EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, EMA

PHARM 678

PHARMACEUTICAL COMMITTEE
17 March 2015

Subject: **Ongoing Court cases**

Agenda item 1b

- **Case T-189/13, Judgment of 11 December 2014, PP Nature v COM**

Background: With its direct action the applicant challenged the results of an Article 31 referral, which obliged Member States to delete certain indications from national marketing authorisations of tolperisone-containing oral formulations. Tolperisone is a centrally acting muscle relaxant used in clinical practice since the 1960's. In 2011 Germany initiated an EU review procedure of those products under Article 31 of Directive 2001/83. Germany considered that reports of hypersensitivity reactions received in the post-authorisation phase are indicative of a safety concern which is not balanced by the limited evidence of efficacy. In its scientific opinion the CHMP concluded that the risk-benefit balance in certain indications is indeed no longer favourable and recommended variation of the marketing authorisations in order to delete those indications. With its implementing decision of January 2013 the Commission followed EMA's scientific opinion and ordered Member States to vary the national marketing authorisations accordingly.

In April 2013 one of the marketing authorisation holders concerned lodged an application under Article 263 TFEU for the partial annulment of the implementing decision of the Commission. With its ruling of December 2014, the Court dismissed the application.

Main considerations of the Court: The General Court confirmed its constant jurisprudence that the burden of proof for a change in the benefit-risk profile of an authorised product is with the regulatory authority that takes action (here: the Commission). However, in light of the precautionary principle the Commission was entitled "to restrict itself to supplying solid and persuasive evidence which could give rise to reasonable doubt" (para. 37). That evidence is provided by the scientific opinion of the CHMP.

The General Court agreed that the scientific opinion, while taking into account all evidence, may focus on the evidence that has the highest validity (e.g. placebo-controlled clinical trials). A simple reference to the well-established medicinal use of the product and the long experience with it cannot be used to question the results of such trials, as it is too unspecific (para. 105/106).

For old products it is not necessary to review the data that was used to authorise the product: "*En effet, afin de prendre des mesures au titre de l'article 116 de la directive 2001/83, il n'est nullement requis de se fonder sur des données qui infirment ou réfutent les preuves qui sous-tendaient les AMM, mais seulement sur des données ou des informations scientifiques ou médicales nouvelles et objectives.*" (para. 75)

The Court moreover clarified that recent assessments of the product at national level (e.g. in the context of a renewal) have no direct impact on the assessment at EU level: "*À cet égard, ne saurait être opposée au comité, au regard des informations qu'il est appelé à analyser pour la première fois, l'appréciation qu'une autorité nationale aurait pu avoir de ces informations dans le passé.*" (para. 89)

[The ruling is under appeal: case C-82/15P.]

- **Case T-140/12, Judgment of 22 January 2015, TEVA v EMA**

Background: The applicant lodged an application under Article 263 TFEU for the annulment of the EMA 'decision' not to validate a generic marketing authorisation application for a copy of the orphan medicinal product Glivec for therapeutic indications for which also the orphan product Tasigna had been authorised. Considering that those indications are covered by the market exclusivity for Tasigna (Glivec and Tasigna are similar products in the sense of the Orphan Regulation), EMA refused to validate these applications because such validation would have led to a violation of the market exclusivity provided under Article 8(1) of the Orphan Regulation to Tasigna. The Commission intervened in support of EMA. With its ruling of January 2015 the General Court dismissed the application.

Main considerations of the Court: This was the first case before the EU courts on the scope of the 10-year market exclusivity provided by the Orphan Regulation (Article 8 of Regulation 141/2000). It provides important clarification on the scope and duration of that exclusivity, in cases where a company develops a second orphan product, which does not contain the same active substance as the first product, but is nevertheless similar to that first product (and still of significant benefit compared to previous treatments).

In order to ensure attainment of the objective pursued by the regulation — namely to encourage investment in research, development and marketing of orphan medicinal products —market exclusivity must be granted in all cases in which an orphan product has been given marketing authorisation. For that reason a second product is eligible to an independent and full 10-year market exclusivity period in accordance with Article 8(1).

"Market exclusivity attaches to that medicinal product for all those therapeutic indications, irrespective of the fact that the medicinal product in question, which is itself similar to another orphan product which has been granted marketing authorisation, relied on one of the derogations laid down in Article 8(3) of the regulation at the time of that authorisation. Thus, the fact that the therapeutic indications for which both orphan medicinal products received marketing authorisation are similar cannot undermine the market exclusivity enjoyed by each of those medicinal products by virtue of Article 8(1) of that regulation for those therapeutic indications." (para. 79)

Consequently, Article 8(3) does not preclude the application of Article 8(1) (para. 78). Moreover, nothing in the wording of the Regulation allows penalising the sponsor for the fact that it relied on the consent derogation. (para. 76)

- **Case C-104/13, Judgment of 23 October 2014, Olainfarm**

Background: In 2003, Olainfarm applied for a marketing authorisation in Latvia. At that time Latvia was not yet part of the EU. The medicinal product was authorised under the national legislation then in force. That legislation corresponded only partly to EU-law provisions governing the authorisation of medicinal products. In 2008, following the accession of Latvia, Olainfarm applied for and received a marketing authorisation for that product in accordance with Article 10a of Directive 2001/83 on the grounds that the medicinal product in question was based on active substances that had been in well-established medicinal use (WEMU) for at least ten years. In 2011, another Latvian pharmaceutical company, applied for and received an authorisation to place on the market a generic. In the application, Olainfarm's product was indicated as the reference product. Olainfarm brought then an action before a national court seeking annulment of the authorisation of the generic.

The national court referred two questions to the Court:

1. Whether a well-established medicinal use product (WEMU - authorised under Article 10a) could be used as a reference product?
2. Whether EU law provides for a right of a marketing authorisation holder (MAH) to challenge a marketing authorisation (MA) that has been granted to a generic company using the other company's product as a reference product?

The Court's answer to both questions is yes.

Main considerations of the Court:

On the first question: In order for it to be possible to grant a marketing authorisation for a generic medicinal product on the basis of the abridged procedure, all the particulars and documents relating to the reference product and demonstrating its safety and efficacy should remain available to the competent authority. (para. 28)

As regards Article 10a of Directive 2001/83 [*legal basis for WEMU applications*], the procedure governed by that provision does not provide for any relaxation of the requirements of safety and efficacy, that procedure being simply designed to reduce the preparation period for a MA application by relieving the applicant of the obligation to perform the preclinical tests and clinical trials, provided that it is established by means of appropriate scientific literature that those tests and trials have been carried out previously. Accordingly, such a product may be placed on the market only after the competent authority has verified its safety and efficacy. (para. 29)

As a consequence, the dossier for the MA granted for a medicinal product under WEMU will contain all the information and documents needed to demonstrate the safety and efficacy of the product. (para. 30) Hence, there is nothing to preclude such a medicinal product from being used as a reference product for the purpose of obtaining a MA for a generic product. However, in view of the wording of Article 10 of Directive 2001/83, the use of a WEMU product as a reference product is precluded for a period of eight years.

In the interim, a competitor may submit its own WEMU application. That application may rely on the same published scientific literature.

On the second question: The holder of a MA for a medicinal product used as a reference product in an application under Article 10 of Directive 2001/83 is, by virtue of that provision, read in conjunction with Article 47 of the Charter, entitled to judicial protection in so far as concerns respect for his rights. (para. 39)

More in particular, the holder of a MA for a medicinal product has the right to demand that that medicinal product is not to be used as a reference product until a period of 8 years has elapsed from the date on which that MA was granted, or to demand that a medicinal product is not to be marketed until a period of 10 years. (para. 38)

Similarly, that holder may demand that his medicinal product is not to be used for another medicinal product in relation to which his own product cannot be regarded as a reference product or for a product which does not fulfil the requirement of being similar to the reference product (as laid down in Article 10(2)(b) of the directive). (para. 38)

Especially, that last point is of interest, as it could be (mis-)understood as giving the marketing authorisation holder of the reference product the right to challenge the generic marketing authorisation in all its aspects.

- **Interesting pending cases**

Cases **T-472/12, T-67/13** and **T-511/14** (*Novartis* v *Commission*), direct actions against the Commission concerning the application of the global marketing authorisation concept to products that received separate marketing authorisations under the 'old' Regulation (EEC) No 2309/93;

Case **T-542/14** (*CTRS* v *Commission*), Orphacol III, direct action by a competitor against the marketing authorisation granted to the medicinal product Kolbam;

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;

Joined cases **C-544 and C-545/13,** a preliminary reference on the applicable advertising provisions for pharmacy and hospital preparations;

Case **C-452/14**, a preliminary reference on the implications of grouping for the calculation of fees in view of Article 3(2)(a) of Regulation 297/95;

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.

- **Withdrawn cases**

Case **T-547/12** (*Teva* v *EMA*), a direct action against the EMA on the application of the global marketing authorisation concept to fixed combination products;

Case **T-48/14** (*Pfizer* v *Commission/EMA*), direct action concerning the alleged failure to include a compliance statement under the Paediatric Regulation into the marketing authorisation.

Action to be taken:

For information