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HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, European Medicines Agency

PHARM 690

PHARMACEUTICAL COMMITTEE
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Subject: **Court cases**

Agenda item 1a

- **Case E-16/14, Judgment of the EFTA-Court of 9 April 2015, Intervet**

Background: The case concerns a reference from a Norwegian Court to the EFTA Court concerning national proceedings between two veterinary pharmaceutical companies. The two companies have developed their own vaccine against pancreatic disease in salmonid fish. The plaintiff's vaccine is based on a virus strain isolated from PD-infected salmon. That strain, which is SAV-3, is the third, out of the six strains of Salmonid Alpha Virus, while the defendant's vaccine is based on virus strain SAV-1.

In the national proceedings the plaintiff contests the validity of a supplementary protection certificate (SPC) granted to the defendant. Such certificate extends the period of protection for medicinal products beyond the normal patent term in order to compensate the patent holder for the lengthy period for obtaining marketing authorisation during which the patent owner cannot enjoy the rewards of the monopoly provided by the patent.

The plaintiff argues that the SPC is not valid because the defendant has been marketing its vaccine for several years on the basis of a derogatory clause provided by the veterinary legislation (Article 8 of Directive 2001/82). Moreover, the scope of the protection should not be deemed to include the plaintiff's vaccine, as it contains a different strain.

The national court referred several questions to the Court. The essential element of Questions 1-4 is whether the existence of the "special approval exemptions" or licences granted by the Norwegian and Irish authorities is sufficient to preclude the grant of an SPC, on the basis that the vaccine has already been "placed on the market" as a medicinal product between 2003 and 2011 within the meaning of Article 2 of the SPC Regulation. In this context the national court asked whether a marketing authorisation issued pursuant to Article 26(3) of Directive 2001/82 (MA under exceptional circumstances) constitutes a marketing authorisation within the meaning of Article 2 of the SPC Regulation. The remaining questions (5-6) concern the scope of the protection provided by an SPC in

accordance with Article 4 of the SPC Regulation, whether it covers only a specific strain or also other strains.

Main considerations with regard to questions 1-4:

According to Article 2 of the SPC Regulation, any product protected by a patent in the territory of an EEA State and subject, prior to being placed on the market as a veterinary medicinal product, to an administrative authorisation procedure as laid down in Directive 2001/82, may be the subject of an SPC.

It follows from Article 3(b) of the SPC Regulation and from Article 5(1) of Directive 2001/82 that the administrative authorisation procedure in question is the one referred to in Title III of Directive 2001/82 for obtaining a marketing authorisation. That procedure includes testing the safety and efficacy of the medicinal product, the results of which must accompany the application for marketing authorisation, in accordance with Article 12(3) of Directive 2001/82.

Accordingly, pursuant to Article 2 of the SPC Regulation, a product is eligible for an SPC only if, before being placed on the EEA market as a veterinary medicinal product, it obtained a marketing authorisation pursuant to an administrative authorisation procedure as laid down in Directive 2001/82, including in particular safety and efficacy testing. This authorisation procedure includes authorisations granted in exceptional circumstances pursuant to Article 26(3) of Directive 2001/82.

In contrast, the supply of a medicinal product on the basis of the first paragraph of Article 8 of Directive 2001/82 does not constitute an administrative authorisation procedure as specified in Article 2 of the SPC Regulation. According to Article 8 of Directive 2001/82, in the event of serious epizootic diseases, EEA States may provisionally allow the use of immunological veterinary medicinal products without a marketing authorisation, in the absence of a suitable medicinal product,

Article 8 constitutes an exemption to the authorisation scheme(s) set out in Directive 2001/82. Such provisional permission does not require the same safety and efficacy testing as the procedure preceding a marketing authorisation and does not entitle the producer to market the product but only to supply it, to the extent necessary to combat the disease in question.

- **Case T-452/14, Judgment of 11 June 2015, CTRS v Commission**

Background: The case concerns a direct action initiated by the company CTRS against a Commission decision granting a marketing authorisation to a product of a competitor. It is claimed that the decision infringes the market exclusivity of CTRS's product.

CTRS holds a marketing authorisation for the orphan medicinal product 'Orphacol', which contains the active substance 'cholic acid'. The product is used for the treatment of a rare genetic abnormality that makes patients unable to produce primary bile acids. Orphacol received marketing authorisation in 2013 following a court dispute between CTRS and the Commission, by which CTRS successfully challenged the initial Commission refusal to grant the marketing authorisation. The Court dismissed the Commission's argument that regulatory concerns over the compliance of the application with legal requirements would prevent the issuing of an authorisation.

As an orphan medicinal product, 'Orphacol' benefits from a 10-year period of market exclusivity during which similar products for the same therapeutic indication are prevented from entering the market.

In 2014 the Commission granted a marketing authorisation for the product 'Kolbam'. Kolbam contains the same active substance as Orphacol. However, the patient population for which both products are used differs, given that Kolbam is authorised for the treatment of deficiencies of different liver enzymes than Orphacol. The Commission considered that as the therapeutic indications of the two products do not overlap, the market exclusivity of 'Orphacol' is not infringed. According to the law market exclusivity affects only similar products that are used for the same therapeutic indication.

CTRS argued instead, that the scientific assessment and other public documents related to the authorisation of Kolbam, as prepared by scientific committees of EMA, would contain statements that could make doctors believe that Kolbam would work in the therapeutic indications of Orphacol. Hence, the marketing authorisation for Kolbam would indirectly cover the same 'therapeutic indications' and therefore infringe the market exclusivity of Orphacol.

Main considerations of the Court:

By its ruling the General Court annulled the Commission Implementing Decision granting an orphan marketing authorisation to the product Kolbam. The Court basically followed the claim of the applicant that certain references included in the assessment report of the European Medicines Agency and the summary of product characteristics, which both form an integral part of the Commission decision, would result in a circumvention of Orphacol's market exclusivity.

The ruling should, however, not be understood as preventing the Commission from authorising Kolbam. The Court only ruled that the Commission decision, especially the assessment report and the summary of product characteristics, should not contain the 'incriminated references' that were subject to the case and which according to the General Court relate to the efficacy of Kolbam in the therapeutic indications for which Orphacol was authorised and which are protected by market exclusivity.

While the Court recognised that Kolbam is not authorised for the Orphacol indications, it holds that "if the effectiveness of Article 8(1) of the Orphan Regulation is to be ensured, the off-label prescribing of a medicinal product for therapeutic indications covered by the market exclusivity attaching to another medicinal product by virtue of that decision should not be facilitated" (para. 78). More in particular:

"[…] the Commission must satisfy itself that a marketing authorisation for a medicinal product is not formulated in such a way that it may induce a prescribing physician to prescribe a medicinal product for therapeutic indications other than those which are covered by that marketing authorisation and for which a marketing authorisation has already been granted for another medicinal product that benefits from the market exclusivity provided for by the regulation.

That would be the case of a marketing authorisation for a medicinal product in which it was stated that a product was effective for therapeutic indications for which a marketing authorisation had already been granted in respect of another orphan medicinal product. Indeed, such statements could tend to facilitate the prescription of the first medicinal product for the therapeutic indications of the second product, which benefits from the market exclusivity provided for by Article 8(1) of Regulation No 141/2000. That would amount to circumvention of the market exclusivity guaranteed by that provision.

The point must also be made that off-label prescribing is the sole responsibility of the prescribing physician […]. That responsibility could in practice be attenuated by the presence, in a medicinal product's marketing authorisation, of statements that the

product is effective and safe for treating other therapeutic indications than those for which its marketing authorisation has been granted." [para. 80-82]

In this context, it is interesting to note that the Court seems to have equated the non-public assessment report, which is part of the Commission decision, with the European Public Assessment Report that is published by EMA and freely accessible, including by prescribing doctors.

In light of those general considerations, the General Court reviewed the incriminated references in the assessment report and the SmPC. The Court concurred with CTRS that those references would contain explicit references to the efficacy of Kolbam for the Orphacol indications.

The Court dismissed all the Commission's justifications to defend the lawfulness of the marketing authorisation as such, as well as those specific references. While the Court accepted that a "complete presentation of the clinical results/trials for Kolbam is justified", it held that such presentation should not include statements concerning the efficacy of Kolbam for therapeutic indications that are still under market exclusivity [para. 100, 121, 126].

- **Cases C-544 and 545/13, Judgment of 16 July 2015, Abcur**

Background: Apoteket, a State-owned company which until July 2009 enjoyed the sole right in Sweden to retail medicinal products, produced and marketed two products without having obtained a marketing authorisation. Abcur, a company which produces and markets two products similar to those and which has obtained a marketing authorisation, sued Apoteket for damages. Abcur's complaint concerns both (1) the fact that Apoteket manufactured the products without an authorisation and (2) the measures employed by Apoteket to promote the products. The case deals with the questions:

- whether the medicinal products in question fall within the scope of Directive 2001/83/EC and/or are covered by one of its derogations (Article 3 and 5),
- whether Directives 2005/29/EC on unfair commercial practices and 2006/114/EC concerning misleading and comparative advertising are applicable and, if so,
- whether some of their substantive requirements are fulfilled.

The national court referred four questions to the Court. The first question concerns the scope of Directive 2001/83 and more particular the correct interpretation of the 'pharmacy'-exemptions provided by Article 3(1) and (2). The other questions concern the applicability and interpretation of the directives on unfair commercial practices and misleading comparative advertising. From a pharma law perspective, the considerations of the Court with regard to Articles 2 and 3(1) and (2) of Directive 2001/83/EC are of particular interest.

Main considerations of the Court:

On the relationship between Article 2 and Article 3 of Directive 2001/83: According to the Court, Article 2(1) makes a positive determination of the scope of the Directive, by providing that it applies to human medicinal products that are either prepared industrially or manufactured by a method involving an industrial process. Article 3 (1) and (2) provides for certain exceptions to that scope. It follows therefrom, in order to fall within the scope of the Directive, the product in question must first satisfy the conditions of Article 2(1) and secondly, must not fall within one of the exceptions provided by Article 3. [para. 38 + 39]

On 'industrially prepared' and 'manufactured by a method involving an industrial process': In view of the public health objective of the Directive those terms cannot be interpreted narrowly. They must include at the very least, any preparation or manufacture involving an industrial process. Such a process is characterised in general by a succession of operations, which may, in particular, be mechanical or chemical, in order to obtain a significant quantity of a standardised product. The standardised production of significant quantities to be stocked and sold wholesale and the large-scale or serial production of magistral formulae in batches are characteristic of an industrial process. [para. 50+51]

On the exceptions provided by Article 3(1) and (2): Those exceptions should be interpreted strictly; they are only applicable, if the cumulative conditions provided for in Article 3(1) or Article 3(2) are satisfied. [para. 59]

On the concept of 'prescription for an individual patient' in Article 3(1): According to the Court a strict interpretation should be applied, meaning that the patient must be identified before the medicinal product is produced [para. 61]. This means that products under Article 3(1) should not be pre-produced, even if the medicinal product will be typically used in emergency situations, where there is insufficient time for an ad-hoc production.

On the concept of 'prepared in a pharmacy' in Article 3(2): In order to benefit from the exception the medicinal product must be supplied *directly* by the pharmacy which *prepared it* to the patients supplied by that same pharmacy. [para. 67]

- **Cases T-472/12 and T-67/13, Judgment of 15 September 2015, Novartis**

Background: The two cases concern the correct interpretation of the global marketing authorisation concept, which is important for calculating the data protection period of a medicinal product, i.e. the period before the data of the originator ('reference') product can be used by generic companies to support their application for the authorisation of a generic copy.

In the present case, Novartis challenged the Commission's decision to grant a marketing authorisation for generic copies of the human medicinal product A, a product of Novartis. Novartis argued that the Commission decision infringed its data protection rights.

In the applicant's view, the Commission miscalculated the data protection period for A and allowed a premature market entry of generic copies. It turns on the allegation that the Commission wrongly treated two separate Novartis products - Z and A - as falling under the same global marketing authorisation. In doing so, the Commission applied the same data protection period to both, even though A was authorised at a later date and through a separate centralised marketing authorisation procedure.

In the applicant's opinion, product A would merit an independent, stand-alone regulatory data protection period, mainly arguing with the fact that A was authorised under a different name and on the basis of a separate, full application.

Main considerations of the Court:

According to the Court, the submission of an application for a separate marketing authorisation and a new name for A rather than the submission of an application for variation and extension of the marketing authorisation for Z was a commercial decision on the part of Novartis. As Advocate General Jacobs observed already in case C-106/01, the market strategy of an undertaking cannot affect the application of the regulatory period of data protection of one and the same active substance because this would elevate form over substance, and would create an easy route for applicants to gain additional data protection in circumvention of previous case law. [para. 59]

The approach advocated by the applicant is clearly at odds with the objectives pursued by the legislation under consideration, as clarified in particular by the case law. [para. 61]

The scope of a global marketing authorisation, as defined in the second subparagraph of Article 6(1) of Directive 2001/83, as amended, encompasses developments for which separate marketing authorisations have been granted under the centralised procedure. The fact that Novartis was able to obtain, by means of that procedure, a marketing authorisation for new therapeutic indications with a new name is irrelevant for the purpose of the application of the regulatory data protection period [para. 82].

- **Case C-452/14, Judgment of 1 October 2015, Doc Generici**

Background: The case concerns Italian provisions concerning fees payable by marketing authorisation holders to competent authorities in the context of variations to existing marketing authorisations. More in particular, it addresses the situation where a company submits a common variation or multiple identical variations that concern several marketing authorisations.

The applicant in the national court case holds several marketing authorisations and notified the competent authority in Italy of the change of company seat. The applicant also requested the corresponding type IA variation to be applied to the respective marketing authorisations.

For this variation, the national authority sought payment of a sum equivalent to the payment of as many fees as there were marketing authorisations affected.

While the fees payable to the Italian Agency are regulated by national provisions, several of those provisions cross refer to the EMA Fee Regulation (Council Regulation (EC) No 297/95). For that reason the national court submitted questions to the Court of Justice regarding the interpretation of the Fee Regulation. It asked whether Article 3(2)(a) on Type I variations must be interpreted as meaning that, where identical type I variations affecting several authorisations are concerned, those variations are subject to a single fee or to as many fees as there are authorisations affected.

Main considerations of the Court:

The Court did not provide a direct answer to this question. It was noted that the subject and scope of the EMA Fee Regulation is limited to fees payable in respect of services provided by EMA. The dispute in the main proceedings related however, to the fees payable to the Italian AIFA.

Against this background the EU Court did not agree with the premise of the Italian Court that the interpretation of the EMA Fee Regulation would have a direct impact on the outcome of national case.

Instead, the Court of Justice decided to focus on the Variation Regulation, as this Regulation is equally applicable to centrally and nationally authorised products, i.e. also to those variations, which are subject to the national case.

The Court noted that Commission Regulation No 1234/2008 authorises the grouping in a single notification of several identical applications for Type IA minor variations submitted at the same time. The Court stressed that according to recital 6 in the preamble to that regulation, such grouping is intended ‘to facilitate the review of the variations and reduce the administrative burden’, but only ‘insofar as all concerned marketing authorisations are affected by the exact same group of variations’.

However, the Variation Regulation does not contain any provision governing the amount of fees that may be charged by competent national authorities for processing such

groupings of Type IA minor variations. The question whether those national authorities may demand payment of as many fees as there are marketing authorisations requiring variation, notwithstanding the fact that the applications for variation are grouped together, falls to be determined, in the absence of any legislative provisions adopted by the European Union, by national law [para. 40].

As a result the Court concluded that neither the Fee Regulation nor the Variation Regulation demand a national authority to require a payment of as many charges as there are marketing authorisations requiring variation; but due to their specific scope they also would not prohibit such an authority from demanding such payment.

- **Interesting pending cases**

Case **T-672/14** (A. Wolff v Commission), direct action seeking the partial annulment of the Commission decision in an Article 31 referral re: estradiol containing medicines;

Case **C-82/15P** (PP Nature Balance v Commission), appeal against the ruling in case T-189/13, by which the Court upheld a decision of the Commission in an Article 31 referral (tolperisone-containing products);

Case **C-138/15P** (TEVA v EMA), appeal against the ruling in case T-140/12, by which the General Court upheld a decision of EMA to refuse the validation of a generic marketing authorisation application in view of the market exclusivity granted to an orphan medicinal product;

Case **T-269/15** (Novartis v Commission), direct action seeking the annulment of the Commission decision to grant marketing authorisation to the medicinal product Vantobra;

Case **T-235/15** (Pari v EMA), an access to document case against EMA concerning the confidentiality of scientific opinions on similarity and clinical superiority under the Orphan Regulation;

Case **C-471/14**, preliminary reference in the context of the Regulation on supplementary protection certificates on the question whether the period of validity of the certificate should start from the date of the Commission decision granting the marketing authorisation or from the date of its notification (Judgement 6 October 2015);

Case **C-114/15**, preliminary reference concerning the possibility of livestock farmers to (parallel) import veterinary medicinal products from other Member States;

Case **C-148/15**, preliminary reference concerning the applicability of the German system of fixed prices to products bought from non-German internet pharmacies;

Case **C-276/15**, preliminary reference concerning pharmacy preparations (Article 3 of Directive 2001/83);

Case **C-296/15**, preliminary reference concerning tendering practices of Slovenian hospitals with regard to the procurement of plasma products.

Action to be taken:
For information