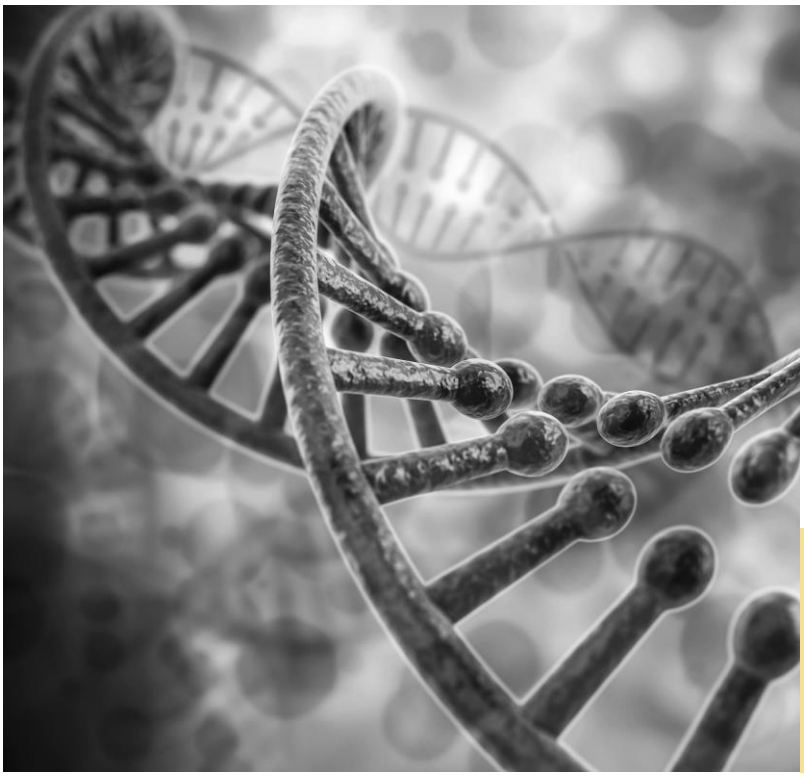

EU life sciences & regulatory newsletter

ASHURST BRUSSELS

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Content

Ashurst has a well-established practice and specialist expertise in life sciences and regulatory, and is regularly listed as one of the leading law firms in the field. Our EU life sciences and regulatory newsletter focuses on important EU case law developments affecting the life sciences sector

Carving-out patent protected indications of generic medicines post-authorisation?

In her Opinion issued on 4 October 2018, Advocate General (AG) Kokott invites the EU Court of Justice (ECJ) to endorse a pragmatic application of the 'carve-out' for indications and dosage forms still under patent when Member States authorise generic human medicines. In particular, the generic applicant should be allowed to introduce a 'subsequent carve-out' after the marketing authorisation has been granted, but before the generic product is actually placed on the market (C-423/17, Warner-Lambert Company).

WHAT YOU NEED TO KNOW

- Where the originator enjoys patent protection only in relation to certain indications or dosage forms, EU law allows the marketing of generic medicines for the unpatented indications and dosage forms (after the data exclusivity period for the reference product has expired).
- To avoid patent right infringements, generic manufacturers are allowed to introduce a 'carve-out' as foreseen in Article 11 of the Human Medicines Directive (2001/83). This ensures the deletion of the still patented indications or dosage forms from the published summary of the product characteristics (SmPC) of the generic medicine.
- The AG favours a pragmatic application of the carve-out mechanism allowing the generic manufacturer not only to introduce the carve-out at the stage of the authorisation application ('initial carve-out'), but also, where necessary, to introduce the carve-out after the marketing authorisation has been granted, but before the generic product is actually placed on the market ('subsequent carve-out').

Background

The case originated in the Netherlands where the pharmaceutical company, Aurobindo, applied for a marketing authorisation for a generic version of the human medicine Lyrica, which can be used to treat epilepsy, generalised anxiety disorder and neuropathic pain.

As the company sought authorisations in several Member States, it made use of the decentralised authorisation procedure. The indication for neuropathic pain was still patented at the time in the Netherlands. However, the company's application submitted in the decentralised procedure did not contain any carve-out in that regard, as foreseen in Article 11 of the Human Medicines Directive.

The company introduced the carve-out in the Netherlands only after the marketing authorisation had been granted, but before the generic medicine had been placed on the market. The company notified the regulator of the carve-out and requested the removal of the patented indication from the published summary of the product characteristics (SmPC), in accordance with the subsequent carve-out.

The Dutch regulator rejected that request and published the complete SmPC, including the still patented indication. The position of the Dutch regulator is that the carve-out must be part of the initial application for authorisation. This led the originator, Warner-Lambert Company, to

initiate court proceedings in the Netherlands for alleged infringement of its patent rights.

It is in the context of these national proceedings that the ECJ has been asked to clarify the application of the EU carve-out rule and in particular to consider the possibility of a subsequent carve-out after the marketing authorisation has been granted.

The AG's Opinion

In her Opinion of 4 October 2018, the AG agrees with the EU Commission that a generic manufacturer must be allowed to introduce a subsequent carve-out.

In the AG's view, this reading is the only possible means to ensure that generic medicines can be authorised in a single procedure in all or several Member States, and, at the same time, to accommodate the patent rights of the originator which may differ in the various Member States (in the absence of a uniform EU-wide patent protection).

This reading is further supported, according to the AG, by the need to ensure that the marketed version of a medicine always corresponds to the authorised version, as described in the SmPC.

On the basis that the notification of a subsequent carve-out limits the scope of a previously granted marketing authorisation, the AG concludes that national regulators, having been notified of a carve-out, must refrain from publishing the full label version of the SmPC, including the patented indication or dosage form affected by the carve-out.

The judgment of the ECJ is still to be handed down and it remains to be seen whether the ECJ will follow the AG's proposed reading reconciling the law on medicinal products and patent law.

Depending on the final outcome of the case, one or more national regulators may have to re-visit their approach to subsequent carve-outs, which will certainly include the Netherlands.

Advocate General challenges neutrality and proper use of EMA referral for estradiol

Following a referral initiated by Germany under Article 31 of the Human Medicines Directive (2001/83), the EU Commission adopted a decision restricting the use of medicinal products containing high concentrations of estradiol. In his Opinion of 4 October 2018, Advocate General (AG) Mengozzi advises the EU Court of Justice (ECJ) to annul the EU Commission decision on appeal and to set aside the earlier EU General Court (GC) judgment of 20 October 2016 which had upheld the validity of the restrictions imposed by that decision (C-680/16 P, August Wolff and Remedia -v- Commission).

WHAT YOU NEED TO KNOW

- This is the first case in which the ECJ is called upon to rule on the conditions for a referral under Article 31 of the Human Medicines Directive and the procedural guarantees for a company in the context of such a referral.
- A Member State can refer a matter to the EMA's Committee for Medicinal Products for Human use (CHMP) under Article 31 of the Human Medicines Directive (i) where the interests of the Union are involved but (ii) before the Member State has taken a decision on the marketing authorisation of the products in question.
- The referral procedure should be conducted impartially. According to the AG, the CHMP chief rapporteur should not be an employee of the referring Member State.

Background

Following a referral initiated by Germany under Article 31 of the Human Medicines Directive, the CHMP recommended measures restricting the use of two high-strength estradiol-containing creams, Linoladiol N and Linoladiol HN.

A referral under Article 31 of the Human Medicines Directive can be triggered in specific

cases, when the interest of the Union is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines.

The CHMP recommendations were sent to the EU Commission which endorsed them in a final decision in 2014 making the restrictions binding across the EU (i.e. treatment of maximum 4 weeks and no repeat usage).

By judgment of 20 October 2016, the GC dismissed the action for annulment brought by the marketing authorisation holders against the EU Commission decision (*Case T-672/1 Remedia and August Wolff -v- Commission*). They decided to bring the case before the ECJ on appeal.

The AG's Opinion

AG Mengozzi recommends to grant the appeal. He proposes that the ECJ annul the contested EU Commission decision for breach of Article 31 of the Human Medicines Directive and the principle of impartiality. Alternatively, the AG invites the ECJ to refer the case back to the GC for a more complete review of the proportionality arguments invoked by the marketing authorisation holders.

The AG agrees with the marketing authorisation holders that Germany did not lawfully trigger the Article 31 referral in this case. The AG recalls that two conditions must be fulfilled for an Article 31 referral: (i) there must be a particular Union interest for the referral; and (ii) the referral must be triggered before any decision is taken on the marketing authorisation of the products in question.

The AG starts its analysis by emphasising that Article 31 grants Member States the possibility to bring any concern regarding an active ingredient before the EMA. Article 31 should therefore not be limited only to instances where new information (e.g. pharmacovigilance data) raises doubts on drug efficacy or safety.

In this case, however, Germany initiated the referral after refusing the renewal of product authorisations at national level. On this basis, the AG considers that the second condition for an Article 31 referral was clearly not met and that the EU Commission should therefore have refused the referral. It is irrelevant that, at the time, court proceedings were still pending against the German refusal.

The AG further considers that there has been a breach of the principle of impartiality rendering the referral procedure, and the resulting EU Commission decision, defective.

Particularly problematic, according to the AG, is the fact that an employee of the referring national authority (*in casu* Germany) was appointed as the CHMP chief rapporteur in charge of the referral procedure. This is so because the rapporteur can exercise decisive influence on the outcome of the procedure.

On the EMA's substantive review underlying the contested Commission decision, the AG recalls the broad discretion regulators enjoy when performing complex scientific assessments. It is thus for the company to demonstrate that a manifest error of assessment has been made. No evidence to that effect was given in this case.

The AG further confirms that the precautionary principle entitles regulators to take protective measures suspending, revoking or varying existing marketing authorisations. In the present case, the AG considers that the CHMP recommendations could legitimately raise serious doubts on safety or efficacy.

Finally, the AG concludes that the GC judgment is not adequately reasoned on the proportionality of the contested decision.

The final judgment in this case is to be watched for as this is the first time the ECJ has the opportunity to rule on the conditions for an Article 31 referral and the procedural guarantees for a company in the context of such a referral, in particular to ensure the impartiality of the referral procedure.

GC upholds EU carcinogenicity classification of chemical substance anthraquinone

On 24 October 2018, the EU General Court (GC) dismissed the action brought by Deza seeking the annulment of the Commission Regulation classifying and labelling anthraquinone as a carcinogenic substance under Regulation 1272/2008 (CLP Regulation) (Case T-400/17, Deza -v- Commission).

WHAT YOU NEED TO KNOW

- The EU Commission enjoys a broad discretion when classifying a chemical substance under the CLP Regulation and in particular as regards the evaluation of scientific studies and the choice of studies which take precedence over others.
- A high burden of proof lies on the applicant to show that the EU Commission failed to take into account all the relevant elements and circumstances.

Background

In 2017, the EU Commission adopted a harmonised hazard classification for anthraquinone (AQ), a substance used in the production of synthetic dyes. As a result, AQ is included as a carcinogen in Annex VI to the CLP Regulation.

The EU classification decision is entirely in line with the scientific opinion delivered by the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) and essentially relies on the results of two carcinogenicity studies conducted in 1996 and published in 2005.

The RAC opinion concluded that there was sufficient evidence in the experimental animals of carcinogenicity. Deza, a Czech manufacturer of AQ, however, disagreed with the RAC findings and the resulting classification upheld by the EU Commission and brought an action for annulment before the GC. Deza in particular questioned the relevance and scientific reliability of the two carcinogenicity studies relied on by ECHA. The company argued that ECHA and the EU Commission failed to consider newer scientific data.

The GC judgment

The GC dismisses Deza's legal action in its entirety and thus upholds the validity of the EU carcinogenicity classification for AQ.

In doing so, the GC relies on the broad discretion enjoyed by the EU Commission when classifying a substance pursuant to the CLP Regulation. This discretion relates to the nature and the scope of the measures as well as to the finding of the basic facts. This includes the Commission's discretion to consider scientific studies and in particular to give certain studies more weight over others, irrespective of their chronology.

In this case, the GC concludes that the EU Commission did not commit a manifest error of appreciation in considering that the two studies were sufficiently reliable to classify AQ as carcinogenic. In doing so, the GC relies heavily on the content of the RAC opinion which appears to have addressed all of the concerns invoked by the company before the GC, including the fact that the studies were conducted more than 20 years ago and concerned AQ with a different purity profile than the AQ currently placed on the market.

ECJ rules against the granting of SPCs for substances used in medical devices

In a preliminary ruling issued on 25 October 2018 (Case C-527/17, Boston Scientific), the EU Court of Justice (ECJ) ruled that a supplementary protection certificate (SPC) cannot be granted in respect of a substance that has been approved for use in a medical device but which has not been the subject of a prior authorisation procedure as a medicinal product.

WHAT YOU NEED TO KNOW

- The protection granted by a supplementary protection certificate (SPC) must be strictly confined to products which have obtained marketing authorisation as a medicinal product under the Human Medicines Directive (2001/83).
- A substance approved for use in a medical device under the Medical Devices Directive (93/42) cannot on that basis be the subject of an SPC.
- In determining whether a product falls under the definition of 'medicinal product' or is part of a 'medical device', regard should be had to the principal mode of action of the product.

Background

The case originated when Boston Scientific (Boston) filed an SPC application with the German Patent Office in relation to a patented substance (Paclitaxel) used as an adjuvant product in a specific medical device (the TAXUS device). The German Patent Office refused that application on the ground that, in particular, the substance had not been the subject of a marketing authorisation issued under the Human Medicines Directive (2001/83) for that particular use.

Boston challenged that decision before the German courts arguing that the substance in question had, during the compulsory certification procedure established by the Medical Devices Directive (93/42), undergone safety, quality and efficacy testing which was equivalent to that required as part of the marketing authorisation procedure for medicinal products. Boston, therefore, took the view that the two procedures were essentially similar and that a substance used as an adjuvant in a medical device should be eligible for an SPC.

The German Federal Patent Court, while having sympathy for Boston's arguments, decided to stay the national proceedings to request a preliminary ruling from the ECJ.

The ECJ preliminary ruling

In its judgment, the ECJ concludes that the concepts of 'medicinal product' and 'medical device' are mutually exclusive and stated that in determining which definition a product falls under, the competent authorities should have regard to the principal mode of action of the product.

In this case, the ECJ finds that the substance concerned did not achieve its principal mode of action by pharmacological, immunological or metabolic means, but exerted an action upon the body that was ancillary to that of the TAXUS device in which it was incorporated. Therefore, the substance had to be considered as forming an integral part of the TAXUS device.

The ECJ goes on to state that the certification procedure for medical devices is not equivalent or comparable to the marketing authorisation procedure for medicinal products. A certification issued under the Medical Devices Directive thus cannot be assimilated to a marketing authorisation issued under the Human Medicines Directive for the purposes of the SPC Regulation (469/2009).

The ECJ also states that the EU legislature intended to reserve the granting of SPCs to medicinal products alone, to the exclusion of medical devices and substances used in such devices. In this case, the substance was therefore not eligible for an SPC in relation to its use in the TAXUS device.

New actions before the EU courts

This section of the newsletter looks at some of the key cases introduced before the EU Court of Justice (ECJ) and the EU General Court (GC) and recently reported in the *Official Journal of the European Union* (*)

(*)Undertakings with an interest in direct actions can request permission to intervene before the court within six weeks of the Official Journal publication (one month for appeals before ECJ). There is no possibility for intervention in the case of requests for preliminary rulings.

Verification of REACH SME status

A new action has been brought before the EU General Court against the European Chemicals Agency (ECHA) for refusing medium-sized status and associated reduced fees. The registrant claims that ECHA mistakenly took account of its former, rather than its current, parent company for the purpose of determining its company size (*T-481/18*, *Electroquímica Onubense -v- ECHA*, *OJ* of 1 October 2018).

Parallel trade of plant protection products

The Dutch Business Appeal Tribunal (College van Beroep voor het Bedrijfsleven) has asked the EU Court of Justice to clarify the conditions for extending a parallel trade permit under Article 52 of the Plant Protection Products Regulation (1107/2009). In particular, where the reference product is no longer manufactured by its initial owner and at the same manufacturing site (*C-445/18*, *Vaselife International*, *OJ* of 15 October 2018).

Plant protection products - Appeal against 'neonics' judgment

Bayer CropScience decided to appeal the EU General Court judgment of 17 May 2018 in *Case T-429/13*, *Bayer CropScience –v– Commission*, upholding the EU Commission restrictions imposed on neonicotinoid substances in 2013 (*Case C-499/18 P*, *Bayer CropScience and Bayer -v- Commission*, *OJ* of 22 October 2018).

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