during the oral proceedings
T 0730/03 3.4.02 January 2006	Massachusetts Institute of Technology / N/A (EPO Examining Division)	Method and apparatus for performing optical measurements using a fibre optic imaging guidewire catheter or endoscope	Sufficiency Added subject matter	The decision appeal is set aside. The case is remitted to the first instance for further prosecution on the basis of claim 1 of auxiliary request 2
T 0604/04 3.3.08 16 March 2006	Genentech / SmithKline Beecham	Human PF4A receptors and their use	Main request: claims 21 and 22 sufficiency of disclosure (no); Auxiliary request I - inventive step (yes); Auxiliary request I - industrial applicability (yes)	The decision under appeal is set aside. The case is remitted to the first instance with the order to maintain the patent on the basis of auxiliary request I

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Case Number / Date	Applicant / Opponent	Title of Invention	Appeal Keywords	Decision
T 0625/04 3.2.02 17 March 2006	Rita Medical Systems / N/A (EPO Examining Division)	Apparatus for ablation of a selected mass	Substantial procedural violation (yes); Reimbursement; the appeal fee (yes)	The decision under appeal is set aside. The case is remitted to the department of the first instance for further prosecution. A reimbursement of the appeal fee is ordered.
T 0786/03 3.3.10 22 March 2006	Mitsubishi Pharma Corporation / Delta Biotechnology	Method for sterilising recombinant human serum albumin pharmaceutical preparation	Amendments: all requests (not allowable) – not occasioned by grounds for opposition – optional feature	Appeal dismissed
T 0380/04 3.2.02 23 March 2006	Fresenius Medical Care Deutschland / N/A (EPO Examining Division)	Hemodialysis apparatus	Novelty (yes, after amendments); Grant and printing fees refunded	The decision under appeal is set aside. The case is remitted to he first instance for further prosecution. The request for reimbursement of the grant and printing fees paid on 1 August 2003 is allowed

Rita Medical Systems profits from EPO examining board's procedural violation

A substantial procedural violation by the European Patent Office's (EPO's) examining division when considering a patent application from Rita Medical Systems for an apparatus for ablation of a selected mass has been condemned by the EPO's Boards of Appeal.

On 11 December 2003 the examining division refused European patent application No. 96929687.0 on the grounds that claim 1 of the application did not meet the inventive step requirement of Article 52(1) EPC. In communications to the company, the division cited a number of documents in support of its objections: D1 (EP-A-0 502 268), D2 (DE-A-38 38 840), and D3 (US-A-4 565 200).

In response to the claims made by the examining division, the applicant argued that, whereas the application related to an apparatus for ablating tissue with RF antennas, the cited documents were associated with different medical fields. The company subsequently declared that they should therefore not be used as a basis for rejected a patent under Article 52(1) EPC in relation to claims concerning ablation apparatus.

Despite claims that D1 referred to an electrosurgical device for cutting tissue and cauterising/coagulating the resulting wound area, D2 to a high frequency coagulating device, and D3 to a device for making heat lesions, the applicant's protestations were ignored. Not only was no written response provided by the examining division, but also the minutes of the oral proceedings did not record that this point was ever addressed by the division, in spite of the fact that the applicant presented printed documentary evidence in support of its claims. The examining division's apparent refusal to confront the issue occurred despite the company's insistence that a person skilled in the art would find it impossible to arrive at the claimed invention – an improved tissue ablation apparatus – if they combined the teachings of the documents.

However, when assessing the "inventive step" the EPO is obliged to provide a reason why the person skilled in the art *would* combine the teachings of two or more documents in order to arrive at the subject matter of a claim.

In fact, the only time the examining board did respond to the issue was in its final refusal to grant a patent. It cited a passage in *Dorland's Illustrated Medical Dictionary* to support its contention that "coagulation is considered to fall under the terms of ablation in the sense of destructive heat treatment".

The Boards of Appeal therefore concluded that the decision of the examining division was based on grounds against which the applicant was not granted sufficient opportunity to defend itself. It deemed this to be a "substantial procedural violation" and not only returned the matter for prosecution to the first instance, but also refunded the appeal fee. ❊

E-labelling is coming: are you ready?

Kristen Giovanis

Outsiders assume that the pharmaceutical, biotech and medical device industries are the vanguard of technology in every way, routinely blurring the boundaries between science and science fiction. While that perception may approximate reality in product development, most companies continue to rely on content management, document control and regulatory processes that are very 20th century. Kristen Giovanis, Managing Director of KJ International Resources, a company that provides language services to, among others, the pharmaceutical, life sciences, and financial services industries, examines how e-labelling may alter this pratice.

Because regulatory requirements change at a much slower rate than technology, and because companies have no room for error in their regulatory affairs, technology in any aspect of business that touches on regulation is only conservatively applied.

Even regulation changes eventually, though. In December 2005, the European Union promulgated revisions to the Medical Device Directive (MDD) that further open the door to electronic formats for product labels. In the US the FDA has specifically permitted e-labelling for prescriptive devices used in healthcare facilities since Congress enacted the Medical Device User Fee and Modernization Act in 2002. The FDA has also required pharmaceutical companies to submit their applications in the regulatory approval process electronically, and there are indications that medical devices are next on the list.

E-labelling is no longer a "maybe, someday", but a "yes, now" for companies that want to position themselves to move quickly in a highly competitive environment. And for those who have long been touting e-labels as a way to improve the quality of patient care while controlling costs, waste and time-to-market, the day is coming for their victory dance.

. . . pieces in the puzzle

The regulatory seal of approval for e-labelling is the last piece in a complex puzzle that includes document management, research and clinical practice, enterprise-wide information systems and more. At last, the biotech, pharmaceutical and medical device industries are facing the perfect storm of factors that make this the right time to move aggressively into development, testing and deployment of e-labels for regulated products entering and already launched in global markets.

By moving from print-based labels to e-labels, manufacturers open up for themselves a host of possibilities in terms of the kind of information they can provide on a label – everything from video product demos to searchable databases can now be incorporated into a label. Even a simple "translation" of a paper manual to a CD-ROM version makes the manual more useful through, for example, search functions and its ability to integrate with online help.

. . . ready, aim –

But user readiness has been a factor in the past: manufacturers have moved cautiously with e-labelling, even when the regulatory path seemed clear, to avoid disrupting the work of practitioners who use their products.

Medical device manufacturer Medtronic launched a pilot study in 2004, to examine the willingness of physicians to use electronic labels. The study surveyed 637 implanting physicians in 11 EU countries, and found that 35% preferred CD-ROM manuals for implants; 28% regarded CD-ROM manuals as equivalent; and only 4% of respondents would not accept a CD-ROM.

The Medtronic study is only a first step, and sometimes the "user" who really needs convincing isn't the practitioner but the government and regulatory agents who must approve e-labelling. Although largely a finished discussion in the US, particularly as the FDA has moved more and more into electronic submissions and Structured Product Labels (SPL) for pharmaceuticals, some members of the EU are still developing their readiness for acceptance. The recent implementation of Product Information Management (PIM) by the EMEA demonstrates that the overall medical field in the EU is moving towards technology, but e-labelling for medical devices still faces opposition. Germany, Belgium, Sweden, Greece and the Netherlands have been notably reluctant to voice approval of e-labelling.

. . . nexus of technology

The increasing marketplace interest in technologies like content management systems (CMS) and enterprise management systems (EMS) also factor into the Zeitgeist of e-labelling. CMS and EMS implementations, when done correctly, create a powerful vortex of information that can be managed in various ways – translated, shared, controlled, submitted, or published – all the while adding to the knowledge stores of the organisation. When CMS and EMS systems are linked with e-labelling initiatives, a manufacturer has the ability to:

a) create single-source files for label publishing across formats that can include traditional paper-based printing, PDF, CD-ROM, extranet and new formats that may be introduced in the future;

b) submit label information electronically to regulatory authorities, avoiding human errors that can be introduced in the process;

d) control and report on document versions, and publish new regulatory-approved versions of labels more quickly than with print;

e) share materials, including label content, securely across the enterprise and with external resources – such as regulatory agents and translators – providing enhanced opportunities for input earlier in the development process and streamlining turnaround times along the way.

. . . staying ahead of the curve

Step by step, regulations worldwide are moving towards the implicit or explicit enabling of e-labelling. Companies that wait until every "T" is crossed and "I" dotted will find themselves left behind the adoption curve. Companies can stay ahead – if not on the –bleeding edge", then at least within the initial wave – by employing several key strategies:

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a) Feasibility Review. For each product in the pipeline and the marketplace, consider carefully the pros and cons of moving towards e-labelling. Some products may best perform with traditional labels, while others may be appropriate candidates for e-labels in specific circumstances – such as professional use. Also, consider the frequency of label updates. Products with few updates may be best managed with traditional labels, while products with multiple updates in several languages may offer a better cost-benefit ratio by moving to e-labels.

b) User Feedback. Regardless of your current plans to implement e-labelling, start talking with your customers and users about their attitudes to and expectations of e-labelling in their practices and professions. Find out how much they know about e-labels, how comfortable they are using them, and assess their technology capabilities for accessing electronic label information. If your users are clamouring for electronic labels, then you face a different kind of opportunity than if your users tell you that they love paper and will never let it go.

c) Technology Updates. Few companies have truly up-to-date technology capabilities for CMS and EMS. Take time to conduct a thorough information management audit to learn what your information assets really are and how close you are to maximising your use of them. Identify any gaps in your IT capabilities, and develop a strategic plan for technological evolution that takes into account regulatory requirements, labelling needs, translation, publication and data access.

. . . from idea to implementation

While there are challenges aplenty in moving to e-labelling, the time is right to make the move. One of KJI's medical device clients has started the process by creating an implementation plan with a step-by-step approach, relying on evaluation at every step.

This company manufactures highly invasive surgical tools and markets its products in 21 countries around the world. To determine the value and potential of e-labelling in its business and marketing strategy, the company did the following:

a) Market analysis

The company conducted a thorough analysis of the countries in which it markets its product, to identify the distribution requirements of its current products and product labelling. This analysis compared real market against potential future markets and identified drivers for realising the potential of future markets.

b) Current labelling and revision updates

The company then determined costs associated with labelling, including: creation, localisation, desktop publishing, printing and distribution. A separate analysis was also conducted to determine the amount of time this process took, and the internal resources allocated to do so.

The company then analysed new revisions/releases of the product and labelling updates it produces each year, as well as the average time and costs associated with revisions.

The result of this analysis demonstrated that, with a high volume of new releases, the company would gain significant benefit from moving to e-labelling. At the very minimum, it stood to realise enormous cost savings on production and printing.

c) Technology review

To achieve the full benefits of e-labelling, the company recognised that it needed to invest in robust, enterprise-wide information management. This stage of the planning process was particularly challenging, because the company had recently – within the past two years – implemented a proprietary document management software system and had a significant investment in it.

To manage all the risks and elements of e-labelling, the company suspected that it needed to shift to an enterprise management system (EMS). Upon further analysis, the company determined that the most cost-effective solution in the long-term would be to implement an EMS that supported content authoring in XML format. With XML, many of the costs associated with publication – particularly localisation costs – would be dramatically reduced. At the same time, an EMS would incorporate all the document control functions, including tracking approval, routing, revision, etc.

. . . transition costs

Making this change means early pain for later profit: Shelving the document management system means taking a hit on the original – and often substantial – investment. The company must also convert its existing document library into the new format – a time-consuming and expensive task.

. . . eye on the future

For its European operations, the company continues to use traditionally printed labels, in compliance with the dictates of the MDD. However, it is poised to move immediately to e-labelling within four months, upon full regulatory approval. Companies that have not done the leg work will be latecomers. ❊

ECJ SPC ruling a blow to research pharma firms

The European Court of Justice gives a restrictive interpretation of the SPC Regulation for medicinal product patents. Will the judgment affect innovators' research? Elisabethann Wright and Linda Horton of Hogan & Hartson's Brussels office discuss a recent judgment that takes a restrictive view of a key intellectual property law.

On 4 May 2006, the European Court of Justice ruled[1] that a medicinal product composed of an active substance and an excipient did not fall within the definition of "a combination of active ingredients" found in the EU Regulation governing supplementary protection certificates[2]. As a result, the product was not entitled to a Supplementary Protection Certificate (SPC)[3]. The Court concluded that this would be the case even where the excipient is necessary for the efficacy of the active ingredient. A product consisting of a combination of ingredients is, thus, entitled to an SPC only where both products are active ingredients.

. . . the purpose of the SPC

SPCs were introduced in the EU by a 1992 Regulation. Their declared purpose is to provide compensation to pharmaceutical patent holders for the loss suffered due to delays caused by the sometimes extensive period that can elapse between the filing of a patent and the grant of a marketing authorisation for a medicinal product. This compensation is by means of extending the protection conferred by the basic patent for up to five years. The extension applies only to the product that is the subject of the marketing authorisation and only to any use of the product as a medicinal or plant protection product that has been authorised before expiry of the certificate. The SPC does not extend the term of the patent itself. An SPC may be obtained for a combination of active ingredients in a medicinal product.

. . . the MIT Case

The present case arose from an unsuccessful application by the Massachusetts Institute of Technology (MIT) to the German patent and trademark office for an SPC for Gliadel Implant, a medicinal product used in the treatment of recurrent brain cancer. Gliadel is an implanted wafer that releases a combination of an active chemotherapy agent (carmustine) and a second composite (polifeprosan), which controls the release of the first substance into a patient's body. MIT is the holder of a patent for the product filed in July 1987. A marketing authorisation for Gliadel was granted in Germany in August 1999. Carmustine had first been authorised as the active ingredient of a medicinal product in the EU in March 1979 for use in intravenous chemotherapy. This earlier authorisation for carmustine precluded MIT from applying for an SPC relating to this ingredient. MIT, therefore, applied for an SPC for Gliadel in France, Germany and the UK, on the basis that the product constituted a "combination of active ingredients of a medicinal product", as described in Article 1 (b) of the SPC Regulation. A successful application would have qualified Gliadel for an SPC for up to five years.

The French and UK patent offices granted MIT an SPC for Gliadel. The German patents and trademarks office, however, rejected the application. It concluded that combinations of medicines qualify for SPCs only if both components constitute active ingredients. MIT appealed this decision to the German federal court of justice. This court chose to suspend its proceedings and refer a Community law question to the European Court of Justice: does the definition "combination of active ingredients of a medicinal product" in the SPC Regulation require that two or more components of the product serve as active ingredients with a therapeutic effect? Further, can this definition include products where only one component of which is an active ingredient while the other renders possible a different therapeutic form of the product with different efficacy for this indication?

. . . Advocate General's Opinion

On 24 November 2005, Advocate General Léger, in his Opinion in the matter, concluded that the ECJ should interpret the SPC Regulation so as to permit an SPC in this factual situation. Considering that the purpose of the SPC Regulation was to grant legal protection to medicinal products that are the result of long costly research, the legal protection granted must be both sufficient to allow pharmaceutical undertakings to cover their investments and equivalent to that enjoyed by other technological sectors. He took the position that a restrictive interpretation of the term "combination of active ingredients of a medicinal product" would not be consistent with the broad logic of the SPC Regulation or the objectives of Community legislation. He reasoned that, as the SPC is the natural extension of the basic patent, nothing should prevent a medicinal combination, which is not only protected by a patent but also is subject to its own marketing authorisation, from likewise enjoying an SPC if that combination is among the therapeutic innovations whose development the SPC Regulation seeks to encourage.

In the view of the Advocate General, the legislation should be interpreted not only as encouraging research and development of new active ingredients to ensure the continuing improvement of healthcare, but also as promoting research into new applications for existing active ingredients. Development of auxiliary substances might enable use of such ingredients or enhancement of their pharmacological properties for a specific therapeutic indication. In the present case, he remarked that the role and effect of the excipient was to increase significantly the intended therapeutic effect of the active ingredient while avoiding certain harmful side-effects associated with the intravenous administration of carmustine. The combination gave the active ingredient entirely new pharmaceutical properties that it did not previously have in terms of efficacy and safety of use. The Advocate General thus concluded that for the grant of the SPC it was of little importance that the active ingredient had been known and used for many years in the treatment of similar medical conditions insofar as it did not have the pharmaceutical properties of the combination.

The Advocate General acknowledged that an SPC could not be granted every time the characteristics of a medicinal combination are slightly changed. However, he concluded that this was not what had happened in the present case. Where the effective treatment of certain illnesses requires an active ingredient to be combined with a substance which, whilst not having any pharmacological properties of its own, allows the active substance effectively to release its therapeutic effects, such a combination must fall within the scope of "combination of active ingredients of a medicinal product" within the meaning of the SPC Regulation. It is the necessity of the excipient in ensuring the therapeutic efficacy of the active ingredient that must be the determining factor in ascertaining whether a combination of these two substances fall within the definition.

The Advocate General thus concluded that, if the Court were to rule that such medicinal combinations are not entitled to an SPC, this ruling would discourage research centres from investing in the development of medicinal combinations of this nature even though such research is essential to the progress of treatment and to the competitiveness of the Community pharmaceutical industry.

continued

. . . Ruling by the European Court of Justice

In deciding not to follow the opinion of the Advocate General, the European Court of Justice chose a literal interpretation of the SPC Regulation and its provision for an SPC for a "combination of active ingredients of a medicinal product." It concluded that SPCs are not available for two ingredients "only one of which has therapeutic effects of its own." This is so even where the excipient renders possible a pharmaceutical form of the medicinal product that is necessary for the therapeutic efficacy of the first substance.

Because the SPC Regulation does not define the term "active ingredient", the Court reasoned that its meaning must be determined considering the general context in which it is used and its usual meaning in everyday language. According to the Court, in pharmacology, it is generally accepted that the term "active ingredient" does not include substances that have no effect of their own on the body.

The Court also cited the explanatory memorandum accompanying the 1990 proposal for the SPC Regulation which stated that only one SPC could be granted to any one product, "a product being understood to mean an active substance in the *strict sense*". The Court concluded that an excipient could not fall within the intended scope of "active substance".

The Court found instruction in the definition of a –product" found in the Regulation governing SPCs for plant protection products. This Regulation, adopted subsequent to that concerning medicinal products, defines a "product" as an active substance or combination of active substances, and an "active substance" as a substance with general or specific action against harmful organisms or plants.

According to the Court, the inevitable conclusion must be that a substance which does not have any therapeutic effect of its own and which is used to enable a certain pharmaceutical form of the medicinal product is not covered by the concept of "active ingredient", which in turn is used to define the term "product". As a result, the alliance of such an ingredient with a substance that does have therapeutic effects of its own cannot give rise to a "combination of active ingredients" within the meaning of the SPC Regulation.

The interpretation of the term proposed by MIT could, in the Court's view, lead to legal uncertainty. The Court further concluded that the definition of "combination of active ingredients" proposed by MIT would be contrary to the aim of uniformity to which the SPC Regulation aspired.

. . . assessment of this Ruling

Industry response to the Advocate General's Opinion had, not surprisingly, been very positive. However, the judgment of the Court, while disappointing, does not come as a complete surprise. The Court has, on previous occasions, adopted strict interpretations of the provisions of the SPC Regulation[4]. In the MIT judgment, it chose a narrow and literal definition of the term "combination of active ingredients of a medicinal product". However, in adopting such a narrow and literal interpretation, the Court arguably failed to consider the stated purposes of the Regulation. The preamble to the Regulation acknowledges that pharmaceutical research plays a decisive role in the continuing improvement of public health and that medicinal products, especially those that are the result of long, costly research, will not continue to be developed in the Community and in Europe unless they are covered by favourable rules that provide sufficient protection to encourage such research.

. . . implications of the Ruling

One of the important aims of the SPC Regulation is to minimise the risk that research centres situated in the EU Member States will relocate to countries that already offer greater intellectual property protection. However, the interpretation of the Regulation provided in this judgment may undermine this purpose, leading researchers and innovative companies to leave the EU for other countries where protection of innovation is perceived to be greater.

Moreover, the judgment may discourage innovative companies from investing in efforts to find new uses of existing ingredients, where excipients might help overcome safety, efficacy or technical issues with the original ingredients. This is because the lack of an SPC for such an improvement enables copies to enter the market earlier.

The MIT decision disappointed the innovative pharmaceutical industry, which, unsurprisingly, favoured a broader interpretation of the provision. As European patent offices will now be obliged to apply the strict and literal interpretation of the term "active ingredient" given by the Court in the MIT case, the concern now is that innovative pharmaceutical companies will be unable to apply for an SPC for a variety of products. This may well limit their incentives to discover and develop new therapeutic treatments.

The ruling of the Court in MIT may further influence a similar case currently pending before the European Court of Justice concerning a product from Yissum Research and Development, the technology transfer company of the Hebrew University of Jerusalem. The case involves Silkis, a combination of calcitriol and certain excipients in an ointment base. The applicant, Yissum Research, filed an application for an SPC based on a UK marketing authorisation for Silkis (RTM) ointment. The application for an SPC was based on a claim that Silkis is a combination product within the meaning of the SPC Regulation given that the ointment base is necessary for the effective application of calcitriol to treat certain skin conditions. It will be interesting to see whether the Court's decision in this pending case will follow or overturn the MIT judgment.

The pharmaceutical industry should consider urging the Commission to return to the legislative drawing boards and tackle the issue of Community incentives for those investing in significant improvements in existing medicines. Already there are serious questions about whether the new "8+2+1" regime for regulatory data protection exclusivity periods provides adequate incentives for research-based product enhancements.

(1) Judgment of the European Court of Justice (Second Chamber) of 4 May 2006 In Case C-431/04, reference for a preliminary ruling from the Bundesgerichtshof (Germany), in the proceedings brought by Massachusetts Institute of Technology.

(2) Council Regulation (EEC) No 1768/92 of 18 June 1992

(3) Under Council Regulation 1768/92, SPCs give the patent owner 15 years of marketing exclusivity for the drug substance from the date of the first marketing authorization in the European Economic Area (EEA), subject to a five year cap on the duration of the SPC.

(4) Joined cases C- 207/03 and C-252/03 Novartis AG, University College London and Institute of Microbiology and Epidemiology v. Comptroller-General of Patents, Designs and Trade Marks for the UK and Ministre de l'Économie v. Millennium Pharmaceuticals Inc. [2005] ECR p. I-03209; Case C-31/03 Pharmacia Italia SpA, formerly Pharmacia & Upjohn SpA [2004] ECR p. I-10001. ❊

New Spanish medicines law promotes quality, efficacy and safety

Marta Pons de Vall Alomar

A new Law on Warranties and the Rational Use of Medicines will soon be approved in Spain. The draft was already enacted by the Chamber of Representatives last April and is currently in the Senate undergoing a second reading. This derogates from the former Law on Medicines from 1990 and incorporates into Spanish Law Directive 2004/27/CE on the Community code relating to medicinal products for human use, and Directive 2004/28/CE on the Community code relating to veterinary medicinal products. Marta Pons de Vall Alomar from Spanish law firm Gómez-Acebo & Pombo Abogados examines the most significant points of the law.

The Law includes a complete regulation on medicines. It covers medicines for human and veterinary use, pharmacy formulae and special medicines, such as vaccines and other biological medicines, medicines of human origin, radio medicines, homeopathic products and medicinal plants.

The review undertaken as a result of this new legislation is based in two main goals: to achieve higher standards for the quality, safety and efficacy of medicinal products; and to promote the rational use of medicines. With these aims the following measures have been introduced by this Law:

1. Generic products and Bolar provision

The market share of generic medicines in the Spanish pharmaceutical market is still low compared to other western European Countries. Thus, the Law intends to facilitate access of generic medicines to the market.

The Law on Medicines has introduced the so called "Bolar Exemption" – which allows manufacturers of generic products to conduct the necessary studies to show that these products meet the definition of a generic medicine, and permits all other activities relevant to submitting an application for a marketing authorisation prior to the expiry of a patent. Such activities shall not be deemed as an infringement of patent rights. However, a generic medicinal product shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. A list of those generic medicines which could be commercialised in the Spanish market during the following five-year period will be published annually.

In the interests of protecting innovations, a period of data exclusivity relating to pre-clinical tests and clinical trials has been harmonised according to the European Directive. Thus, during this period the competent authorities (the Spanish Medicines Agency) cannot use the innovator's data when assessing the safety and efficacy of the generic product. This data exclusivity safeguards the interests of innovative companies, seeking to protect their investments. Only after the expiry of the data exclusivity period, may second applicants refer to the original innovator's product dossier. The second applicant is exempted from providing pharmacological and toxicological tests and clinical trials (demonstrations of efficacy in humans). Data exclusivity is protected for ten years, and can be extended for one additional year, provided that the holder of the marketing authorisation obtains an authorisation for a new therapeutic indication that shows significant clinical improvement compared to the existing treatments.

As far as trademarks for generic products are concerned, the preliminary draft of the law proposed by the Government allowed the commercialisation of generic products under commercial trademarks. However, this has now been rejected. A generic product must henceforth be identified by the name of its active ingredient or the scientific name of the substance contained in the drug. Consequently, generic products will not receive a trademark advantage.

2. Pricing and other financial measures

Spain is amongst those European countries with high pharmaceutical costs. As a result, public reimbursement of medicines by the social security or public health funds will be conditional on the level of innovation of the product, its therapeutic and social use and the need to control public expenditure. Decisions on public reimbursement will be adopted taking into account reports on therapeutic use prepared by the Spanish Medicines Agency and independent scientific experts. Moreover, the law sets forth a minimum tax of 1.5% on sales, to be paid quarterly by the companies that manufacture, import or offer for sale medicines subject to reimbursement. The amounts paid according to this tax will be devoted to clinical research.

The Spanish Medicines Agency is obligated to review the price of many of the medicines currently commercialised in Spain, particularly those which have already been on the market for more than ten years. As price revisions may take place frequently, the price does not need to be printed in the medicine package.

Medicinal products which have been commercialised in Spain for a period of ten years will have their price reduced by 20%, provided that a generic product has been approved in any other Member State of the European Union (except Member States that are subject to provisional periods for intellectual property issues) with a lower price than the price approved in Spain for the same medicinal product.

3. Transparency

In order to guarantee transparency, the new law makes the competent authorities more accountable for their decisions in granting marketing authorisations. The authorities must make publicly available without delay the assessment report, and the reasons for their opinion. However, information of a commercially confidential nature is to be deleted to maintain this confidentiality. Moreover, the authorities must also make publicly accessible their meeting agendas and records

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of these meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions.

4. Quality and safety requirements

One of the aims of the Law is to achieve high standards for the quality and safety of medicines for human and veterinary use, taking into account compliance with rules regarding good manufacturing practice. Therefore technical requirements applicable to manufacturers and distributors of medicines are to be strengthened. The criteria of quality, safety and efficacy enable the risk-benefit balance of all medicinal products to be assessed both when they are placed on the market and at any other time the competent authorities deem this appropriate. Moreover, the marketing authorisation holder shall ensure that the safety information of the product is continuously updated and shall perform a continuous risk-benefit balance evaluation of the medicine in accordance with European rules. Should the health authorities deem such information useful for public health, they will permit public access to the appropriate data.

With the aim of improving the safety of medicines, the law has increased certain information requirements regarding the use of medicines, which will affect the packaging of medicines. A white area must now be made available on the packaging, to allow the pharmacist to indicate the specific questions regarding the treatment to be followed. It is also stated that the packaging shall include information regarding the product in Braille.

5. Publication of clinical trials

Although pharmaceutical companies are already committed to increase the transparency of clinical trials sponsored by them, the Medicines Law has set forth a rule to protect transparency in the event that the trial sponsor fails to publish these results. Should this occur, the competent health authorities will be permitted to publish the results of clinical trials, both positive and negative. This rule is intended to ensure transparency of clinical trials particularly when the trial results highlight efficacy or safety issues relating to the medicine tested.

6. Rational use of medicines

Chapter VI of the Law is devoted to the rational use of medicines. This chapter includes, among other questions, certain rules intended to control information and the promotion of drugs to physicians. Special concern is shown regarding the source of the funds aimed at promoting these activities. For instance, contributions to facilitate attendance to meetings, conventions or similar events by persons involved in the manufacturing, distribution or prescription of medicines shall be made public and shall be limited only to scientific activities addressed to health entities or specialists. Moreover, brochures and publications of the conferences shall indicate the financial funds, if any, and the quantities obtained from such funds.

7. Sales over the internet

The option to permit sales of medicines over the internet was discussed in depth during the procedure for approving the Law. Pharmacists were pushing to make it possible, but the law has ultimately adopted the more conservative point of view advocated by the Ministry of Health, which, on grounds of protecting public health, wanted to limit the activity to very specific cases. The Law on Medicines only authorises sales of medicines over the internet for non-prescription medicines (OTCs). However, delivery of these products is required to be made at the pharmacy, in order to ensure that the customer received adequate advice and information when the medicinal product was purchased. The law appears, however, to allow consumers to place the medicines order from home, but how this will apply is still under discussion. ❊

Changes to Polish pharma legislation cheer domestic market

Some of the amendments proposed in the Polish pharmaceutical law will not comply with EU rules, especially those related to data protection periods for innovative drugs. Although the new rules will be very favourable for the domestic market of pharmaceuticals, some of them will certainly be viewed as disadvantageous by foreign drug producers.

Proposals concerning innovative drugs and their data protection period are a particular bone of contention. Whereas in the EU data is protected for ten years, in Poland this is only six. The government has no intention to harmonise Polish rules with those in force in the EU.

According to the Polish health authorities, an extension of the protection period would have adverse consequences not only for patients forced to buy more expensive medicines, but also for the National Health Fund, which would then spend more on drug reimbursement.

The controversies around the protection period unfolded when Poland, shortly before joining the EU, made a motion to postpone the enforcement of the regulation in Polish law for 15 years. The EU has never formally agreed to this, and if Poland breaches Directive 2001/83 on medicinal products for human use, the European Commission will be entitled to report it to the European Court of Justice. The official EU standpoint on this matter is expected to be announced in summer.

The amended pharmaceutical law should please Polish pharmacists. The regulations currently in force oblige them to implement EU technical standards with regards to the size and technical content of a pharmacy by October 2007. According to the draft proposal, the rules mentioned above will not apply to pharmacies opened before Poland's accession. Should the new regulation be implemented, some 4,000 pharmacies will be exempt from meeting the EU requirements by the date given.

But not all the amendments are good news for the Polish pharmaceutical market. Before EU accession, Poland negotiated transitional periods with regards to drug registration. This means that by 1 January 2008, drug manufacturers must submit all necessary documents in order to fulfil EU registration requirements. However, the draft proposal shortens the period by a year. This is because the Office of Registration of Medical, Medicinal and Biocidal Products has voiced concerns that pharmaceutical companies will be submitting applications at the very last minute, which may have a negative impact on the reliable verification of a given drug. The draft proposal of the pharmaceutical law will be discussed by the Polish parliament this month.❊

Litigation, the analyst and the investor

The outlook for the pharmaceutical industry has been incredibly tough over the last five years, says Andrew Baum, Managing Director, Co-head European Pharmaceutical Research at international investment bank Morgan Stanley.

Speaking at the recent Pharmaceutical Regulation and Product Liability conference hosted by the British Institute of International and Comparative Law, he cited shortened product cycles due to faster genericisation – particularly in the US – fewer product cycles, and a lack of industry success in developing drugs. Furthermore, higher risks, associated with the raising of benchmarks of the regulatory indices, lower returns and a weakened public image and negotiating power – again, particularly in the US – were all detrimental factors, he added.

"And if that wasn't enough, you know an industry is in for a bad time, when, following Bowling for Columbine and the gun lobby, and George Bush with Fahrenheit 9/11, you then have Michael Moore on his next project, which is provisionally entitled: 'Sicko', which is about the pharmaceutical industry," warned Mr Baum.

But during these turbulent times, financial analysts are seeking to help generate alpha capital or performance for investors in the capital markets by, on a superficial level, putting ratings on stocks, to buy, sell or hold. They compile reports, which contain insights, information and results of access to management and to important individuals about the pharmaceutical space. "We have a long and extensive relationship with a range of individuals, ranging from competition lawyers, FDA lawyers, intellectual property lawyers, tax specialists, biostatisticians, clinical trialists, in fact anything that impacts on the value that a pharmaceutical company hopes to create," explained Mr Baum.

Litigation has a profound impact on share prices and performance and therefore a significant influence on predictions of analysts. Mr Baum sought to outline examples of: value transfer, in which there is a win/lose phenomenon; value creation, where, because of a patent settlement both generic and brand companies benefit; and value erosion with the classic example being the Merck share price, following the withdrawal of Vioxx and the impending liabilities.

Pfizer's successful defence of its Lipitor intellectual property against Ranbaxy in the US had a significant impact on its share price. This rallied some 10% on the day the court ruled that the company had won the intellectual property debate. "In contrast, Ranbaxy's share price decreased by a somewhat greater amount," said Mr Baum.

Plavix, an anti-stroke blood thinner, is the world's second largest selling drug, generating some $5bn (€3.9bn) per annum for patent holders Bristol-Myers Squibb and Sanofi-Aventis. "The drug was challenged by a generics company, but when an agreement was announced concerning a settlement with the generics company, the share price jumped by some 10%, as it looked like it was a win scenario for the brand company, by buying themselves insurance against the risk of erosion from a generic," explained Mr Baum. The generics company also benefited, although, because it was private, no share price was forthcoming in the public domain.

Investor insecurity also surfaced over potential unfavourable verdicts in a product-liability case involving Merck's Vioxx drug. As a result the company witnessed a collapse in its share price down from about $45 down to about $30 due to the uncertainty over liability associated with the court cases.

These cases raise questions as to how an analyst assesses when it is the right time to buy a stock. There is a need to determine whether it is already reflecting the risk that has occurred and whether in fact there is more upside opportunity than downside, said Mr Baum.

"There is a variety of techniques and methodologies we use to address this question. Before you do any of that, the first question an analyst will ask is: before the event actually occurred, what was the share price already discounting?" he explained. This is a key function of the capital markets, which will try and anticipate a trend. A very simple methodology would be to say that a drug should be 10% of earnings and therefore if a drug is then withdrawn, 10% should consequently be subtracted. "But that is very crude and ineffective," warned Mr Baum.

The way that analysts tend to look at the contribution of drugs or risk to a company's value is through a methodology called "discounted cash flow", which is essentially an assessment of the value of a drug's current and future cash flows to the group's overall cash flows.

Plavix contributes somewhere around 7%. It might therefore be argued that any risk to Plavix from an intellectual property point of view could equate to a 7% drop in the value of the share price, putting the idea of discounting aside, said Mr Baum. But using the idea of the discounted cash flow, the value of the contribution is only 2.4%. "Why is this an order of magnitude different? The reason is that Plavix, irrespective of what happens in the ongoing patent challenge, will face generic entrants in 2012. So the drug is only going to be on the market for five years and therefore you are going to have to adjust that in the valuation calculation and hence you get a much lower contribution," he explained. The analysis therefore shows a scenario that reflects the risks and rewards of various patent challenges and an assessment of pipeline development risk.

. . . has litigation and regulation shaped industry strategy?

Regulation and litigation clearly set the rules by which the industry operates. The Vioxx liabilities and before that the fen-phen liabilities – where a number of people claimed injury after taking the popular diet pill combination, manufactured by American Home Products Corporation – mean that the industry as a whole is very reluctant to take in leverage or debt. "Therefore it potentially reduces the returns it could make for investors. Another example would be the unwillingness to invest in vaccines," Mr Baum explained.

The second point Mr Baum highlighted was the Hatch Waxman Act – designed to promote generics while maintaining a financial incentive for R&D – and the expansion/explosion of the US generics market over the last ten years. "Consequently you now have pharmaceutical companies directly investing in the generics industry as well as looking to diversify outside the US in order to reduce their exposure," he said.

Biogeneric legislative guidelines now available in Europe were also impacting on company strategies, Mr Baum claimed. "Companies like Sandoz have invested heavily in this space because they can see the opportunity that this will facilitate," he said.

And shortened cycle times because of increasingly aggressive genericisation is one important driver for consolidation or mergers between these companies. "The point is that a much larger company can withstand an individual generic entry far greater than a smaller company," he explained.

Diversification is now happening with almost every company. The

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idea of having high-growth, primary care products with high volume, low value being pumped by heavy marketing is a model that is fading fast, Mr Baum suggested. "If you look at the strategy of the industry now, there is a focus on specialist products where the barriers to entry are higher and the reimbursement arguments are more persuasive. There are also non-pharma asset classes, such as diagnostics, generics and biosimilar medicinal products," he pointed out.

. . . patent settlement

The recently announced settlement of Plavix has seen four challenges by generics companies to its key patent. About one month ago, Sanofi and Apotex announced that they were settling out of court and postponing the ongoing litigation, in order to facilitate the visibility of revenues for both the generic and the brand company.

"This is a wonderful idea, because as a pharmaceutical company your valuation is crippled by the lack of visibility of earnings growth and, of course, having a generic challenge significantly increases risk; having a settlement takes it away, so the brand company benefits. But the generics company also benefits because it has a guaranteed contribution of revenues that is may not have realised, had the case gone to court. -So if you like, it is a very cheap form of insurance," Mr Baum suggested.

The issue is a legal one and there is an ongoing and significant debate between the Federal Trade Commission (FTC) and the appeals courts in the US over whether the terms of this settlement and even settlements more broadly are inherently anti-competitive.

The role of the analyst, given that this is the largest drug in Sanofi's portfolio, is trying to work out a number of things:

1) What are the timelines? When is the FTC going to come back and give a decision on whether this settlement is valid or not?

2) What is the valuation contribution?

3) What is the effect on the two or three other generics companies that are also challenging?

4) What does it mean for the stock?

"What I will explain to my clients is: what happens if the FTC accepts or rejects the settlement; if renegotiation is required. But it could also go through the FTC, the district courts, an appeals court and by that time five years will have passed when the case has finally been decided," Mr Baum said.

By this time, the generic would have been delayed and Sanofi would have made its money. Furthermore, the generics company will gain from a higher base level of sales almost irrespective of the outcome of the appeal, Mr Baum advised.

A settlement is therefore to be considered a form of insurance against risk, in which a company is looking to preserve cash flows associated with that drug. "In fact, it preserves cash flows associated with that drug, which may not have existed, had the drug faced generic competition," Mr Baum explained. This has strategic value for a follow-on drug in that it allows a company to buy itself time to convert cash flows from an old drug to a new drug, which further increases the value of the settlement beyond the simple revenues. ❊

It pays for regulatory authorities to know how to handle the press

Intense media scrutiny of the regulation of medicinal products has made it all the more necessary for the activities of regulatory bodies to become more transparent, says Simon Gregor, Director of Communications at the UK's Medicines and Healthcare products Regulatory Agency (MHRA). A proper reflection in the press of the regulator's efficiency was essential to increase consumer confidence, he said.

Mr Gregor presented two examples illustrating how differently a crisis situation in the healthcare regulatory sphere could be handled by the regulatory body and the media reaction to this.

The first example concerned the confusion surrounding the routine use of the MMR vaccine, "the handling of which has been widely cited as an example of Government's communication at its worst". Mr Gregor stressed that the Government could have done much more to engage earlier with those patients' and consumer groups who might have helped to better communicate important public health messages about the vaccine. He pointed out, however, that the handling of the MMR vaccine crisis was "not a complete disaster and coverage did not spiral out of control", explaining that scientists were themselves regularly publishing information on the safety and efficacy of the MMR vaccine. "In addition to that, every new release of data on vaccine uptake was very carefully managed with a bespoke media handling plan and media spokespeople available," he added.

The second case study Mr Gregor focused on was the TGN1412 clinical trial at Northwick Park Hospital, claiming that this was an example of a series of efficient actions undertaken by the MHRA to manage a crisis. The agency, by being proactive and open, was able to provide fast and accurate responses to journalists' questions, which allowed it to manage the story rather than be driven by it, he explained. Among those actions taken by the MHRA was a decision to release a public statement announcing that the clinical trial authorisation had been suspended. "We have also more recently published a variety of information associated to the clinical trial application on our website including the clinical trial protocol, the investigator's brochure and our own assessment reports," said Mr Gregor.

These two case studies should be a lesson for the regulatory authority, warned Mr Gregor. He suggested that these experiences meant that in a crisis situation the agency should be able to respond more rapidly to media requests. The MHRA's efficient handling of the press was apparent during the TGN1412 crisis, Mr Gregor maintained. "When we released our interim report on the investigation into the clinical trial incident, we had three experts sitting next to the press officers, so the questions could be answered immediately," he explained.

Another important thing in light of the case studies presented is the issue of the language used by the MHRA. In order to inform people about the benefits and risks in the area of pharmaceuticals and medical devices, the MHRA should use precise and accurate wording, Mr Gregor said. For example, the agency has started using the term "acceptably safe" in stead of simply "safe", in order to stress the idea of risk/benefit. ❊

Informed consent a must to avoid liability

The importance of obtaining truly informed consent cannot be overemphasised in the light of avoidance of civil liability for trespass to the person and criminal liability in the event of death or injury, says Leigh-Ann Mulcahy, a product liability and professional negligence specialist at 4 New Square, a London, UK-based commercial and civil set of barristers.

Speaking at the recent BIICL-sponsored Pharmaceutical Regulation and Product Liability Conference, Ms Mulcahy asserted that, regardless of any agreements to compensate, it would be wise for investigators and sponsors of clinical trials to seek to avoid liability for gross negligence in case of manslaughter in the event of death. "This is also relevant to ethics committees and to the [regulatory body] MHRA," she added.

There is undoubtedly a greater risk in relation to non-therapeutic research – where it is not of direct benefit to the research subject – that has been done in the public interest or in the interest of society, Ms Mulcahy suggested.

In situations where the issues of capacity to consent or volunteers' risk are in doubt, such as in children and the mentally ill, liability time limits are extended, she advised.

Ms Mulcahy pointed out that in the case of trespass to the person, a company is liable for six years instead of the usual three, after which action for negligence is barred. And there is no limit on going back and opening up criminal prosecutions in relation to events that occurred even up to half a century ago, Ms Mulcahy warned. ❊

EU is addressing the issue of class actions

"I is strictly speaking not within the competence of the EU to implement measures in the field of court procedure, however, we have seen some developments that help facilitate a collective action," says Ina Brock, a partner at international law firm Lovell's Munich office.

Speaking at the BIICL conference on pharmaceutical litigation, Ms Brock pointed to the Legal Aid Directive as one of these mechanisms that operated in cross-border cases. These are cases where plaintiffs who are not resident in one Member State sue a defendant in another Member State and are, under the terms of the Directive, able to obtain legal aid from the national Member States, Ms Brock explained.

In line with the Brussels Regulation on the jurisdiction, recognition and enforcement of judgments in civil and commercial matters – which replaced and modified the Brussels Convention – there are some European jurisdictions where you can bring actions in personal injury cases. Article 5.3 allows patients to sue the manufacturer at the place where the harmful event occurred. "Alternatively, they can sue a manufacturer under Article 2 at the domicile of the manufacturer," said Ms Brock.

The EU is also working on collective redress for consumers. The issue of class actions in product liability cases was first aired in the Green Paper on product liability in 1999 and came again recently in the context of damages for antitrust litigation and litigation involving small claims issues, which are rarely pursued in courts because of the low sums involved.

In 2005, the European Commission tendered its study on alternative means of consumer redress other than individual redress. It is set to evaluate consumer reactions to the forms of redress available and improvements will then be made. ❊

Risk/benefit of medicinal products must be subject to updates

In view of the fact that drug development has changed beyond all recognition in the last fifty years, it is important to bear in mind that regulation must always follow the science, says Peter Feldschreiber, who is both a barrister at 4 New Square and medical assessor at the MHRA.

Regulators now recognise that at the time of licensing, the risk/benefit profile of a drug may not be the same as when the product is in extensive use in the population at large, said Dr Feldschreiber. Speaking at the BIICL conference on pharmaceutical litigation, he advised that risk benefit be assessed intermittently during the life cycle of a drug.

"regulators now recognise that at the time of licensing, the risk/benefit profile of a drug may not be the same as when the product is in extensive use"

Because of developments in science, the rapid advances in regulations, the flood of new products onto the market and the number of innovative molecules created, new products and challenges arise Dr Feldschreiber warned. The withdrawal of some of Cox-2 inhibitors is as an important watershed in regulatory terms, he added. –The Vioxx issue has emphasised the tremendous importance of mandatory pharmacovigilance and risk minimisation by drug developers and regulators and that has now been enacted in legislation in the European Directives," he said.

At the same time, the perception of risk/benefit changing, Thalidomide – a drug that was sold during the late 1950s-1960s as a sleeping aid and antiemetic for pregnant women, but was later withdrawn when it was found to cause defects in foetuses – is now re-emerging. In 1998, however, it was approved for treating leprosy. It is now available for use off-label in HIV/AIDS related conditions, in new diseases and in cancer and current research involving Thalidomide includes research concerning Crohn's disease. "So here we have a drug that was pilloried but now is coming back as a very important therapeutic advancement," said Dr Feldschreiber.

He suggested that the current regulatory system may well have intrinsic defects in both structure and funds. In terms of structure, it may not be able to accommodate the requirements of consumer protection legislation as regards product liability. –There is a tension there between the different objectives of the regulator to assess risk benefit and the European Product Liability Directive, which imposes strict product liability on manufacturers of defective products," he warned. ❊

Swiss see rise in adverse incident reporting for vet drugs

Adverse incident reports to the Swiss medical products agency, Swissmedic, concerning veterinary medicines rose by a third – from 62 in 2004 – to 85 last year. The agency stresses that this comes not as a result of a rise in the number of incidents themselves, but is rather due to increased exploitation and simplification of the reporting system, as well as the provision of more comprehensive guidance information to veterinary professionals and manufacturers.

The system has only been in place for three years, but Swissmedic is convinced that last year's figures are proof that it is now operating successfully. In 2005, for the first time, it received more reports from practising veterinarians rather than from companies. The number of reports distinguished by preparation group followed the same trend as previous years, says Swissmedic, with the largest proportion linked to antiparasitics. 73% of reports were related to adverse incidents involving pets. ❊

Sweden and US authorities agree on data exchange

The Swedish medical products agency, Läkemedelsverket, has signed an agreement with its US counterpart, the FDA, to exchange non-published information. The move comes as part of a major effort by the US agency to establish mechanisms with other medicines authorities to facilitate the exchange of health information, said the FDA's acting commissioner of food and drugs, Andrew von Eschenbach.

Data that may be considered for exchange includes product safety information that could result in regulatory measures being implemented in both Europe and the US, says Läkemedelsverket. It could also apply to information on the implementation of new laws, or internal agency decisions. Läkemedelsverket adds that the agreement also aims to circumvent time differences between the two continents that have hitherto proved an obstacle to agencies' interaction.

Läkemedelsverket Director General Gunnar Alvan said that the agreement, which immediately operational, represented a milestone and was an indication that the processes for the authorisation of medicines and pharmacovigilance were becoming more international. ❊

Russian authorities clamp down on illegal advertising practices

The Russian Federal Antimonopoly Service of the Russian Federation (FASRF) and the Federal Service of Surveillance in Health and Social Development (FSSHSD) have recently signed a co-operative agreement related to tracking down and preventing illegal advertisement practices in the field of healthcare.

Under the terms of the agreement, the parties of the agreement decided to organise mutual consultations and exchange data, information and documents concerning illegal practices in advertising.

The FASRF will inform the FSSHSD of any breach of the law committed by companies or individuals in this field and will provide access to any data related to such activity, unless they are strictly confidential.

The FSSHSD, among other things, will grant its counterpart the access to information on pharmaceuticals and medical devices registered in the Russian Federation. The agreement is valid for three years. ❊

Polish drug reimbursement change to benefit patients

The reduction in the official prices of reimbursable drugs in Poland is expected to cut the National Heath Fund's (NFZ) annual expenditure by PLN400,000,000 (€101,173,000) and patient spending on pharmaceuticals by PLN210,000,000 respectively. These levels of savings will be reached thanks to the health minister's ordinance on reimbursable pharmaceuticals which is expected to be implemented shortly.

The reduction is due mainly to the currency appreciation and will cause a 13% price decrease in drugs imported into Poland. The price alterations will be followed by changes in the levels of reimbursement limits, which are set by the health ministry in every therapeutic category and indicate the maximal levels of reimbursement in a given category. In order to reflect the official price alterations, most limits are going to be lowered, and only a small number of limits will increase.

The lowered limits are expected to result in a minor increase in patient expenditure on drugs, particularly if patients refuse to switch to a cheaper generic substitute available in a given therapeutic category. However, the combined effect of changes introduced in drug pricing and reimbursement levels will have a positive influence on both patients' and the NFZ's finances, said a health ministry spokesmen. It is believed that it will contribute to the reduction of the average official price of reimbursable drugs by 7.8%. ❊

Changes to Bulgarian transplant law will speed up procedures

Every Bulgarian citizen is to be considered a potential organ donor, unless the opposite is stated in his official health records according to plans set out by the ministry of health.

The ministry is currently working on amendments to the organ transplant law. These changes will shorten the waiting period for the reception of a donor organ and will speed up the requisite decision process. According to the existing law, implemented in January 2004, potential donors require a written declaration clearly stating that they are willing to donate their organs. If a donor does not have this declaration, the individual's relatives will be called upon to consent to donation, which could significantly slow down the process of organ retrieval. In addition to this, the process itself of granting consent by a donor or relatives is complicated and time-consuming.

There is no current indication as to when the new law will be discussed by the parliament. ❊

The Charter of Rights: a legal boost for Polish healthcare staff

Polish Minister of Health Zbigniew Religa has announced that the Polish government will draw up its first Health Service Staff Charter. The statute will help the employees of the National Health Service to enforce their rights.

The petition for the Charter has been handed over to the government by the Tripartite Commission for the National Health Service which is made up of representatives of the government, employers and trade unions. During a recent press conference, Mr Religa informed journalists that Polish Prime Minister Kazimierz Marcinkiewicz will shortly appoint an interdepartmental commission composed of the representatives of the ministries of health, finance and labour, healthcare organisations and trade unions to work on a draft of the Charter. The Commission will attempt to create a document that clearly states the rules and principles of employment and remuneration in the public health sector.

However, in order to draw up the Charter, it is necessary to issue an act with a view to increasing salaries in the healthcare sector. At the moment various health authorities are being consulted on the draft proposal and it may soon be discussed by the Polish parliament. There is currently no indication as to when either the Charter or the Act will be ready, but Mr Religa is optimistic and hopes they will be implemented shortly. ❊

Changes in Polish pharmaceutical law will help to cut the NHF expenditure on reimbursible drugs

Drug manufacturers in the Polish market are to be forbidden from offering discounts or varying prices to different pharmacies or wholesalers. Also, pharmacies will no longer be able to sell drugs at promotional prices, often as low as "1 eurocent". These are just a few of the many changes which the Polish government is going to introduce in the pharmaceutical law.

...penalties for corruption

The prohibition will apply to drug manufacturers, importers, wholesalers and pharmacists with penalties for non-compliance. Any dishonest practices will be penalised. Those, who derive financial profit from selling reimbursible medicines at "rock-bottom" prices may be fined or imprisoned for up to three years. Where a company or an individual has been profiting from such activity on a regular basis, a five-year prison term may apply.

Another change discussed by the government is a move to grant the National Health Fund (NHF) the right to inspect trade agreements concluded between the participants of the pharmaceutical market. If pharmacy managers refuse to comply with this rule, they may lose the right to run an outlet.

The amendments will make it impossible for pharmacies to use price-promoting strategies and instruments when it comes to drugs reimbursed by the NHF. Currently, many pharmacies sell reimbursed drugs at a symbolic price below 1 eurocent. The price encourages patients to buy reimbursed drugs in larger amounts. This, in consequence, allows pharmacies to increase their turnover and receive significant discounts from manufacturers and wholesalers.

...public to suffer

The NHF authorities stress that the real cost of such promotions is borne by the agency itself, with its expenditure on reimbursement increasing every year. Last year, the agency spent PLN205,000,000 (€53,000,000) more on reimbursement than in 2004. The NHF authorities argue that patients do not actually save any money because, in the end, the agency and its expenditure is financed from health insurance premiums paid by the Polish citizens.

Meantime, pharmacy owners fear that the new regulation could worsen their economic situation and increase drug prices up to 10%. ❊

Revised German Medical Devices Act ready this year

Germany's federal cabinet is set to update the Medical Devices Act (MPG) before the August summer recess with a view to obtaining parliamentary approval by the end of the year. This was the message delivered recently by Wilfried Reischl, director of the medical devices expert division at the federal ministry of health, to delegates at the medical devices industry association (BVMed) conference on the MPG in Wiesbaden.

Mr Reischl also spoke of the need for a fundamental revision of the medical devices operator ordinance (MPBV) which regulates the setting up, operation and application of medical devices. The expert draft of the revised ordinance, which should be available by summer 2006, is aimed at cutting bureaucracy and achieving deregulation. It has been compiled with the co-operation of a working group comprised of the federal and regional state authorities.

At a European level, the review of the Medical Devices Directive is likely to have a significant impact on the medical devices sector. It is now clear that software will now been included in the definition of a medical device, said Mr Reischl. –Furthermore, a quality management system for Class I medical devices is set to be introduced. Germany remains the only country to be sceptical of this measure," he added.

There was hope that political agreement could be achieved under the Austrian presidency of the EU, which is set to end in June 2006, however, this is no longer a likely scenario, Mr Reischl said. He believes that unity can be achieved on the issue by the time Germany has acceded to the presidency in the first half of 2007.

Enterprise and Industry Commissioner Günter Verheugen's plans to cut regulatory red tape are also likely to have a significant impact on the medical devices sector" Said Mr Reischl. The same can be said of attempts to revise the "New Approach" to regulation. "What is being discussed more often is the setting up of only a framework of regulation by the Commission and more self commitment to regulation by industry," a spokesperson for BVMed told *EURALex*. There will also be an increased focus on a "risk-based" safety approach. ❊

Will a change to the German medtech aids register speed up procedures?

The German medical technical aids register (HMV) lacks the necessary legal clarity to fulfil its role as a steering mechanism for the market. Whereas the register should simplify the provision of care, it is often viewed by industry and healthcare providers as a bureaucratic impediment.

These were the views put forward by Hans-Georg Will, Director of the medtech aids department at the federal ministry of health at a recent MedInform conference, hosted by the German medical technology association, BVMed, in Bonn. Professor Will said that problems with the register were compounded by disparities between the aims of the two legislative bases for the mechanism, namely the medical products act (MPG) and the Social Law Code V (SGB V).

The MPG advocates the free of movement of goods, as well as the functionality and safety of products, whilst the SGB V focuses on the therapeutic benefits. However, in order for a product to qualify for inclusion in the register it must show evidence of efficacy, quality and therapeutic benefit.

…understanding is key

Essentially it is the interpretation of "therapeutic benefit" that creates the confusion. Health insurance funds maintain that when a product is granted a CE-mark – required by the MPG – this is simply evidence that it functions according to its specifications and that it is safe. However, the mark says nothing about the therapeutic benefit of the product, they claim.

When it comes to providing reimbursement for the medtech aids in accordance with the regulations laid down in SGB V, it is essential that evidence of therapeutic benefit is provided. Therefore, health insurance funds have demanded that, in addition to the CE-mark, more information and documentation is provided concerning the product.

But Class I medical devices – which represent the lowest risk – fall under the category of "self-certification", meaning that companies themselves can offer proof of their efficacy and safety. However, health insurance funds increasingly demand that this certification is carried out by an independent body. Professor Will opposes this type of approach. "Essentially, evidence required for the granting of a CE-mark should not be systematically demanded again by the health insurance funds," he maintained.

…variety of opinions

BVMed acknowledges that there are differing views in Germany on this practice, but it supports Professor Will's demand for clarity. He is adamant that the law must define which additional requirements by health insurance funds are permissible and which are not. Furthermore, he remains convinced that, once the legislation has been rendered less ambiguous, then processing times for adopting a medtech aid into the register could be shortened significantly, to three months.

The question remains as to whether the register will actually be revised to offer the legal clarification demanded by medical device manufacturers and if so when this could be expected. "We are quite optimistic, but it will probably not be part of the healthcare reform that we are discussing at the moment in Germany; it will be part of the additional regulatory effort of the government later on," a spokesperson for BVMed told *EURALex*. ❊

Poland introduces new organ donation regulations

A recent decree issued by the Polish health ministry details health requirements of potential organ donors, medical examinations to which they must be submitted, and contraindications that would render inadvisable the procurement of cells, tissues and organ donations. The regulation has been introduced with respect to the law on the donation and procurement of cells, tissues and organs, implemented in July 2005, and is aimed at providing a clear guideline during the medical assessment of a potential donor.

The regulation stresses that data concerning potential donors should provide evidence that the donation and procurement of organs would pose no health risk to either donor or recipient. In order to obtain such information, the donor must be submitted to a detailed medical examination followed by a doctor's interview. The examination will include morphological and biochemical blood analysis, a urine test and an ultrasound scan of the kidneys or the liver.

The statement of the doctor who performs the examination must include a sentence stating that "there are no contraindications that would prevent the procurement of cells, tissues or the organ", or that the examined person may not be considered as a potential donor. ❊

Sweden warns against unauthorised slimming product

The Swedish medical products agency, Läkemedelsverket, is throwing its efforts into combating a large-scale, illegal advertising campaign for a suspect weight-loss product called Ephidril. In recent weeks, Swedish households across the country have received flyers concerning the unlicensed, untested product, void of comprehensive details concerning the manufacturer.

The product claims to be 100% natural and guarantees a weight reduction of 8-12kg within four weeks. The advertisement claims that this is achieved through –reversing the calorie effect and significantly stimulating basal metabolism, which is responsible for burning fat". Läkemedelsverket stresses that there is as yet no evidence to support such a claim and no indication regarding possible side-effects.

The product can be obtained through Danshop, a business that has previously promoted slimming products through misleading advertising campaigns. However this represents a potential problem for probable damage-limitation activities undertaken by Läkemedelsverket in that the company operates from abroad. ❊

Czech President vetoes healthcare bill

A bill establishing a network of non-profit hospitals in the Czech Republic has been vetoed by President Vaclav Klaus. He argued that the Bill in its current form destabilises the healthcare sector and is opposed by doctors and patients. The Bill has also been rejected by the Senate (Senát).

President Klaus insisted that the new law denies basic principles of the democratic system such as the respect to private ownership or the freedom of choice regarding doctors or health facilities. The Bill creates a network of 146 public non-profit health facilities in which health treatment would be automatically paid for by insurance companies operating in the Czech Republic. This means, however, that hospitals not willing to join the non-profit network would only receive reimbursement for acute treatment, and patients would have to pay for any additional treatment provided by such hospitals. According to Czech health minister David Rath, the new law would help to protect hospitals and the healthcare system against the unforeseen consequences of privatisation. Critics of the Bill argue that the implementation of the law would mean *de facto* bankruptcy and closure for the facilities that do not join.

The Bill has been under discussion since November 2004. After being rejected by both the Senát and the President, it will return to the Lower House of the Parliament (Poslanecká snemovna). The Social Democrats and the Communists, the two parties supporting the Bill, have the majority in the Lower House, therefore the President's veto is likely to be rejected, and the new law will be implemented before the general election in June 2006. ❊

Aldecin and Inflammide withdrawn from the Czech pharmaceutical market

As alternative drugs become more available, Aldecin and Inflammide 0.1mg and 0.2 mg, drugs which contain chlorofluorocarbons (CFCs) are being withdrawn from the Czech pharmaceutical market in accordance with EU Regulation 2037/2000 on substances that deplete the ozone layer.

Pharmaceuticals containing CFCs may only be withdrawn after an alternative drug has been introduced into the market. This ensures that patients' health is not put at risk.

An alternative for Aldecin has been available since 2005. Currently, the manufacturer of the withdrawn drug is in the process of negotiations with the ministry of environment and the EU Commission as to whether it is still possible to sell the remaining volume of the drug that was originally manufactured to fulfil the EU quota.

With regard to Inflammide 0.1mg and Inflammide 0.2 mg, an alternative drug is currently being introduced into the market. This ends the exemption period granted for the drug in accordance with the EU strategy aimed at the elimination of pharmaceuticals containing CFC substances. The Czech government has announced that further distribution of the drug is prohibited, and from July 2006 the drug cannot be offered for sale in pharmacies. ❊

The Czech Republic: Chamber of Pharmacies and the Office for the Protection of Competition will meet in court

The Czech Chamber of Pharmacies will appeal a decision of the Office for the Protection of Competition (UOHS) that saw the Chamber penalised for a breach of the competition protection law, and fined CZK300,000 (€10,560).

In accordance with rules laid down by the Chamber, pharmacies are not allowed to advertise their activities, outlet locations or drug prices anywhere, except on their premises. A pharmacy would therefore not be permitted to advertise its existence or services in any other location. According to Martin Pecina, the President of the UOHS, this situation causes a "protective zone" to be created, where a pharmacy does not have to compete with similar outlets in order to attract customers. Furthermore, customers cannot access information that allows price comparisons to be made between pharmacies.

The Chamber was also fined for issuing a ban forbidding pharmacies to carry out price promotions and distribute price coupons among their customers. The UOHS is concerned that, by this regulation, the Chamber is trying to control drug prices in the pharmaceutical market and is maintaining higher prices, in breach of competition law.

...customer choice is wide

The Chamber authorities counter that all the information customers may need is available on pharmacies' premises, so customer choice is not limited. With regards to the problem of price coupons, president of the Chamber Lubomír Chudoba believes that such promotional activities could cause customers, influenced by a reduced price, to buy a drug they do not actually need or in larger quantities than necessary.

The Chamber intends to approach the administrative court within the next three weeks. ❊

MHRA cracks down on illegal sale of medicines over the web

The UK's regulatory agency, the MHRA has mounted a co-ordinated operation across the country against a number of premises connected with the illegal sale of medicines over the internet.

Having investigated 27 websites linked to this practice, MHRA enforcement and intelligence officers seized unlicensed medicines, computers, documents and cash. Police accompanying the officers also made a number of arrests in connection with offences under the Misuse of Drugs Act. The websites in question have now been closed down, says the MHRA.

The agency views the illegal sale of medicinal products over the internet as not only an increasing European, but also a global problem. "We work and share intelligence with our counterparts in other countries on these issues and we are now putting a lot of effort into this particular area of our work," a spokesperson for the MHRA told *EURALex*.

The agency is also concerned that the web-based sale of illegal products is becoming increasingly linked with organised crime both in the UK and abroad. "Clearly there are websites that are based overseas; where we come across them, we refer them to our counterparts in those particular countries," the spokesperson said.

And in addition to its vigilance in this area, over the past year, the MHRA has been working to raise public awareness about the issue of buying medicines over the internet. "There are legitimate online pharmacies and people can check whether there is an authentic website by speaking to the Royal Pharmaceutical Society," the spokesperson advised. ❊

TCM alert sparks herbal medicines concern for MHRA

Having received suspected adverse drug reaction reports linked to polygonum multiflorum – a root tuber used in traditional Chinese medicines (TCMs) as an anti-ageing remedy and to treat hair loss – the UK's MHRA has issued a warning about its potential risks and those of herbal medicines.

Reports suggest that the products containing the substance could cause liver disease and the MHRA has therefore advised patients experiencing associated symptoms to see a doctor immediately. Also known as He Shou Wu, the substance may be present in Shen Min, Shou Wu Pian and Shou wu wan hair products.

Assumptions by the general public that herbal medicines – the class to which polygonum multiflorum belongs – are risk-free, are a cause for concern, said the MHRA's head of herbal policy, Richard Woodfield.

"At the end of the day, traditional Chinese medicinal products fall under herbals, and for these a registration scheme will come into force in 2007," a spokesperson for the MHRA told *EURALex*. Companies wishing to register products will need to supply evidence of safety, quality and traditional use of the remedy. This measure stems from the UK's implementation of the Traditional Herbal Medicinal Products Directive (Directive 2004/24/EC) and represents a –significant improvement in legislation", because hitherto, unlicensed herbal remedies in the UK have not had to meet set standards for safety, quality and consumer information, said the MHRA. ❊

Compulsory licensing adopted despite German concerns

The abstention of the German delegation to the European Council failed to dent prospects for countries suffering from public health problems to acquire swift access to patented medicines. In its first reading, the Council adopted a Regulation on compulsory licensing for these products for export to countries hit by affected by serious health-related emergencies – such as the advent of avian flu – in cases where they are unable to manufacture medicines locally.

The German delegation said that, whiles it recognised and supported the Doha Declaration on the Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) and public health adopted by the WTO, it was concerned that part of the Regulation went beyond the internationally binding framework established by the WTO General Council. "Germany abstains because of these concerns," it added.

"the German delegation said it was concerned that part of the Regulation went beyond the internationally binding framework established by the WTO General Council

But the measures adopted by the Council can be viewed as a triumph for the co-operative approach taken by the Council and the European Parliament. Both parties agreed to extend the European Commission's original proposal to include a broader range of eligible countries. The Commission itself had urged Member States to adopt the Regulation, which in essence implements a World Trade Organisation (WTO) agreement of December 2005, under which national authorities may grant compulsory licences, if certain conditions are fulfilled by candidate countries.

The WTO decision amended the TRIPS agreement. Hitherto, intellectual property regulations have ensured that such licences could only be granted for domestic markets.

The agreement, however, does not appear to be the end of the road in terms of a global agreement. Although the Regulation will be in place 20 days after its publication in the Official Journal – and will therefore be binding on EU Member States – the amendment to the TRIPS agreement may only enter into force once two-thirds of the WTO membership have consented to it. They have agreed to aim for an agreement by 1 December 2007. ❊

New Slovak pharma code targets advertising

The Slovak Association of Distributors of Drugs and Medical Aids (ADL), the Association of Generic Medicine Producers (GENAS) and the Association of Research Based Pharmaceutical Companies (SAFS) have joined forces to introduce a new Code of Conduct for the Pharmaceutical Industry, which lays down standards for the marketing of prescription-only medicinal products.

...code offers guidelines

Although the advertising of prescription drugs to the general public is forbidden in the Slovak Republic, the promotion of these drugs to healthcare professionals is permitted, in order to ensure that all necessary information that may influence their prescribing decisions is available. The Code is aimed at providing the industry with guidelines related to this type of marketing.

The Code ensures that when a promotional claim is made for a drug, it is always backed up by either full or abridged product information. Also, a drug manufacturer must ensure that data provided in support of a drug claim are correct and accurate. According to the Code, information cited in advertising material must be made available to healthcare professionals upon request and supplied within ten working days. The authors of the Code stress that any promotional activity should encourage the rational use of a pharmaceutical and present this objectively.

Upon receiving a written request, drug samples may be distributed to doctors by pharmaceutical companies. This is however restricted to two samples of any particular drug per annum. According to the Code, this would allow physicians a certain amount of time with which they may familiarise themselves with the medicine.

...additional areas

The Code also covers other potential drug marketing and promotion issues, such as those linked to comparative statements and the imitation or employment of a medical professional during a promotional campaign. Other areas addressed by the code include research that involves or is sponsored by the pharmaceutical industry; industry's relations with the public, media and healthcare professionals; and marketing over the internet. ❊

Slovak Republic close to implementing Braille requirements

Subject to authorisation by President Ivan Gasparovic, drug manufacturers in the Slovak Republic will be obliged to place the names of drugs in Braille format on the packaging, in accordance with the amended Act on pharmaceuticals and health supplies.

The revised law is based on Directive 2001/83/EC on the community code relating to medicinal products for human use. It will apply to all drugs introduced into the market after November 2005. Manufacturers of products where the marketing authorisation precedes this date have not been given any specific time constraints to adjust the packaging. However, the government estimates that they should be able to meet the new requirements within three years.

Drugs that are only intended for administration by health professionals, are veterinary products, or are used during blood transfusion may be exempt from coverage by the amended law, says the ministry of health.

Health ministry spokesman Karol Farkasovsky told *Euralex* that Parliament had already enacted the amended law, and that it is due to be signed by the President in the near future. ❊

Slovak authorities introduce stricter law on organ donation

Activities related to the donation and procurement of organs, tissues or cells, their preservation, testing, storage, transport and distribution for use in transplantation or scientific research, may only be carried out by specially accredited healthcare providers, according to the amended law on healthcare enacted by the Slovak parliament.

The amendments mainly concern tissue banks and biobanks. The law states that any person involved in handling human tissues and cells should file a report to the healthcare provider with whom they are working in order to ensure traceability, safety and quality control. Any procured organs, tissues or cells will undergo a special examination before further use and may be quarantined if necessary. The results will be recorded in the health documentation of a donor.

The healthcare provider will be obliged to establish and maintain a register, which would allow the origins of all tissues and cells to be traced within the territory of the Slovak Republic, as well as records to be maintained concerning their use. It will also be obliged to store the information for at least 30 years. Healthcare providers who wish to import tissues or cells from other countries will be required to obtain a separate licence. The amended act will be implemented on 1 June 2006. ❊

German abstention in devices QMS vote was well-founded

Germany is the only one of the 25 Member States not to have voted in favour of the introduction of a quality management system (QMS) for Class I medical devices. Wilfried Reischl, Director of the medical devices expert division at the federal health ministry told *EURALex* that his country's abstention during the vote was considered and logical.

One of the tasks of the German representation in the European Council's working group on medicines and medical devices is to review policies to determine whether they will cut bureaucracy or introduce more. "Only if it serves to optimise the regulations that have an impact on the safety of medical devices – such as improved clinical trials guidelines – do we agree to increased bureaucracy," Mr Reischl explained.

Germany does not see any noticeable advantage in terms of safety for consumers by the "abstract demands" for the introduction of a QMS for Class I medical devices, he added. On the other hand, the ministry of health is concerned that such a measure would lead to additional costs that must be financed by the respective Member States' health systems. "Hitherto, there has been no evidence provided by the proponents of the legislation that the amendment would lead to increased patient safety," he said.

Furthermore, Germany views the potential introduction of the QMS as being prejudicial towards European manufacturers. "Whereas via a greater – and more expensive – emphasis on monitoring the introduction of a quality management system for Class I medical devices can for the most part be guaranteed amongst European manufacturers, it cannot by any means be certified for manufacturers outside Europe," Mr Reischl complained. He argued that, as long as no parallel system for a global QMS was in place, European manufacturers of Class I medical devices would be at a competitive disadvantage. ❊

New Swedish herbals law amends application procedure

Amended regulations for herbal medicinal products were introduced in Sweden this month and are based, among others, on EU Directive 2004/24/EC. The new law means that the medicinal products agency, Läkemedelsverket, can no longer approve herbal-based products as natural remedies, namely medicinal products containing active ingredients derived from natural sources, including parts of plants or animals, bacterial cultures, minerals, salts or salt solutions.

the medicinal products agency, Läkemedelsverket, can no longer approve herbal-based products as natural remedies

As a result, companies seeking approval for herbal medicinal products now have a choice between two application procedures. The first is an application for a so-called traditional herbal medicinal product (THMP). This is a medicine that contains: exclusively one or more herbal-based components; one or more herbal-based components as active ingredients; or one or several of these components in accordance with paragraph 2c of the Swedish Medicines Act. A simplified registration procedure is in place for traditional herbal medicinal products in line with Directive 2004/24/EC. "This is not an approval, which is the case for regular medicinal products," says Läkemedelsverket.

The second procedure applies to herbal medicinal products (HMPs) and, as with conventional medicines, requires a full application or bibliographic documentation. Läkemedelsverket points out that the relevant application route for various products is often dependent on the documentation that can be made available during the application process.

The health ministry has published a draft proposal concerning the transition period for those herbal medicinal products that were previously approved as natural remedies until 31 March 2006. This envisages that, as long as a registration for a THMP or an authorisation for an HMP has been sought by 1 April 2008, the products may continue to be sold as natural remedies. If neither of these has been applied for, then Läkemedelsverket will consider any sales authorisation to have been invalidated. ❊

Delayed Belgian AED law making progress

Local councils and public sports associations pressing the Belgian government to make automatic external defibrillators (AED) available for use by non-medical personnel may have to wait a little longer.

A proposal to authorise this practice is on its way back to the parliament's Chamber of Representatives (Lower House), following amendments in the Senate (Upper House). Furthermore, the ministry of social affairs and public health is working on a legislative decree with a view to setting safety standards and other standards applicable to the use of AEDs in connection with resuscitation.

Dirk Cuypers, President of the executive committee of the federal public health service, has warned that, until the measures under consideration are officially authorised and published, access to AEDs must remain in the hands of the emergency services. At a later date, there are also plans – should the law be passed – to ensure that each time a publicly-installed defibrillator is used, an automatic message will be relayed to the emergency services.

"The draft royal decree also envisages a registration obligation," he added. It is therefore imperative that each regional public authority maintains an up-to-date list of all AEDs installed in public places, together with details of the owner, who will be responsible for the maintenance of the equipment.

"The use of manual defibrillators, or AEDs that function manually, remain in essence the prerogative of doctors on the basis of requisite medical know-how," said Mr Cuypers. Public authorities will be required to monitor the use of AEDs in order to ensure that guidelines will continue to be respected. ❊

Conferences/Meetings/Courses

1-2 June 2006

EU Regulatory Response to Innovation and Global Competitiveness
Lisbon, Portugal. Call RAPS on +1 301 770 2920

7-8 June 2006

Global Protein Summit
London, UK. Call SMI on +44 (0) 20 7827 6000

12-13 June 2006

Dosage Forms – EU Licensing and GMP Regulatory Procedures
Prague, the Czech Republic. Call Management Forum on +44 (0) 1483 730071

19-21 June 2006

Basic Course on Pharmacovigilance
London, UK. Call Management Forum on +44 (0) 1483 730071

19-21 June 2006

The 9th IGPA Annual Conference
Monte Carlo, Monaco. Call GPA Conferences on +377 93 50 1348

20-21 June 2006

Export and Import in Pharmacy Sector – Regulations and Practice
Warsaw, Poland. Call Top Consulting Poland on +48 22 438 93 94

26 June 2006

GCP for Investigators and Study Site Professionals
London, UK. Call Management Forum on +44 (0) 1483 730071

26-27 June 2006

Regulatory Science – Legislation, Guidelines & Procedures in Europe
Amsterdam, Holland. Call Management Forum on +44 (0) 1483 730071

26-29 June 2006

Transmissible Spongiform Encephalopathies
Vienna, Austria. Call IBC LifeSciences on +44 (0) 20 7017 5758

27 June 2006

Effective Monitoring Visits
London, UK. Call Management Forum on +44 (0) 1483 730071

27-28 June 2006

The Evolving Regulatory Framework for Herbal Medicinal Products
Vienna, Austria. Call IBC LifeSciences on +44 (0) 20 7017 5758

28-30 June 2006

EFPIA Annual Meeting 2006
Prague, the Czech Republic. Call EFPIA on +32 2 626 25 77

28-30 June

Implementing REACH
London, UK. Call IBC LifeSciences on +44 (0) 20 7017 5758

29-30 June 2006

Biosimilars
Zurich, Switzerland. Call IBC LifeSciences on +44 (0) 20 7017 5758

29-30 June 2006

Pharmaceutical Regulatory Affairs in Russia, Belarus and Ukraine
London, UK. Call Management Forum on +44 (0) 1483 730071

Conferences/Meetings

The major meetings of the European Medicines Agency in May are as follows:

01 June 2006
Committee for Human Medicinal Products (CHMP)

08 June 2006
Management Board (MB)

13-15 June 2006
Committee on Orphan Medicinal Products (COMP)

20-22 June 2006
Committee for Veterinary Medicinal Products (CVMP)

22-23 June 2006
VCo-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMD (v))

26-27 June 2006
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD (h))

26-29 June 2006
Committee for Medicinal Products for Human Use (CHMP)

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