Legal and regulatory update

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Legal and regulatory update

EU HEALTH MINISTERS REACH AGREEMENT ON THE COMMISSION'S PROPOSALS FOR PHARMACEUTICAL REFORM

On 2nd June, 2003, the Health Council adopted, with a qualified majority, a political agreement regarding the European Commission's proposals for a new Regulation to replace existing Council Regulation 2309/93 concerning the centralised marketing authorisation procedure and the European Agency for the Evaluation of Medicinal Products (EMEA), and a Directive to modify Directive 2001/83/EC establishing a Community Code on medicinal products for human use. The proposals for the new Regulation[1] and Directive[2] were finalised on 12th June, 2003.

With regard to the proposed replacement for Council Regulation 2309/93, one of the most important changes will be in the scope of the mandatory centralised marketing authorisation procedure. While biotechnological medicinal products (ie those developed by means of recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes or eukaryotes, including transformed mammalian cells, or hybridoma and monoclonal antibody methods)[3] are already required to take the centralised route, the new Regulation introduces a further category of products which must do the same.

This new category[4] is to include all medicinal products for human use containing a new active substance for which the therapeutic indication is the treatment of AIDS, cancer, neurodegenerative disorders or diabetes. Moreover, it is proposed that this additional category should be capable of review via a simplified decision-making procedure, although not before the expiry of four years from the date the Regulation comes into force.[5] There is therefore the possibility that further diseases may be added to this list at a future date. It should be noted that the Commission had originally proposed that all medicines containing new active substances should be centrally authorised but it was agreed that the current choice available under Council Regulation 2309/93 of either the centralised or a decentralised route for other non-biotechnologically derived products should remain.

The second important aspect of the agreement reached by the Health Council concerns the protection period available for preclinical and clinical trial data. With regard to generic products, Article 5(7) of the proposed Directive will replace Article 10 of Directive 2001/83/EC with a new Article 10. Paragraph 10(1) will permit generic manufacturers to rely on the preclinical and clinical trial data of reference products authorised under Article 6 after only eight years from authorisation of the reference product. The Article prohibits the placing of such generic products on the market until ten years after authorisation of the reference product has expired. This reflects the position of the European Parliament in its proposed Amendment 34 in the Amended Proposal for a Directive amending Directive 2001/83/EC[6] reported in the last edition of the Journal, but represents a significant inroad into the 10 year period initially proposed by the Commission.

In the case of new reference authorisations, Article 5(8) of the proposed Directive inserts new articles 10a, 10b and 10c into Directive 2001/83/EC. Article 10a provides that the data protection period is to be ten years, although pursuant to Article 10(b), applications can be filed after eight years in accordance with the provisions of Article 10(1) (referred to above) for new preclinical and clinical trial data generated

for new products containing previously authorised substances in a previously unauthorised therapeutic combination. Article 10(c) states that authorisation holders may allow use of such data with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

The ten year protection period for preclinical and clinical trial data for reference products imposed by the Directive also applies to centrally authorised products[7] but may be extended for products that are subject to mandatory authorisation following the centralised procedure. The Regulation proposed to supersede Regulation 2309/93 provides that the medicinal products for human use appearing in Annex I (as described above) may benefit from an additional one year of protection if, during the first eight years of protection, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring significant clinical benefit in comparison to existing therapies.

Although not all of the Commission's proposals were followed by member states at the meeting of the Health Council, the European Commissioner for Enterprise (Erkki Liikanen) has stated[8] that the agreement reached is a 'well balanced compromise' and that it represents 'an important step towards ensuring that Europe gets a more robust, modern, effective and competitive regulatory framework for pharmaceuticals'. The next step will be to discuss these latest proposals for pharmaceutical reform with the European Parliament with a view to formal adoption of the new regulatory framework by the end of 2003.

ARTEDOGAN[9] REVISITED

The case reported in Vol. 9, no. 3 of the Journal regarding the fate of various amphetamine-like anorectic agents[10] has now come before the ECJ. To recap, concern was initially voiced by the German authorities about the safety of such drugs,[11] which are known to be cardiotoxic and capable of precipitating primary pulmonary hypertension, both of which may be fatal. This led to a referral by the Federal Republic of Germany to the Committee for Proprietary Medicinal Products (CPMP) for its views on the matter pursuant to the procedure provided for in Article 12 Chapter III of Directive 75/319/EEC.[12]

The opinion that emerged from the CPMP as a result of this pursuant to Article 13 of that Directive was subsequently adopted by the Commission under Article 14 as a binding decision.[13] The result was that member states were ordered to amend the various Summary of Product Characteristics (SmPC)[14] for the drugs in accordance with the CPMP's opinion. Basically this required emphasis to be placed, *inter alia,* on the risk of treatment. The products themselves nevertheless remained on the market because of the lack of other suitable pharmaceuticals with the comparatively serious consequences of obesity going untreated.

Following further concerns raised by the Belgian authorities about sympathomimetic anorectics causing heart defects, the situation was reviewed by the CPMP under the Article 13 procedure.[15] The CPMP issued three opinions in this regard[16] advising that anorectics should no longer be authorised. The opinions were subsequently adopted by the Commission under Article 15a, resulting in the 'obligatory' removal of the anorectics from the market. However, this was successfully challenged by the relevant manufacturers in the Court of First Instance on the basis that the Commission had no competence to adopt a binding decision based on an opinion of the CPMP relating to nationally authorised products.

This was on the grounds that although there had been a degree of

'harmonisation' with regard to SmPCs for these products in 1996, this did not bring the products into the ambit of Article 15a of the Directive. Harmonisation on grant under Article 10 following the mutual recognition procedure does not equate to harmonisation following reference to the CPMP under Article 12. Article 15a applies exclusively to authorisations *granted* pursuant to Chapter III and the voluntary compliance by manufacturers of an otherwise non-binding adoption of an opinion given by CPMP does not change that fact. The CFI therefore ruled that competence remained with the national authorities for the management of the authorisations in question and the consequential annulment of the Commission's decisions to withdraw them.

Agreeing with the finding of the CFI on appeal, the ECJ has now held that since the 1996 decision merely ordered the partial amendment of certain terms of the authorisations, namely those required to be included in the SmPCs under Article 4a Directive 65/65, it cannot amount to a grant under Chapter III. Article 15a is not to be construed more broadly, as argued by the Commission, so as to amount to a follow-up procedure applying to any reference to the CPMP for an opinion under the provisions of Chapter III to prevent member states from adopting divergent measures. As such, it was considered to be of no importance whether the amendment was the result of voluntary compliance or that of a binding decision by the Commission. The appeal was therefore dismissed and the products in question will remain on the market for the time being.

COMMISSION PROPOSAL OF ETHICAL GUIDELINES FOR STEM CELL RESEARCH

On 9th July, 2003, the Commission adopted a proposal for guidelines to be adhered to in relation to stem cell research funded by the EU, in the form of the EU 6th Research Framework Programme (FP6 2003-2006). The proposal reflects the opinions of the European Group on Ethics (EGE).

It is important to note that these are not universal guidelines but are limited to EU-funded research. They do not impose any obligations on member states or undermine the existing member states' rules, since, under the current regime, no funding will be made available for research to be carried out in member states where research on stem cells is prohibited. They do not relate to the creation of human embryos for research purposes that are excluded from the scope of the framework programme. Further, the guidelines relate only to the derivation of stem cells from supernumerary embryos with no parental project which are a maximum of seven days old, frozen as a result of IVF treatment and donated by parents for research.

In addition to funding the creation of a European registry (with the goal of reducing the need for the derivation of stem cells from human supernumerary embryos in the future) and committing to encourage the promotion of sharing resources and results within European projects (with the goal of reducing the duplication of research), the Commission has proposed the following guidelines:[17]

- The EU will not fund human embryonic stem cell research where it is forbidden by a member state.

- Human embryonic stem cells can only be divided from supernumerary embryos that are donated for research by parents and that were created before 27th June, 2002, the date of the adoption of the Framework Programme and these embryos must be destined to be destroyed at some point in time.

- Potential research project partners applying for EU funding must seek ethical advice at national or local level in member states where the research will take place, even in countries

where obtaining such ethical advice is not mandatory.

- Research will be funded only when it is demonstrated that it meets particularly important research objectives.
- Research will be funded only when there is no adequate alternative available and in particular it must be demonstrated that one cannot use existing embryonic or adult stem cell lines.
- Supernumerary embryos will be used only if informed consent has been given by the donors.
- Embryo donors will not be permitted to make any financial gain.
- Data and privacy protection of donors must be guaranteed.
- Traceability of stem cells will be required.
- Research consortia will be required to engage in making available new human embryonic stem cells to other researchers.

These proposals form the ethical guidelines that the Commission agreed would be published during 2003 and will apply to EU-funded research projects involving the derivation of stem cells from human supernumerary embryos.

COMMISSION RESPONSE TO THE REPORT OF THE HIGH-LEVEL GROUP ON INNOVATION AND PROVISION OF MEDICINES ('G10 MEDICINES REPORT')

On 1st July, 2003, the Commission published its response to the G10 Medicines Report. It addresses the 14 recommendations made in the report by dividing them into five key themes as follows: benefits to patients; developing a competitive European-based industry; strengthening the EU science base; medicines in an enlarged EU; and member states learning from each other. The report describes the key tasks that are required to implement the recommendations of the G10 Medicines Report and sets out key actions and responsibilities for each part of the implementation.

The Commission emphasises the underlying importance of an EU-based pharmaceutical industry as being central to the healthcare systems and also to achieving social and public health goals. The Commission says that the industry should support new technology and seeks to link the industry to the wider EU economy with the aim that it should become 'capable of sustainable growth with more and better jobs and greater social cohesion'. The Commission went further, saying that both 'the Commission and member states must embrace new technologies, such as biotechnology'.

Overall, the Commission endorsed the G10 Medicines Report and its implementation; however, it said that implementation must balance the requirements of public health and competitiveness. The Commission set out measures to ensure the effectiveness of implementation of the Report. The process of monitoring implementation must be measurable, and while the G10 Medicines Report identified a mechanism for implementation, the Commission concluded that the indicators of the degree and success of implementation must be regularly updated (it suggests on an annual basis), be easily accessible and should support the exchange of best practice between member states. Looking forwards, the Commission suggested that the European Parliament and the Council should discuss them regularly. The Commission will establish a secretariat to work on the monitoring of the indicators and to support other work following the G10 Medicines Report. The Commission emphasised repeatedly its concern that

what it referred to as the momentum of the G10 Medicines Report should not be lost and that the development of 'the competitiveness of the pharmaceutical industry' should continue in the context of achieving high-level EU public health objectives.

ASTRAZENECA: MISUSE OF PATENT AND REGULATORY PROCEDURES FOR PHARMACEUTICALS?

The Commission has sent a Statement of Objections (SO) to Anglo-Swedish group AstraZeneca, which has allegedly misused the patent system and other regulatory procedures for the marketing of pharmaceutical products. The Commission believes that this was done abusively with the purpose of blocking or delaying market entry for generic products, in breach of Article 82 EC.

The first alleged abuse of dominant position concerns representations by AstraZeneca before a certain number of national patent offices with a view to obtaining supplementary protection certificates (SPCs) for the medicinal product LOSEC® (omeprazole). Towards the end of the 1990s, LOSEC®, a revolutionary treatment for stomach ulcers, had become the world's best-selling prescription medicine ever. SPCs extend the basic patent protection for medicinal products by a maximum of five years to take into account the period of time that may have elapsed between the filing of a patent application and the later authorisation to market the patented product. According to the SPC legislation, products such as LOSEC® which were already on the market when the legislation entered into force, were entitled to extra protection only if the first market authorisation in the EU was granted after certain cut-off dates. According to the Commission, AstraZeneca concealed from these patent offices the exact date at which it received its first marketing authorisation, thereby enabling AstraZeneca to obtain extra protection for LOSEC® in certain countries.

The second practice under scrutiny relates to the alleged misuse of rules and procedures applied by the national medicines agencies that issue market authorisations for medicinal products. In particular, the practice relates to AstraZeneca's switch of its LOSEC® capsules (the original formulation) for a tablet formulation (LOSEC® MUPS) combined with requests by AstraZeneca to certain national medicines agencies to de-register the market authorisations for the capsules. De-registration is relevant for generic producers because generic products can, in principle, only obtain a marketing authorisation and parallel importers can in principle only obtain import licences if there is an existing reference authorisation.

The Commission believes that both practices were intended to block or delay access to the market for generic versions of LOSEC® and that the second practice was also intended to prevent parallel imports of LOSEC® capsules.

The SO marks the opening of a formal antitrust investigation. AstraZeneca now has the opportunity to present its defence in writing and may, subsequently, request an oral hearing.

WORLD TRADE ORGANIZATION (WTO) COMPROMISE ON IMPORTS OF GENERIC PHARMACEUTICALS UNDER COMPULSORY LICENCE

The TRIPS general council has finally adopted a decision waiving article 31(f) of the TRIPS Agreement in respect of pharmaceutical products to allow the production and export of generic versions of patented pharmaceuticals under compulsory licence to least-developed countries and countries with no manufacturing capacity of their own for the drug. Article 31(f) previously

restricted compulsory licensing to production in order to supply the domestic market of the generic producer. The 2001 Doha Declaration on TRIPS and public health had called upon the TRIPS council to agree means by which this restriction could be changed in order to assist poorer countries to import cheaper generic pharmaceuticals and this decision is the result.

All WTO member countries are in fact eligible to import under the decision – provided that they are a least developed country or have insufficient or no manufacturing facilities for the drug in question – but 23 developed countries have announced that they will not use the system (including the EU member states, the USA and Japan) and 11 other territories have said they would only use the system in situations of national emergency or other circumstances of extreme urgency, namely Hong Kong, Israel, Korea, Kuwait, Macao, Mexico, Qatar, Singapore, Taiwan, Turkey and the United Arab Emirates.

The scheme is not limited to any particular disease and includes products obtained by means of a patented process. In order for the exporting country to issue a compulsory licence under the patent in question, the importing country must confirm to the TRIPS council the precise need for the product in question, its own intention to grant a compulsory licence and that it has insufficient or no manufacturing capacity for the product. The compulsory licence shall be restricted to meeting the needs of the importing country, shall require that the products manufactured shall be packaged, coloured or shaped in a distinctive manner and shall require that the manufacturer publishes details of the product to be supplied and details of the distinctive packaging.

The decision is accompanied by a statement by the TRIPS general council's chairman in order to address concerns of the USA that had caused it to veto the agreement originally reached by the other WTO members in December 2002. This confirms that the decision should be used in good faith to protect public health and not for industrial or commercial policy goals. It also draws attention to the fact that measures are include to prevent the diversion of product produced under these compulsory licences from their intended destination and gives examples of packaging used by branded pharmaceutical manufacturers for donated products, suggesting that a similar approach could be adopted in this context.

The decision contemplates a permanent amendment of TRIPS Agreement along the same lines as the current waiver and the amendment process will commence by the end of the year.

COMMISSION ACTION FOR NON-IMPLEMENTATION OF DIRECTIVE ON LEGAL PROTECTION OF BIOTECHNOLOGICAL INVENTIONS

The European Commission has referred Germany, Austria, Belgium, France, Italy, Luxembourg, the Netherlands and Sweden to the European Court of Justice for failing to implement Directive 98/44/EC on the legal protection of biotechnological inventions, which should have been implemented by 30th July, 2000. The history and aims of the Directive are well known and after adoption by the European Parliament and Council following a ten year debate, the Directive was subjected to an unsuccessful challenge that was rejected by the European Court of Justice (ECJ) in October 2001. Ultimately the ECJ could order financial sanctions against the member states that have failed to comply with the obligation to implement the Directive.

NOTES FROM THE USA

Courts narrow the 35 USC Section 271(E) patent infringement exemption for drugs and devices

Approved in 1984 under the 'Drug Price

Competition and Patent Term Restoration Act', commonly known as the Hatch–Waxman Act, 35 USC §271(e)(1) states that it

> shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

Legislative history suggests that the US Congress adopted the provision to permit generic drug manufacturers to seek regulatory approval of an otherwise infringing drug prior to the branded drug's patent expiration.[18] Notwithstanding its objectives, the language and structure of §271(e)(1) have presented persistent challenges to the courts. At best, the statute is described as 'awkward',[19] at worst as 'not plainly comprehensible'.[20] It is not surprising, then, that courts often wrestle with the scope and applicability of the safe harbour that the statute provides. In *Eli Lilly* the Supreme Court was asked what patented inventions fell within the scope of §271(e)(1), specifically whether the safe harbour pertained only to patents relating to drugs or whether it also covered devices.[21] There, the court upheld the Federal Circuit's ruling that the safe harbour was not limited to drugs, but rather extended to medical devices for which FDA marketing approval was necessary.

The continuing expansion of the safe harbour peaked in 2001, when a New York district court held that the use of patented intermediates and related analogues for drug research and for the creation of a structure–activity relationship database was exempted from infringement under §271(e)(1). In *Bristol-Myers Squibb Co. v Rhone-Poulenc Rorer, Inc.*,[22] the court found latitude in prior cases to read the term 'patented invention' broadly and to consider Bristol-Myers Squibb's use of that invention as reasonably related to seeking FDA approval.

That case sent shock waves through the pharmaceutical and biotechnology industry.[23–25] Many voiced concern over the court's interpretation of §271(e)(1) and sought clarification from the Federal Circuit. Such clarification came in the Federal Circuit's ruling in *Integra Lifesciences I, Ltd v Merck KGaA*.[26] There, the Federal Circuit upheld the district court's ruling that Merck's infringement of patents covering certain research technologies belonging to Integra was not exempted under §271(e)(1). In agreeing with the lower court, the Federal Circuit narrowed the application of §271(e)(1).

The facts of the case are straightforward. Merck conducted preclinical angiogenesis research using Integra's patented technology. This research did not produce information for submission to the FDA; instead, it led to additional research studies by Merck. Upon this evidence, the district court found Merck liable for infringement and denied its claim that such infringement was exempted under §271(e)(1).

On appeal, the Federal Circuit focused on the preclinical nature of the Merck research and its tenuous relationship to the direct production of information for FDA regulatory approval. Noting that the FDA has 'no interest in the hunt for drugs that may or may not later undergo clinical testing', the court was unwilling to allow protection of infringing behaviour that related to 'general biomedical research to identify new pharmaceutical compounds'. The Federal Circuit stated that §271(e)(1) 'does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process.' Nor, according to the court, did the safe harbour permit 'exploratory research that may rationally form a predicate for future FDA clinical trials.' Indeed, *in dicta* the court noted that any infringing activity that does not directly produce information useful to the

FDA's approval processes assessing the safety and effectiveness of drugs and other FDA-related technologies strained the safe harbour's central purpose. The court reasoned that extending §271(e)(1) to include such upstream research could 'effectively vitiate the exclusive rights' of biotechnology tool patentees. Thus, the court concluded that the reach of the safe harbour was much narrower than Merck, and perhaps other courts, had expected.

Owing to its ambiguous language and structure, the §271(e)(1) patent infringement safe harbour has for many years been difficult to measure. Notwithstanding the narrower interpretation offered by the *Integra Lifesciences* court, lingering questions about the future application of §271(e)(1) to research tools remain. Such uncertainties include the type of research that triggers §271(e)(1) and the type and amount of damages that courts can award to deter non-exempted patent infringement of research tools by pharma with large legal budgets. Future court decisions may shed additional insight with regard to these issues.

References and notes

1. 2001/0252 (COD), 12th June, 2003.
2. 2001/0253 (COD), 12th June, 2003.
3. Annex to Council Regulation 2309/93 Part A.
4. Annex 1, 1(3) of proposed Regulation.
5. Article 3(4) of proposed Regulation.
6. COM (2003) 163 final, 3rd April, 2003.
7. Article 13(8) of proposed Regulation.
8. DG Enterprise press release IP/03/785, 2nd June, 2003.
9. Case C-39/03. Appeal against the judgment of the Court of First Instance of the European Communities (Second Chamber, Extended Composition) 26th November, 2002, in joined cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T137/00 and T-141/00 *Artegodan & Ors v Commission* [2002] ECR II-4945.
10. Amfepromone, clobenzorex, fenproporex, norpseudoephedrine and phentermine.
11. Clobenzorex, norpseudoephedrine, phentermine, fenproporex, mazindol, amfepromone, phendimetrazine, phenmetrazine and mefenorex.
12. *Off. J.* 1975 L 147, as amended by Directive 93/39 EEC of 14th June, 1993, *Off. J.* 1993 L 214.
13. Commission Decision C(96) 3608 final/1 9th December, 1996.
14. Required by Article 4 Directive 65/65.
15. In respect of phentermine, amfepromone and other anorectics, *inter alia* clobenzorex, fenproporex and norpseudoephedrine.
16. 31st August, 1999.
17. DN: IP/03/969.
18. *See* H.R. Rep. No. 98-857(I), at 15 (1984) and H.R. Rep. No. 98-857(II), at 5 (1984). *See also*, *Eli Lilly & Co. v Medtronic, Inc.*, 496 US 661, 669–670 (1990).
19. Donald Chisum, Chisum on Patents, §16.03.
20. *Eli Lilly*, 496 US at 669.
21. *Eli Lilly*, 96 US at 672–674.
22. 2001 WL 1512597 (SDNY 28th November, 2001).
23. Stiefel, A. (2002), 'Right to Use Patented Research Tools Expanded' (detailing the implications of the district court's decision in *BMS I* on biotechnology companies) (URL: http://www.kayescholer.com/frames.html?http://search.atomz.com/search/?sp-q=stiefel&sp-a=sp1000ee1e).
24. Goldstein, J. A. (2001), 'Patenting the tools of drug discovery', *Drug Discovery World*, Vol. 9 (noting that the §271(e)(1) exemption is not limited to candidate drugs, but extends to research tools as well).
25. Jones, P. B. C. (2002), 'Navigating the Hatch–Waxman Act's Safe Harbor', *Food Drug L. J.*, Vol. 57, p. 475 (chronicling the development of an expansive interpretation of §271(e)(1)).
26. 2003 WL 21299492 (Fed. Cir. 6th June, 2003).