Legal and regulatory update

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VOLUNTARY WITHDRAWAL OF MARKETING AUTHORISATIONS AND CONSEQUENCES FOR PARALLEL IMPORTERS

Summary

When a reference marketing authorisation is withdrawn for reasons unconnected with the protection of health, as in cases C-15/01[1] and C-113/01,[2] it is not acceptable that a parallel import licence granted there under should automatically terminate unless an actual risk to public health can in fact be demonstrated.

Background

While Directive 65/65/EC states that no medicinal product may be placed on the market for the first time in a member state unless a marketing authorisation has been issued in that state, that is subject to the rules of the EC treaty relating to the free movement of goods. In particular, a parallel importer is entitled to import products marketed in one member state into another where that product is also authorised without having to apply for authorisation under Directive 65/65/EC. Although parallel importers may not be required to obtain such authorisation however, many states of import impose a simplified procedure requiring grant of a parallel import licence by reference to the primary authorisation under Directive 65/65/EC.

The facts of the two cases are as follows. Both concern the parallel import of omeprazole capsules, marketed as Losec, into Sweden and Finland. In the Swedish case,[3] the authorisation of reference for Losec was held by Hässle Läkemedel AB (Hässle) while a parallel import licence was held by Paranova Läkemedel AB and several other companies. In the Finnish case,[4] the authorisation of reference was held by Suomen Astra Oy (Astra), while Paranova Oy held the parallel import licence.

Astra and Hässle subsequently sought withdrawal of their authorisations for Losec capsules following the introduction of a new formulation, Losec MUPS tablets. The new formulation contained the magnesium salt of omeprazole, as opposed to the free acid, but was otherwise bioequivalent and equally therapeutic. Authorisations for original Losec capsules in other member states remained unaffected and the product continued to be marketed there.

Following withdrawal of the marketing authorisations for Losec capsules in Sweden and Finland, the respective national authorities informed Paranova that since the reference authorisations were no longer valid, the parallel import licences were also no longer valid since they would not be able to properly comply with their pharmacovigilance obligations in such circumstances. This resulted in Paranova challenging the decision as being incompatible with Articles 28 and 30 EC.

Reasons for Opinion

According to the recent case law of the Court in *Ferring Arzneimittel*,[5] the automatic withdrawal of a parallel import licence on withdrawal of the reference authorisation constitutes a restriction on the free movement of good contrary to Article 28 EC unless it can be justified under Article 30 EC on the grounds of the protection of public health. Member states of import are entitled to restrict parallel products, according to the principle of proportionality, only to the extent necessary in order to achieve such protection.

Therefore where a marketing authorisation of reference is withdrawn at the request of its holder for reasons other than the protection of health it would appear to be unjustified. Withdrawal of

the original authorisation does not necessarily imply that the quality, efficacy and non-toxicity of the original product are called into question, and pharmacovigilence in accordance with Chapter Va Directive 75/319 would normally be achievable by cooperation with the national authorities of other member states where full authorisations for the original product were still in force.

However, if it could be demonstrated that there is in fact a risk to public health, for example caused by the co-existence of two forms of the same product in the member state of import, restrictions on import of the original version of the product might be permissible. Whether there is such a risk is a matter for the competent authorities of the member state of import to determine. A mere assertion by the holder of the authorisation that there is such a risk is insufficient.

In the present case therefore, the Advocate General was of the opinion that the withdrawal of parallel licences for Losec capsules in Sweden and Finland contravened Article 28 EC. He also made the observation that in light of the amendment to the pharmacovigilance provisions of Chapter Va Directive 75/319 made by Directive 2000/38, it would only be in exceptional cases that the competent authority of a member state of import would be able to prohibit such imports on the ground that it could not ensure pharmacovigilence.

SELECTING EMBRYOS FOR IMPLANTATION BY TISSUE TYPING

Summary

The Human Embryology and Fertilisation Act 1990 does not allow the tissue typing of embryos in conjunction with pre-implantation genetic diagnosis (PGD) to ascertain whether such an embryo might develop into a child whose tissue will be histocompatible with that of a sibling.[6]

The Human Embryology and Fertilisation Authority's (HFEA) recent decision in this regard to allow embryo selection with a view to treating a sibling with beta thalassaemia major was therefore unlawful.

Background and reasons for decision

In essence, section 11(1)(a) HFEA restricts licences under the Act for *in vitro* fertilisation (including cloning[7]) and implantation techniques to those activities which are for 'treatment services'. Such services are defined in s. 2(1) as being medical, surgical or obstetric, provided to the public or a section of it, for the purpose of assisting women to carry children.

In the present case therefore, and reluctantly noting that its role was confined to construing parliamentary legislation, the court dismissed the argument that genetic screening of this nature was to assist pregnancy. It went beyond that. As such the HFEA had exceeded its authority.

MARKETING AUTHORISATIONS FOR ANORECTICS – FENFLURAMINE

Summary

As mentioned in the previous edition of the journal with regard to *Artegodan & Others v Commission*[8] that the adopted decision to withdraw marketing authorisations for various centrally acting anorectics should be annulled, the Court of First Instance has now ruled on the fate of the serotonergic compound fenfluramine.[9] Both the racemate as well as the D-enantiomer are to remain authorised in the EU.

Facts

Les Laboratoires Servier is the holder of national marketing authorisations for both fenfluramine and its D-enantiomer dexfenfluramine. Both drugs have been the previous subject of a Commission decision[10] under Article 12 Directive 75/319 following referral to the Committee for Proprietary Medicinal Products (CPMP) by the Federal Republic of

Germany. That referral related not only to fenfluramine preparations but also to other centrally acting anorectics due to concerns about primary pulmonary hypertension (PPH).

In summary, the outcome of the referral was that while it was concluded that fenfluramine, in common with other anorectics (excluding fenbutrazate and propylhexedrine) did indeed pose a risk of PPH,[11] anorectic drugs were nevertheless the only available pharmaceutical treatment for obesity. Moreover, since fenfluramine has the advantage of not inducing dependence, unlike amphetamine-like compounds, it is suitable for long-term use. The CPMP therefore advised that the benefit/risk balance for treatment with fenfluramine was favourable and that authorisations should remain in force, but that the relevant summary of product characteristics (SmPCs) should be modified, *iter alia*, to reflect the risk of PPH.

Following unfavourable publicity as to the safety of fenfluramine with regard to the increased risk of cardiac valve disorders (CVD) however,[12] Les Laboratoires Servier and its licensees immediately and voluntarily withdrew the drug from the market pending further safety studies. Shortly afterwards, authorisations for both the racemate and the D-enantiomer were suspended throughout the EU and the USA.

After several member states had informed the European Agency for the Evaluation of Medicinal Products of their decisions to suspend authorisations, the matter was referred to the CPMP for review under Article 15 Directive 75/319/EC. That referral led to the Commission adopting its decision to withdraw authorisations for products containing fenfluramine[13] on the basis that the CPMP had advised that in the context of the drug's limited efficacy, the benefit/risk balance was now unfavourable as a result of safety concerns in connection with both PPH[14] and CVD[15] under normal conditions of use.

Judgment

Les Laboratoires Servier challenged the Commission's decision primarily on the basis of a breach of Article 11 Directive 65/65 when assessing the benefit/risk balance of fenfluramine with regard to the criteria to be applied for withdrawal of a marketing authorisation. In particular, it criticised the scientific studies underlying the CPMP's revised assessment of the risk of PPH, which it must be remembered had already been investigated under the earlier Article 12 reference, as well as the apparent new risk of CVD.

However, reiterating the reasons for the decision in *Artegodan,* the Court emphasised that not only did harmonisation under Article 12 not bring the matter within the competence of the Commission on referral under Article 15, it was the role of the competent authorities of member states to assess whether new data raised reasonable doubt, in accordance with the precautionary principle, as to whether a marketing authorisation should be suspended or withdrawn.

Against that background, it was the task of relevant competent national authorities to re-evaluate data in relation to the risks of CVD associated with treatment for obesity using fenfluramine. The Commission's decision to withdraw authorisation was therefore without legal basis and was annulled with costs.

PARALLEL IMPORTS: THE APPLICATION OF COMMUNITY JURISPRUDENCE RELATING TO RELABELLING AND REPACKAGING OF PHARMACEUTICAL PRODUCTS

Summary

In the second judgment in *Glaxo Group & Others*[16] the UK has ruled on the implementation of the decision of the European Court of Justice (ECJ) regarding the manner and extent to which

pharmaceutical products may be repackaged or relabelled for parallel trade. Guidance was sought as to whether a proprietor of a trade mark could object to repackaging when neither the origin or quality functions of the mark had in reality been affected. The ECJ ruled that *prima facie* a proprietor can.

The ECJ was also asked to confirm whether or not a parallel importer is obliged to give prior notice of repackaging even where it would not be possible for the proprietor to object to it. The ECJ has made it clear that there is always such an obligation. In the UK Court's view, this means there is little doubt that such notice will now also be required for mere relabelling. The judgment therefore significantly facilitates the ability of proprietors to interfere with parallel trade.

Background

Glaxo Wellcome, Boehringer Ingelheim, SmithKline Beecham and Eli Lilly had all objected to the repackaging and relabelling by Dowelhurst and Swingward of various pharmaceutical products. This was because they felt there was no justification for it and it had been carried out in a way which was impermissible. Glaxo and Boehringer also argued that the notice requirements in *Hoffman-La Roche*[17] had not been complied with.

In the first judgment, Laddie J concluded that in the light of the decisions in *Parfums Christian Dior*[18] that a proprietor can only override the principle of the free movement of goods where there is substantial damage to the specific subject matter of the right, particularly damage to reputation, and the decision in *Paranova* which comments that hypothetical risk is insufficient for a proprietor to oppose repackaging, it was necessary for the proprietor to demonstrate real and substantial damage to the mark before being able to object. Therefore absent evidence of any real damage an importer was free to decide how to market the goods. However, since he felt that the jurisprudence in this area was not clear, he referred the matter to the ECJ for further explanation.

The ECJ's response was that the UK Court had significantly overstated the position. In summary the ECJ reiterated that although a proprietor may interfere with the free movement of goods only to the extent necessary to safeguard the rights that form the specific subject matter of the mark, which is to guarantee origin, repackaging of pharmaceutical products is in itself inherently prejudicial to those rights.[19] In such circumstances it is not necessary to assess the actual effects of repackaging.

There is therefore an irrefutable legal presumption that repackaging is damaging and that a proprietor may object without demonstrating actual harm. This is subject, however, to the condition[20] that if repackaging is objectively necessary[21] for the importer to gain effective access to the market in the state of import, a proprietor may not object, provided that the repackaging is done in such a way that the legitimate interests of the proprietor are respected. The corollary of all this is that a proprietor may always object to repackaging when mere relabelling alone would suffice. The former is therefore deemed to be inherently harmful while the latter is not.

Repackaging and relabelling in Glaxo

In essence, the claimants' objections to repackaging in *Glaxo* fell into two categories. The first relates to de-branding, where a proprietor's mark is partially or entirely removed from the product, while the second relates to repackaging in a livery which serves to build up the importer's reputation on the back of the proprietor's product. Regarding de-branding, Eli Lilly and SmithKline Beecham both complained that the repackaging of their respective products, PROZAC,[22] SEROXAT[23] and FAMVIR,[24] had resulted in a reduction in the prominence and location of their marks while unfairly emphasising the association of the products with

Dowelhurst. Since this had been carried out in a way that was not necessary, either to achieve market acceptance or to meet regulatory requirements, their objections to this repackaging were upheld.

With regard to the remaining claimants, Glaxo Wellcome and Boehringer Ingelheim, their primary complaints related to the relabelling of ATROVENT,[25] giving undue prominence to the word DOWELHURST, and the repackaging of SEREVENT[26] by Dowelhurst and Swingward in distinctive styles of livery. Since Laddie J had already found in the first judgment that the relabelling of ATROVENT had not in fact inflicted any real or substantial harm to the specific subject matter of the mark, and given that there is no presumption of damage in the case of relabelling, no objection could be justified. However, the repackaging of SEREVENT using distinctive livery was held to be objectionable for the same reasons that Eli Lilly's and SmithKline Beecham's objections to repackaging were upheld.

Notice

Finally, with regard to the question of giving prior notice to a proprietor when repackaging, the ECJ has confirmed that this is necessary in any event because the requirement does not depend on whether there is actual harm. In such circumstances notice is required so that the proprietor has the opportunity to assess whether there is any actual harm. While there is no presumption of harm to a mark in the case of relabelling in the way there is in relation to repackaging, Laddie J has therefore held in the light of this and the decision in *Loendersloot*,[27] which suggests that notice should be given for relabelling anyway, there are now no reasonable grounds to doubt that the ECJ will require notice to be given whenever there is a *prima facie* risk of infringement. The need to give advance notice therefore applies as much to parallel imported pharmaceuticals that have been relabelled as to those that have been repackaged.

Laddie J did express the view, however, that the 15 day notice period previously suggested by the ECJ in the case of repackaging was excessive in cases of mere relabelling. He therefore decided that 7 days should be sufficient since the only burden on proprietors in those circumstances would be to examine their own product to which a new label has simply been applied.

COMMISSION COMMUNICATION ON 'eEUROPE 2002: QUALITY CRITERIA FOR HEALTH-RELATED WEBSITES'

The 'eEurope 2002 Action Plan – An Information Society For All' was adopted by the Commission and endorsed by the Council in 2002. In light of the fact that it is estimated that there are now over 100,000 websites offering such information,[28] the Council supported an initiative within eEurope 2002 to develop a core set of quality criteria for health-related websites.

In this Communication the way is paved for the implementation of these criteria based on a broad consensus among specialists in the field, health authorities and prospective users. Certain ways of implementing these criteria are also discussed, notably the adoption of an EU trust mark akin to the CE mark, but as it was not the objective to develop methods of implementation at European level, initiatives such as trust marks for health-related websites are outside the ambit of the eEurope 2002 action. They may be considered within future eEurope action plans or other European programmes, however.

There are six key criteria relating to 'Transparency and Honesty', 'Authority', 'Privacy and Data Protection of Health Data', 'Updating Information', 'Accountability' and 'Accessibility'. These are designed to be applicable to the development and maintenance of health-

related sites irrespective of the type of information or audience, but care should be taken by providers to meet the criteria within the context of the actual audience so that both the style and nature of the information are presented in a way which is appropriate. In summary the criteria are as follows:

- **Transparency and honesty**. This relates to transparency of the identity of the provider of the site, which should include a physical as well as electronic address, the purpose and objectives of the content of the site, the target audience and details of sources of funding. In particular, whenever advice is given which implicitly or explicitly endorses a medicinal product, funding from producers of such products must be apparent to the site user. Existing Community legislation relating to information and transparency requirements is included.[29]

- **Authority**. This requires a clear statement of the source of information. If the site adopts a policy of including information and advice from accredited medical professionals only then this must be adhered to. If information is sourced from a variety of content providers such as medical professionals, journalists or individual's personal testimony, then that source must be apparent to the site user in each case. Where scientific evidence is cited, the source of that evidence must be identifiable. Community law on the advertising of medicinal products and the fact that a face to face consultation is always preferable to advice over the internet should be borne in mind if any product is recommended.

- **Privacy**. There should be a privacy and data protection policy and system for processing that complies with Directive 95/46/EC on Data Protection, particularly Article 8, and Directive 2002/58/EC.

- **Updating of information**. The site should be updated on a regular basis and it should be clear to the user when the last update occurred. Where specific health-related data are provided on the site, the relevance of such content should be regularly verified.

- **Accountability**. Where health-related user feedback is provided by the site, particularly where personalised advice is offered, the provider must make every effort to ensure that the advice is bona fide and that the advisor is suitably qualified to offer that advice. Providers should also try to ensure that partnering with or linking to other sites is undertaken only with trustworthy individuals or organisations who themselves comply with relevant codes of good practice. Finally there should be an editorial policy and a statement as to the procedure used for the selection of the site content.

- **Accessibility.** Attention should be paid to guidelines on the physical accessibility of information. As well as ensuring that information is correct, providers should make sure that the content of the site is accessible to people with disabilities including sensory impairment and learning difficulties. Attention should also be paid to the general ease of finding, searching, reading and using information.

While the Commission does recognise that the criteria must be satisfactorily implemented throughout the EU to ensure all citizens have access to reliable health information on the internet, it doubts that the same method of implementation should necessarily be used everywhere, or that any particular mechanism would be appropriate in all

circumstances in all member states. For example, the Commission is considering specific ways of meeting patient demands to access information online in the case of pharmaceutical products and has included proposals within the current review[30] of EU pharmaceutical legislation to take account of this.

In view of the rapid increase in the number of sites and viewers of health-related information, the Communication does not consider that at present a Community-sponsored system for implementation would be appropriate because of the considerable resources that would be required to set up and operate such a system. Therefore it is now the responsibility of national and regional health authorities, relevant professional associations and website providers to implement the criteria in a manner appropriate to the website and its users. In that regard they must educate site developers and users about minimum quality standards, draw on the range of health information available from across Europe, and exchange information about how the criteria are being implemented in practice at national level.

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