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Health systems, medical products and innovation
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PHARM 758

PHARMACEUTICAL COMMITTEE
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Subject: **Update on Court cases**

Agenda item 1i

- **"*The one with the multiple orphan designations*" - Case T-80/16 – Shire v EMA – Judgment of 22 March 2018**

Background: In 2015 the pharmaceutical company Shire, submitted to EMA an application to receive orphan designation (under Article 5 of Regulation 141/2000) for a product development, which is referred to as 'Hunter-IT'. The application covered an intrathecal formulation of the active substance idursulfase. The proposed indication for orphan designation was treatment of Hunter Syndrome, a rare disease.

At the time of this application for orphan designation, Shire was already in possession of an orphan designation for the active substance idursulfase being used to treat Hunter-IT, which was granted in 2001 and served as a basis for the authorization of the orphan medicinal product "Elaprase" in 2007.

The existence of the 2001 designation and the marketing authorisation for Elaprase led EMA to refuse to validate Shire's request from 2015 for a new, separate orphan designation for idursulfase. Shire disagreed and took EMA to court. Amongst other things, it was argued that Hunter-IT and Elaprase are not the same product, as Hunter-IT would deliver idursulfase directly into the cerebrospinal fluid, i.e. the fluid that surrounds the brain and the spine using a special device.

Findings: According to the General Court, the Agency was wrong to refuse the validation. While the case turns on the interpretation and scope of the designation procedure in accordance with Article 5 of the Orphan Regulation (Regulation (EC) No 141/2000), it essentially concerned the question whether Hunter-IT and Elapase are different medicinal products in the sense of the Orphan Regulation or whether they are the same, as they contain the same active substance, are authorised for the same company and will be used in the same indication.

The Agency had argued that the constituent elements of an orphan designated product are the active substance, the targeted indication and the developing company (as listed in Article 5 of the Regulation). This would mean that any subsequent development that consists of the same constituent elements would be covered by the initial designation and does not merit a separate designation. This restrictive interpretation is also meant to avoid "ever-greening" strategies.

The Court disagreed. It first noted that Elaprase differs from Hunter-IT in its composition, method of administration and therapeutic effects. Hunter-IT moreover would constitute a supplementary treatment for patients suffering from cognitive disorders, as it does not replace the use of Elaprase, but allows for the use of active substance for patients with a more severe form of the disease the treatment of which requires the injection of the substance in the brain. In view of that, it would not appear that the two products can be considered the same product.

More generally, the Court held that it follows neither from the wording of Article 5 of Regulation No 141/2000, on which the contested decision is based, nor from the context in which that provision occurs, nor from the general scheme of the regulation, that a sponsor cannot apply for designation as an orphan medicinal product of a medicinal product containing the same active substance as another product authorised in its own name for the same indication, provided that it can demonstrate that the criterion for designation laid down in the second alternative of Article 3(1)(b) of Regulation No 141/2000 is met. According to the Court, 'significant benefit' within the meaning of Article 3(1)(b), may be based on the assumption of a more efficient formulation and means of administration than an authorised medicinal product with the same active substance and intended to treat the same condition.

The Court dismissed the EMA argument that this interpretation may allow strategic approaches of companies, leading to the duplication of marketing exclusivity periods for very similar products. In this regard, the Court argued with the interest of patients: where, a medicinal product meets the criteria for designation as an orphan medicinal product, criteria laid down in Article 3(1) of Regulation No 141/2000, including where that product contains the same active substance as another medicinal product already designated as an orphan product, it must itself be designated an orphan medicinal product. It would be in the interest of patients suffering from a rare disease to have access to a similar medicinal product giving them a significant benefit compared to a previously authorised orphan product.

[*The judgment is under appeal by the European Medicines Agency, supported by the Commission.*]

- **"*The one with the cooking metaphors*" - Case C-557/16 – Astellas Pharma – Judgment of 14 March 2018**

Background: In 2014, Helm AG obtained a Finnish marketing authorisation for a generic copy of medicinal products previously developed by Astellas Pharma GmbH. That authorisation was granted pursuant to the decentralised procedure regulated by Directive 2001/83/EC. In that procedure, Finland was one of the concerned Member States. Denmark acted as the reference Member State. Astellas Pharma GmbH disagreed with the calculation of the data exclusivity period carried out in the assessment of Helm AG's application, arguing that the wrong starting date has been chosen. It challenged the marketing authorisation issued by the competent Finnish authority before the Finnish courts.

The legal question referred to the Court was twofold: to what extent are the Member States participating in a decentralised procedure responsible for the calculation of the data protection period and/or do national bodies have the competence to review such calculation, i.e. may a regulator of a concerned Member State, such as the competent Finnish authority, and/or the courts of the same concerned Member State, review a previous determination of the data exclusivity period made within the decentralised procedure?

Highlights from the Judgment:

- The Court recalled that the decentralised procedure under Article 28 of Directive 2001/83 consists of several stages. Once the European part of the decentralised procedure closes with the general agreement (end of procedure notice), the competent authorities of the participating Member States are required to adopt a marketing authorisation decision in conformity with the assessment report. "*Therefore, once that general agreement is acknowledged, the competent authorities of those Member States may not, when making their decision on the placing on the market of that medicinal product in their territory, call into question the outcome of that procedure*." (para. 26)

- The decentralised procedure for a generic marketing authorisation application includes the verification of the expiry of the data exclusivity period for the reference medicinal product, as it is a pre-condition for the granting of a marketing authorisation for a generic medicinal product. "*In the decentralised procedure for MAs, compliance with that condition must be verified by all the Member States participating in that procedure.*" (para. 29) In the event of disagreement on this point, a Member State may refuse to approve the assessment report (para. 30).

- The Court moreover confirmed that a court of a Member State concerned by the decentralised procedure for MAs, hearing an action brought by the holder of the MA for the reference medicinal product against the MA decision for a generic medicinal product in that Member State taken by that State's competent authority, has jurisdiction to review the determination of the point in time from which the data exclusivity period for the reference medicinal product starts to run and to ascertain whether the initial MA for the reference medicinal product, granted in another Member State, was granted in accordance with that directive.

- This is due to the fact that the decentralised procedure does not provide for the adoption of other measures against which the marketing authorisation holder of the reference product could bring court proceedings. "*It follows that effective judicial protection of the rights held by the holder of a MA for the reference medicinal product as regards the data exclusivity of that medicinal product can be ensured only if that holder can rely on those rights before a court of the Member State in which the competent authority adopted a MA decision for the generic medicinal product and if it can, inter alia, plead before that court an error relating to the determination of the point in time from which the exclusivity period, affected by that decision, starts to run."* (para. 39).

- Such review is however limited to review the determination of the start of the data exclusivity period. The national court does not have jurisdiction to review whether the initial marketing authorisation for the reference product granted in another Member State was granted in accordance with Directive 2001/83.

- The Advocate-General had summarised the gist of this reasoning using a cooking metaphor: *"the Member States' authorities cannot be said to be obliged to serve a meal that was forced on them. They were in the kitchen when it was being prepared and could have had their say in what was being cooked. They are therefore co-responsible for its quality.*" (para. 103 of the preceding opinion)

➢ "*The one on off-label use*" - Case C-29/17 – Novartis – Opinion of 25 July 2018

Background: The case concerns the decision of the competent Italian authorities to include in the list of medicinal products that are reimbursed under the national health system the off-label use of the medicinal product Avastin (marketing authorisation holder: Roche). That decision was subsequently attacked by the company Novartis, which holds a marketing authorisation for the product Lucentis, which is authorised for the indication in which the off-label use of Avastin takes place. The Italian court referred several question to the ECJ, which essentially concern the question to what extent the reimbursement decision may infringe principles laid down in the EU regulatory framework for pharmaceuticals as set out by Directive 2001/83 and Regulation 726/2004.

Highlights from the Opinion:

- The Advocate-General considers that the EU regulatory framework for pharmaceuticals does in principle not prevent Member States from taking the decision to reimburse the off-label use of medicinal products, even if this decision is driven by cost-containment considerations. In this regard, the AG recalls the competence of Member States for the organisation of health care services, as recognised in the Treaties and in Directive 2001/83 itself.
- However, when exercising this competence Member States must respect EU law and refrain from any action that could endanger the "effet utile" of the pharmaceutical framework. This means that the product to be reimbursed must be manufactured and placed on the market in accordance with EU law: « *Il en découle, selon moi, que le droit de l'Union ne s'oppose pas à la prise en charge, par les régimes d'assurance des soins de santé des États membres, d'un médicament utilisé hors AMM, à condition toutefois que ce médicament soit, en particulier, mis sur le marché et fabriqué dans le respect de la réglementation pharmaceutique de l'Union. » (para. 47)*
- The Advocate-General therefore scrutinises in detail whether the way Avastin is made available for off-label use, which includes in particular the repackaging of Avastin by hospital pharmacies in Italy with a view to its use in ophthalmology, would infringe Directive 2001/83. In this context, the AG takes the view that this preparatory steps do not lead to the manufacture of a new product distinct from Avastin: « *Cette approche était, me semble-t-il, sous-tendue par l'idée selon laquelle, pourvu que la substance médicamenteuse elle-même n'en soit pas altérée, les changements apportés au dosage, au conditionnement et à la voie d'administration de l'Avastin en vue de son utilisation hors AMM n'aboutissent pas à la création d'un médicament distinct aux fins de l'application de la réglementation pharmaceutique de l'Union. » (para. 60)*
- The Advocate-General also clarifies that off-label use is no necessarily limited to situations that comply with Article 5(1) of Directive 2001/83, so-called named-patient use. In this context, the AG also recalls that the prescription of a medicine for reasons of its (cheaper) cost, does not justify the use of this derogation.

- **"*The one where before becomes after*" - Cases C-680/16P –August Wolff – Opinion of 4 October 2018**

Background: In September 2014 two marketing authorisation holders brought the Commission to court requesting the (partial) annulment of the Commission decision that completed a Union interest referral under Article 31 of Directive 2001/83 initiated by Germany on high-concentration estradiol containing products (national marketing authorisations). Those 'referral procedures' are used to address concerns regarding the safety, efficacy or quality of authorised products with the aim to come to a harmonised view whether the marketing authorisation should be varied, withdrawn or maintained. In this case, it was concluded based on the available evidence, especially new knowledge regarding systemic effects of hormone-replacement therapies, that the risk of this hormone therapy using a crème containing estradiol in high concentration is higher than previously thought and that the use of the products should be restricted.

The applicants alleged several procedural mistakes (related to the timing of the initiation of the procedure and the handling at EMA), as well as the scientific soundness of the EMA opinion (CHMP) on which the Commission decision is based.

All those claims were dismissed by the General Court in its first instance ruling of 2016 but the companies appealed the ruling.

On 4 October the Advocate-General published its legal opinion considering that the first instance ruling should be overturned and the Commission decision annulled.

Opinion of the Advocate-General

- As every appeal before the EU courts, the 2nd instance is not a full review of the first instance ruling, but is limited to a scrutiny of legal errors. While rejecting most of the pleas of the Applicant, the Advocate-General considered that the General Court erred in three instances, two of them are of procedural nature and one relates to the reasoning of the General Court.
- **Criteria for the initiation of the EU review procedure**: According to Article 31 of Directive 2001/83, a review procedure under this provision can only be initiated by a Member State *before* a decision at national level is taken. In the case at hand, Germany took an initial decision in 2005 (refusing the renewal of the MA - Nachzulassung). This decision never became effective due to the immediate initiation of legal proceedings which had suspensive effect. Hence, the product remained on the market as before. Moreover, Germany claimed that in 2005 it was not aware that the same product was available in other Member States. In the first instance ruling the General Court agreed with the Commission's reading that under those circumstances Germany could still initiate a referral in 2012. The Advocate-General however disagrees and recommends a stricter understanding of the provision. Once an initial decision at national level is taken, the procedure under Article 31 is no longer available. Instead, the AG refers to the procedure under Article 30, which can be used to harmonise marketing authorisations in case of divergent decisions at national level [*however, this would not have solved the issue, as at the time of the Commission decision, there were no divergent decisions, as the 2005 'decision' by Germany was annulled in last instance in 2013. Moreover, it may lead to a situation where a*

Member State despite a valid concern would not be able to initiate a safety review at EU level.]

- **Impartiality**: The Agency appointed as main rapporteur in the EU review procedure Germany, in line with the internal rules of EMA that were applicable at the time. The rapporteur prepare the initial assessment, which is subsequently discussed by the CHMP. The main rapporteur was in this case supported by three other rapporteurs, two of them conducted an independent review of the initial assessment in view of the re-examination requested by the company. Still, the Advocate General considers that with the appointment of German rapporteur the impartiality of the assessment could not be guaranteed for objective reasons, given that the main rapporteur may have had a decisive influence on the outcome of the assessment. The AG links this decisive influence to the fact that according to the wording of Article 62 the rapporteur would be responsible for the "coordination of the evaluation". [*however, this argument is based on a wording of Article 62 that does not correspond to the current wording of the provision – that part has been deleted by an amendment adopted in 2010; in accordance with Article 57 the coordination of the evaluation is primarily the task of the Agency*]
- **Reasoning of the General Court**: Finally, the Advocate-General considered that the General Court did not sufficiently deal in its judgment with the argument of the applicant that the recommended restriction to the use of the estradiol crème is not proportionate, as it would lead to making the product devoid of any purpose. The scientific reasoning concluded that the product should be used only once and not repetitive.

➢ "*The one with the carve-out*" - Cases C-423/17 – Staat der Nederlanden v Warner-Lambert – Opinion of 4 October 2018

Background: Generic copies of reference medicinal products may be authorised and placed on the market once the regulatory data protection period has expired (8+2 year sysem). However, the marketing may still be precluded by patent or-patent-like rights such as SPCs. In order to allow the possibility of a generic medicinal product being placed on the market only for indications and dosage forms of the reference medicinal product which are no longer patented, Directive 2001/83 (Article 11) permits an exception to the principle of the uniformity of the reference medicinal product and the generic medicinal product: manufacturers of generic medicinal products can introduce a 'carve-out', whereby still patented indications or dosage forms of the reference medicinal product are deleted from the summary of characteristics of the generic medicinal product.

It is not expressly regulated what effects the introduction of a carve-out in the summary of characteristics of a generic medicinal product has on the scope of the marketing authorisation for that generic medicinal product; i.e. whether the carve-out changes the scope of the marketing authorisation or not.

That was the question of this preliminary ruling where the Dutch authorities published the full SmPC on their website even if the generic company had applied for a carve-out.

Opinion of the Advocate-General

- The AG recalls that "*the carve-out arrangement in the second sentence of Article 11 of Directive 2001/83, whereby still patented indications or dosage forms of the reference medicinal product need not be included in the summary of*

characteristics of a generic medicinal product, permits an exception to the principle of the uniformity of the reference medicinal product and the generic medicinal product." (para. 42)

- A carve out may be requested with the initial application or subsequently, e.g. as a consequence of patent litigation.
- By introducing a carve-out at the time of the initial application, the manufacturer of a generic medicinal product reduces, at its own request, the number of indications or dosage forms for which its medicinal product is to be approved. There is no obligation to introduce a carve-out; rather it is an option which the directive offers manufacturers of generic medicinal products in order to avoid infringements of patent rights. The manufacturer of a generic medicinal product must itself assess whether there is a risk of an infringement of patent rights in the absence of a deletion of still patented indications or dosage forms, since it is for the manufacturer of the generic medicinal product to determine autonomously the indications and dosage forms for which it wishes to place its generic medicinal product on the market. (para. 56) The authorities are bound by the scope of the application submitted and would have neither any reason nor any power to grant a marketing authorisation that also covered indications or dosage forms excluded by the applicant by means of the carve-out. (para. 57).
- The carve-out may also be requested after the initial application has been submitted. This may be especially relevant for decentralised procedures, where the duration of patent protection differs between Member States. Still, this should not bar the applicant from making use of the decentralised procedure. (para. 59)
- It is a fundamental principle of the law on medicinal products that the authorised version of a medicinal product and the version placed on the market must be identical. Consequently, the authorisation holder may not under any circumstances autonomously and without the consent of the competent authorities modify the SmPC and the package leaflet for a medicinal product. (para. 62)
- As the carve-out that has been requested with the initial application a subsequently introduced carve-out must therefore result in the limitation by the competent authorities of the authorisation granted. (para. 65) The notification of a subsequent carve-out must therefore be regarded as an application to limit the previously granted marketing authorisation for a medicinal product. In this connection, Directive 2001/83 and Regulation No 1234/2008 lay down various provisions which give an authority the right to vary the previously granted authorisation. (para. 71)
- The effect of carve-outs introduced in various Member States concerned is that the marketing authorisation for a single medicinal product differs in extent in the Member States concerned. This cannot be avoided, however, in the absence of uniform Union-wide patent protection, as the same indication or dosage form can be protected in various Member States with a different scope and for different periods of time. In the light of this, the carve-out arrangement provided for in Article 11 of Directive 2001/83 and in Article 3(3)(b) of Regulation No 726/2004 is an essential instrument, as it is the only possible means, after the expiry of the data exclusivity period for a reference medicinal product, which is uniformly regulated in EU law, to have a generic medicinal product authorised in a single procedure in all or several Member States and, at the same time, to take account of the potentially different patent protection in those Member States.

- Under Article 21(3) of Directive 2001/83, the competent authorities must make publicly available the SmPC for each medicinal product which they have authorised. If a carve-out limits the scope of the marketing authorisation and the marketing authorisation and the SmPC thus have the same scope, there is therefore no reason to publish a summary of product characteristics going beyond the scope of the marketing authorisation. (para. 84)

- **Watch list - Interesting pending cases on regulatory issues**

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-303/16** (Novartis v Commission), direct action against the Commission decision in an Article 29 referral on tobramycin-containing products;

Case **T-329/16** (BMS v Commission/EMA), direct action against the Commission/EMA challenging the decision to withdraw the orphan status of a product at the time of marketing authorisation;

Case **T-191/17** (Boehringer Ingelheim v Commission), direct action against Commission marketing authorisation challenging the wording of an authorised indication;

Case **T-733/17** (GMP-O v Commission), direct action against the Commission challenging the decision to withdraw the orphan status of a product at the time of marketing authorisation;

Case **T-783/17** (GE Healthcare v Commission) direct action against the Commission decision in an Article 31 referral on gadolinium containing contrast agents;

Case **T-211/18** (Vanda Pharmaceuticals v Commission) direct action against a Commission decision to refuse the marketing authorisation for the medicinal product Fanaptum;

Case **T-549/18** (Hexal v EMA) direct action against an EMA decision not to validate a generic marketing authorisation in view of the reference product (Aubagio) still being under regulatory data protection – new active substance status;

Case **T-594/18** (Pharma Mar v Commission) direct action against a Commission decision to refuse the marketing authorisation for the medicinal product Aplidin;

Case **C-680/16P** (August Wolff v Commission), appeal against first instance ruling dealing with an Article 31 referral on high-concentration estradiol containing products;

Case **C-359/18P** (EMA v Shire) appeal against T-80/16;

Case **C-387/18** (Delfarma), preliminary reference concerning parallel trade of generic medicines.

- **Watch list - Interesting cases on the SPC Regulation**

- **"*The one on the combination SPC*" - Cases C-121/17 – Teva v Gilead – Judgment of 25 July 2018**

Background: The case concerns the interpretation of Article 3(a) of Regulation (EC) No 469/2009 (the SPC Regulation) which sets out the conditions for obtaining a supplementary protection certificate, one of which is that the product for which the SPC is granted "is protected by a basic patent in force".

The case was referred to the CJEU by the UK High Court in view of national patent and SPC litigation concerning the medicinal product Truvada, an HIV medicine. The product has been authorised by the Commission (*and not by the European Medicines Agency as the Court wrongly claims*) in 2005 under the centralised procedure. Truvada is a fixed-dose combination consisting of two active substances tenofovir disoproxil and emtricitabine.

Gilead hold a patent which indicates that the patent covers, in general terms, a series of molecules which are helpful in the therapeutic treatment of a number of viral infections, in particular HIV. The patent expressly mentions tenofovir disoproxil (TD) as one of the claimed compounds, but there is no mentioning of emtricitabine. Instead, the patent refers to "a pharmaceutical composition comprising a compound according to any one of claims 1-25 together with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients". In 2008 Gilead obtained an SPC for Truvada based on this patent. That SPC relates to a 'composition containing [TD], optionally in the form of a pharmaceutically acceptable salt, hydrate, tautomer or solvate, together with emtricitabine

The SPC was subsequently challenged by generic companies, leading to the question whether the product Truvada is indeed protected by the basic patent in force.

Considerations of the Court:

The rules for determining what is 'protected by a basic patent in force' within the meaning of Article 3(a) of Regulation No 469/2009 are those relating to the extent of the invention covered by such a patent. In this regard the claims of the patent play a key role. (para. 32 and 34)

A product cannot be considered to be protected by a basic patent in force within the meaning of Article 3(a) of Regulation No 469/2009 unless the product which is the subject of the SPC is either expressly mentioned in the claims of that patent or those claims relate to that product necessarily and specifically. It is not the purpose of the SPC to extend the protection conferred by that patent beyond the invention which the patent covers

In view of the interests referred to in recitals 4, 5, 9 and 10 of Directive 469/2009, it cannot be accepted that the holder of a basic patent in force may obtain an SPC each time he places on the market in a Member State a medicinal product containing, on the one hand, an active ingredient, protected as such by the holder's basic patent and constituting the subject matter of the invention covered by that patent, and, on the other, another substance which does not constitute the subject matter of the invention covered by the basic patent (para. 42).

It follows from the above that the subject matter of the protection conferred by an SPC must be restricted to the technical specifications of the invention covered by the basic patent, such as claimed in that patent.

For that purpose, from the point of view of a person skilled in the art and on the basis of the prior art at the filing date or priority date of the basic patent:

- the combination of those active ingredients must necessarily, in the light of the description and drawings of that patent, fall under the invention covered by that patent, and
- each of those active ingredients must be specifically identifiable, in the light of all the information disclosed by that patent.

In the present case it is apparent, first, from the information in the order for reference that the description of the basic patent at issue contains no information as to the possibility that the invention covered by that patent could relate specifically to a combined effect of TD and emtricitabine for the purposes of the treatment of HIV. Consequently, it does not seem possible that a person skilled in the art, on the basis of the prior art at the filing date or priority date of that patent, would be able to understand how emtricitabine, in combination with TD, necessarily falls under the invention covered by that patent.

Pending cases:

Case **C-443/17**: This preliminary reference touches on some questions concerning the interpretation of Regulation (EC) No 469/2009 on supplementary protection certificates (SPC) with regard to the scope of eligible products and in particular with regard to the interpretation of Article 3(d) of the SPC Regulation.

Article 3 sets out the conditions for obtaining a certificate, which are as follows:

"A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:

a. the product is protected by a basic patent in force;
b. a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC or Directive 2001/82/EC, as appropriate;
c. the product has not already been the subject of a certificate;

the authorisation referred to in point (b) is the first authorisation to place the product on the market as a medicinal product."

The national court essentially asks whether Article 3(d) of the SPC Regulation is to be interpreted as permitting the grant of an SPC where the product is a new formulation of an old active ingredient.

Case **C-527/17**, preliminary reference regarding the SPC coverage of an ancillary medicinal product in a medical device. The national court asks whether a combined product consisting of a medical device and an ancillary medicinal substance could be eligible for the SPC protection (or at least the ancillary medicinal substance contained in that product. => ruling expected for 25 October 2018

Action to be taken:
For information