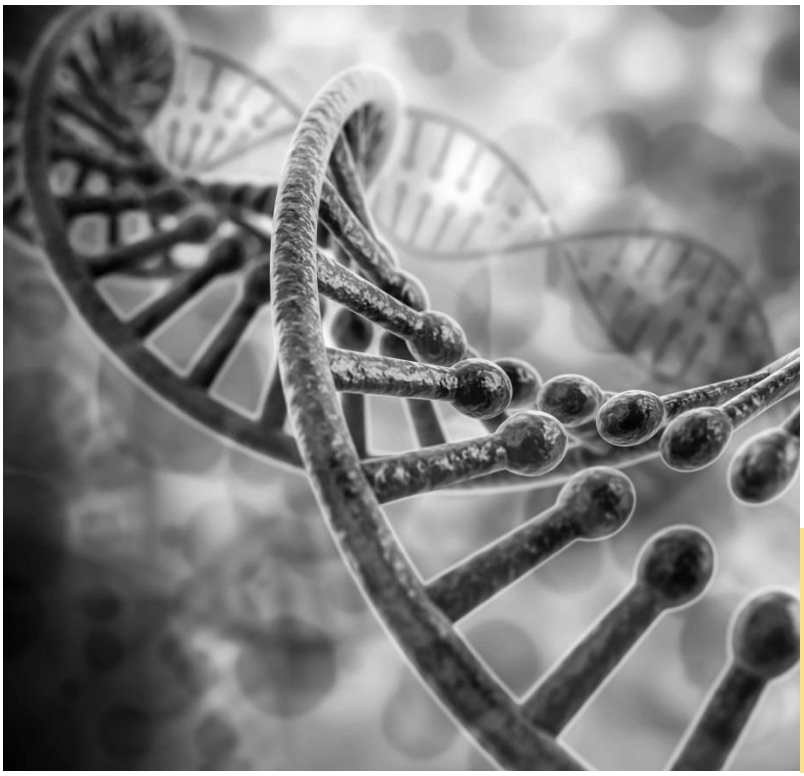

EU life sciences & regulatory newsletter

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, ECHA appeal and European Ombudsman decisions affecting the life sciences sector.

EU Court upholds EFSA publication of unredacted conclusion on diflubenzuron review

In a judgment of 14 December 2018, the EU General Court ("GC") concludes that EFSA was entitled to publish the conclusion on the peer review of the active substance diflubenzuron in its entirety (T-725/15, Arysta LifeScience Netherlands -v- EFSA). The GC considers that EFSA cannot be criticised for having disclosed the conclusion in its entirety in the interests of protecting public health, including sections identifying human health concerns from exposure to a metabolite. Such information relates to "foreseeable health effects" which EFSA arguably must disclose under Article 39(3) of Regulation 178/2002.

WHAT YOU NEED TO KNOW – KEY PRACTICAL TAKE-AWAYS

- Public disclosure of EFSA conclusions on the review of plant protection substances is governed by Regulation 178/2002 and the sector-specific confidentiality rule laid down in Article 63 of Regulation 1107/2009 (PPPR). Article 63 PPPR seeks *inter alia* to protect commercial interests from harmful disclosure.
- Confidential treatment for information in EFSA conclusions may be requested prior to publication. To this end, the company must provide "*verifiable evidence*" that disclosure might undermine commercial interests. Confidential treatment may nevertheless be refused on the basis of an overriding public interest in disclosure. This implies the weighing of opposing interests by EFSA.
- The judgment of 14 December 2018 appears to give prevailing weight to Article 39(3) of Regulation 178/2002 to set aside confidentiality claims under Article 63 PPPR. It would imply that EFSA conclusions relating to "*foreseeable health effects*" are on "*no account to be kept confidential*", even if they contain commercially sensitive information deserving of protection from disclosure under Article 63 PPPR.

Background

Diflubenzuron is an insecticide substance approved since 2009 for use on various crops, mainly apples, pears and mushrooms. In 2013, the EU Commission initiated the procedure under Article 21 PPPR for the review of an approved substance, in the light of new scientific and technical knowledge. In August 2015, EFSA delivered its conclusion identifying an *a priori* concern from potential exposure to metabolite 4-chloroaniline (PCA). In 2017, the EU Commission adopted an Implementing Regulation restricting the use of diflubenzuron only to non-edible crops.

The applicant brought an action against the EU Commission challenging the legality of the Implementing Regulation. This action is still pending before the EU General Court (Case T-476/17, *Arysta LifeScience Netherlands -v- Commission*). In addition, the applicant brought the present proceedings against EFSA challenging the publication of the conclusion. EFSA did give the applicant the opportunity to claim confidentiality before publishing the conclusion on its website, but refused to redact the sections

which, in the applicant's view, would undermine its commercial interests if disclosed.

The Court's judgment

The applicant unsuccessfully tried to prevent publication of the unredacted EFSA conclusion pending the court proceedings. Interim relief was rejected on appeal by the EU Court of Justice and, as a result, the conclusion has been accessible to the public since 2016. Still, the applicant was found to retain an interest in proceedings against EFSA, in view of the possibility to claim damages caused by an unlawful publication.

The GC first confirms that the sector-specific confidentiality regime of Article 63 PPPR applies to all documents held by EFSA, including the conclusion on diflubenzuron, and that the applicant could therefore request confidential treatment under Article 63. It rejects EFSA's extremely narrow reading of Article 63 PPPR as applying only to "*information submitted under [the PPPR]*", excluding information produced by EFSA. The GC rightly underlines that such a narrow reading conflicts with the very purpose of Article 63 PPPR and with the general provisions on access to documents of Regulation 178/2002. Also, EFSA conclusions essentially rely on information submitted by applicants and cannot therefore be seen in isolation from such information.

The GC then finds that EFSA did not breach the confidentiality rule of Article 63 PPPR in rejecting the applicant's claim that publication of certain sections would harm its commercial interests. The applicant failed to provide "*verifiable evidence*" as required under Article 63. Disclosure of scientifically incorrect information, as claimed by the applicant, is not capable as such to undermine commercial interests. Neither did the applicant explain the harm that could have come from potential procedural irregularities in the adoption of the conclusion.

The GC appears to attach particular importance to Article 39(3) of Regulation 178/2002 as a basis for setting aside confidentiality claims under Article 63 PPPR. Article 39(3) provides that EFSA conclusions relating to "*foreseeable health effects*" are on "*no account to be kept confidential*". The conclusion on diflubenzuron identified adverse effects on human health from the exposure to metabolite PCA which, in the GC's view, qualify as information on "*foreseeable health effects*" which EFSA must disclose.

In any event, even if EFSA had to carry out a balancing exercise, the Court concludes that EFSA cannot be criticised for having disclosed the conclusion in the interests of protecting public health, thereby giving precedence to the requirements related to the protection of those interests over economic interests.

Advocate General proposes to limit the scope of SPCs for patented new formulations

Under Article 3 of Regulation 469/2009 (SPC Regulation), the grant of a Supplementary Protection Certificate ("SPC") is subject to the condition that the 'product' (i.e. the active ingredient or combination of active ingredients) is (a) protected by a basic patent, (b) has been granted a marketing authorisation, (c) has not been subject of an SPC before and (d) the authorisation under (b) is the first authorisation to place the product on the market as a medicinal product. Problems in applying that provision arise where the 'product' in question is old but has been reformulated and has, as a result, obtained patent protection. Is a marketing authorisation for that new formulation the 'first marketing authorisation' within the meaning of Article 3(d) of the SPC Regulation? That is the question put to the EU Court of Justice ("ECJ") by a UK court in Case C-443/17, Abraxis Bioscience. In his Opinion of 13 December 2018, Advocate General Saugmandsgaard Øe ("AG") proposes to answer in the negative.

WHAT YOU NEED TO KNOW – KEY PRACTICAL TAKE-AWAYS

- An SPC can only be granted on the basis of the first marketing authorisation in the EU for a 'product' (active ingredient or combination of active ingredients).
- According to the Advocate General, even if a new formulation of a human medicinal product is patented, it cannot receive a SPC on the basis of marketing authorisation for that new formulation, if there was a previous marketing authorisation for the old formulation.

Background

The active ingredient paclitaxel has in the past received marketing authorisations for medicinal products under various brand names for use in eliminating cancer cells. Abraxis Bioscience reformulated paclitaxel into 'nab-paclitaxel' - which had the same use but with enhanced therapeutic effects – and obtained patent protection for it. Abraxis obtained marketing authorisation for formulations with nab-paclitaxel (sold under the brand name Abraxane). It later applied for and obtained an SPC for nab-paclitaxel in several Member States. However, the UK authorities refused to grant an SPC. The UK authorities argued that the marketing authorisation for nab-paclitaxel was not the 'first' within the meaning of Article 3(d) of the SPC Regulation, since the active ingredient paclitaxel had obtained marketing authorisations in the past. The reformulation into and patenting of nab-paclitaxel did not change that.

The AG's Opinion

In his Opinion the AG agrees with the UK's position on the basis of a literal reading of Article 3(d). As previous marketing authorisations exist for the 'product' (i.e. the active ingredient paclitaxel), the 'first marketing authorisation' condition under Article 3(d) is not fulfilled. In the AG's view, that conclusion cannot be changed by arguments relating to the purpose of the SPC Regulation, which is to encourage research, or its context. Key to the AG's reasoning on that point is the delicate balance struck by the legislator between competing interests of pharmaceutical companies, manufacturers, patients and insurers. According to that balance, the SPC can be used to give extra protection for new active ingredients, but not new formulations thereof, even if those new formulations are innovative and so patentable. In coming to that conclusion the AG considers in depth the Explanatory Memorandum accompanying the proposal for the SPC Regulation. Although that proposal refers to the grant of SPCs for 'new processes' and 'new applications' of products (not just new products), that is always subject to the requirement that all conditions for obtaining an SPC are fulfilled.

The AG's Opinion acknowledges that there are tensions in the EU case law. In particular, in *Neurim* (C-130/11) the ECJ did sanction the granting of an SPC in case of a new therapeutic use of an 'old' product already on the market as a *veterinary medicine*. Perhaps in light of those tensions, the AG does offer an alternative solution to the ECJ. That solution would allow for the grant of SPCs in cases of 'old' products with new therapeutic applications (as in the *Neurim* case) or 'old' products with new formulations. However, that would be allowed *only* where the new marketing authorisation relates to *human medicinal products* and the previous ones to *veterinary medicines.* It is noted however that that solution also appears at odds with yet other case law of the ECJ, in particular *Pharmacia Italia* (C-31/03), according to which the SPC Regulation does not distinguish in principle between marketing authorisations granted for human medicinal products and those for veterinary medicinal products. Moreover, since in this case the previous marketing authorisations were indeed granted for human medicinal products, even the alternative solution proposed by the AG would be of little practical use to Abraxis.

Finally, the AG confirms in his Opinion the possibility to transpose reasoning on the conditions of granting an SPC under the SPC Regulation to the equivalent legislation in the area of plant protection products (Regulation 1610/96).

ECHA Board of Appeal rejects challenge to ECHA decision requiring new study

In a Decision issued on 11 December 2018 (A-006-2017), the ECHA Board of Appeal ("BOA") dismissed the appeal brought by Dutch-based Climax Molybdenum B.V. against a decision by ECHA finding that a prenatal developmental toxicity study included in that company's registration dossier did not comply with OECD test guideline 414 and requiring the performance of a new study.

WHAT YOU NEED TO KNOW – KEY PRACTICAL TAKE-AWAYS

- ECHA is not bound by the OECD rules on the mutual acceptance of chemical data. Therefore, scientific studies accepted by agencies in other OECD countries may be rejected by ECHA if they do not comply with applicable test guidelines.
- The preliminary compliance check carried out by ECHA is an automatic process. Accordingly, if it finds that a study included in the registration dossier does not comply with applicable test guidelines, ECHA has no discretion and must identify a data gap and require the performance of a new study.

Background

In October 2010, Climax Molybdenum B.V. (the "*Appellant*") filed a registration dossier with ECHA for the substance *disodium molybdate* (the "*Substance*"). The dossier included the results of a prenatal developmental toxicity study (the "*Study*") that had been previously accepted for regulatory purposes by the US Environmental Protection Agency. The object of that Study was to establish the effects of prenatal exposure to the Substance on the pregnant test animal and on the developing organisms.

When carrying out the required compliance check of the registration dossier, ECHA concluded that the highest dose used in the Study (40 mg Mo/kg bw/day) was too low to comply with OECD test guideline 414 ("*TG 414*"), which requires that the highest dose should be chosen "*with the aim of inducing some maternal and/or developmental effects but not death or severe suffering*". In this case, however, the Study had not shown any relevant effects at the chosen highest dose. On 13 March 2017, ECHA therefore adopted a decision finding that the Study did not fulfil the relevant information requirement under REACH and requiring the performance of a new TG 414 study (the "*Decision*").

The Appellant challenged that Decision before the ECHA BOA, alleging (i) a manifest error of assessment; (ii) a violation of the OECD rules on the mutual acceptance of chemical data and of the principle of good administration; and (iii) a breach of the proportionality principle and the animal welfare provisions of REACH.

Decision

The BOA dismissed the appeal. The BOA firstly found that the various scientific studies relied on by the Appellant (which did show some relevant effects at the chosen highest dose) did not constitute "*adequate and reliable*" scientific information for the purposes of determining the appropriate highest dose to be used in a TG 414 study. Indeed, these studies were long-term studies whereas a TG 414 study is a short-term study. As such, these studies did not demonstrate that relevant effects could be expected to occur at the chosen highest dose in a TG 414 study.

The BOA also found that ECHA had not acted in breach of good administration principles and of the OECD rules on the mutual acceptance of chemical data, to the extent that those rules were not binding on ECHA and in any event would not prevent it from verifying whether the Study complied with the conditions set out in TG 414.

Finally, the BOA rejected the Appellant's claim that the Decision was disproportionate and in violation of animal welfare rules on the basis that the chosen highest dose in any event exceeded the measured levels of actual human exposure to the Substance, so that the Study was sufficient to exclude any risk for human health. In that

connection, the BOA stressed that the compliance check under REACH is not meant to take into account actual exposure to a substance in real life, as the levels and patterns of exposure of a substance may vary over time, so that regulators need to be fully informed about the intrinsic properties of substances irrespective of exposure. Accordingly, ECHA had no discretion, upon finding that the Study did not comply with TG 414, but to identify a data gap and require the performance of a new TG 414 study.

ECHA Board of Appeal annuls ECHA decision requiring new information

In a decision of 15 January 2019 (A-004-2017), the ECHA Board of Appeal ("BOA") upheld the appeal brought by 3v Sigma SpA against a decision by ECHA requiring it to provide further information on uses and environmental emissions of the UV filtering substance referred to as UVASORB HEB. The BOA rejected the other grounds aimed at annulment of the decision to request an OECD TG 308 study.

WHAT YOU NEED TO KNOW – KEY PRACTICAL TAKE-AWAYS

- REACH requires an exposure assessment *inter alia* for (very) Persistent, (very) Bioaccumulative and/or Toxic (PBT and/or vPvB) substances. Where ECHA requests information on uses and environmental emissions on the basis of an absence of exposure assessment and the potentially PBT/vPvB nature of that substance, it may breach the principle of proportionality.
- ECHA requests for information on use and environmental exposure should indicate what information is required to meet the request.

Background

UVASORB HEB ("*Substance*") was included in the rolling action plan for substance evaluation due to initial grounds for concern relating to its potential PBT and vPvB properties. On 20 December 2016 ECHA adopted a decision requiring an OECD TG 308 study to be conducted and further information on uses and environmental emissions to be provided ("*Decision*").

One of the Substance registrants, 3v Sigma SpA ("*Appellant*"), challenged that Decision before the BOA, alleging that the Decision was disproportionate, vitiated by manifest error and *ultra vires* in relation both to the OECD TG 308 study requirement and the further information requirement.

Decision

The BOA dismissed the appeal as far as it concerned the requirement for an OECD TG 308 study but upheld it in relation to the further information requirement.

There was no dispute that the Substance itself was not PBT or vPvB. The concern was rather that degradation products, transformation products or metabolites may have these properties.

On the OECD TG 308 study, the BOA rejected the Appellant's arguments that there was no potential risk. In doing so it considered in particular the reliability of the QSAR models used for screening for bioaccumulation, accepting that ECHA was correct to conclude that in this case the models were *unreliable* for calculation of bioconcentration factor. The BOA also held that the OCDE TG 308 study was appropriate to achieve the objective of clarifying the potential risk. Finally, the BOA confirmed ECHA could request identification of transformation products >10% concentration, and not only those already known to exist. A typo in the Decision – requiring identification of transformation products in concentrations >0.1% instead of >10% - had been acknowledged by ECHA and was effectively considered irrelevant.

By contrast, the BOA annulled the Decision in so far as it requested further information on uses

and environmental emissions. ECHA had justified that request on the basis of the absence of exposure assessment in the registration dossier. However, such assessments are required *inter alia* if a substance is PBT or vPvB. In this case it was not yet known whether any transformation products were in fact PBT or vPvB. As a result ECHA had failed to demonstrate the necessity or appropriateness of the request. Moreover, ECHA failed to identify the information requested. The request therefore breached the principle of proportionality and the Decision was annulled in that regard.

Ombudsman clears EFSA of maladministration in relation to use of the TTC approach

On 17 December 2018, the European Ombudsman ("Ombudsman") adopted its decision in Case 747/2016/PL concerning the European Safety Authority ("EFSA")'s use of the Threshold of Toxicological Concern ("TTC").

WHAT YOU NEED TO KNOW – KEY PRACTICAL TAKE-AWAYS

- The TTC approach helps regulators to set priorities and to decide whether further data are needed in a given case.
- When using the TTC approach, EFSA acts as a risk assessor and not a risk manager.
- The Ombudsman recommends EFSA to screen experts who participate in conferences or meetings organised to inform EFSA's decision-making process.

Background

The TTC is a risk assessment tool based on the principle that there are exposure levels below which chemicals do not pose a significant risk to human health. Typically, this tool is used by regulators to prioritise the assessment of chemicals posing a greater potential risk to human health.

EFSA decided to use the TTC approach in 2012. In 2014, EFSA and the World Health Organisation ("*WHO*") convened an expert meeting to review the science underlying the TTC concept. In a report published in March 2016, the experts concluded that the TTC is a valid screening tool that is fit for purpose.

In August 2016, PAN Europe filed a complaint before the Ombudsman. It questioned both EFSA's use of the TTC and the independence of the experts who took part in the workshop.

Decision

The Ombudsman first recalled that it not a scientific body and cannot therefore take a view on the merits of a particular risk assessment tool.

This said, it considered that EFSA's use of the TTC is based on extensive and up-to-date scientific knowledge.

Moreover, it confirmed that when using the TTC approach, EFSA acts as a risk assessor (i.e. it provides advice based on a scientific analysis) and not as a risk manager (i.e. it does not use this advice as a basis for decision-making). In particular, in setting a threshold for pesticide metabolites in ground water, EFSA applies the Commission's Guidance document and therefore carries out a risk assessment.

As regards the experts who participate in the workshop, the Ombudsman found that EFSA was not required to screen them for conflict of interests and could rely on WHO's prior screening of these experts. However, it recommended EFSA to screen in the future the declaration of interests of experts who take part in events organised with a view to informing its decision-making process.

The Ombudsman's decision confirms that the TTC approach is a valid screening tool to focus resources on those substances posing a greater potential risk to human health.

New actions before the EU Courts

Access to documents relating to EFSA guidance on risk assessment on bees

On 18 December 2018, the European Ombudsman opened a case into the EU Commission's refusal to grant access to correspondence and documents related to discussions in the Standing Committee on Plants, Animals, Food and Feed regarding EFSA's guidance document on the risk assessment of plant protection products on bees (Case 2142/2018/TE).

Human medicines – Market authorisation for Aplidin

An action has been brought before the EU General Court against the EU Commission's refusal to grant a marketing authorisation for the medicinal product Aplidin (T-594/18, *Pharma Mar -v- Commission*, *OJ* of 10 December 2018).

Generics and regulatory data protection

An action has been brought before the EU General Court against the European Medicinal Agency ("*EMA*")'s refusal to validate the marketing authorisation application for Dimethyl Fumarate Polpharma, a generic version of Tecfidera. Insofar as the EMA based its refusal on the regulatory data protection in favour of the reference product, the applicant also seeks to challenge the legality of the decision granting a marketing authorisation to the reference product (T-611/18, *Pharmaceutical Works Polpharma -v- EMA*, *OJ* of 17 December 2018).

Notion of environmental information on emissions

Rogesa Roheisengesellschaft Saar mbH decided to appeal the EU General Court judgment of 11 July 2018 in Case T-643/13, *Rogesa Roheisengesellschaft Saar mbH -v- Commission* upholding the EU Commission's refusal to grant access to information on the CO2 efficiency of an industrial plant (C-568/18, *Rogesa Roheisengesellschaft Saar mbH -v- Commission*, *OJ* of 14 January 2019). In particular, the applicant claims that the EU General Court interpreted too broadly the exception on the protection of commercial interests and failed to recognise the existence of environmental information on emissions.

Damages claims following partial annulment of classification of coal tar pitch

Damages actions have been brought before the EU General Court against the EU Commission following the EU Court of Justice's judgment in Case C-691/15, *Commission -v- Bilbaína de Alquitranes and Others* upholding the partial annulment of the CLP classification of pitch, coal tar, high-temp (CTPHT) as toxic for the aquatic environment. (T-635/18, *Industrial Química del Nalón -v- Commission*; T-636/18, *Tokai erftcarbon -v- Commission*; T-637/18, *Bawtry Carbon International -v- Commission*; T-638/18, *Deza -v- Commission*; T-639/18, *SGL Carbon -v- Commission*, T-645/18, *Bilbaína de Alquitranes -v- Commission*, *OJ* of 14 January 2019).

SPCs for different therapeutic applications

The Paris Court of Appeal has asked the EU Court of Justice to clarify the scope of its ruling in the *Neurim* case (C-130/11, *Neurim Pharmaceuticals (1991) Ltd -v- Comptroller-General of Patents*) regarding the conditions for obtaining an SPC.

The Court ruled in *Neurim* that an earlier marketing authorisation does not preclude the grant of an SPC "*for a different application of the same product*" on the basis of a corresponding new marketing authorisation, "*provided that the application is within the limits of the protection conferred by the basic patent relied upon*".

The French Court seeks in particular guidance on the concept of "*different application*" and wonders whether it should be interpreted broadly as including not only different

therapeutic indications, but also different formulations, dosages and/or means of administration (C-673/18, *Santen SAS -v- Directeur général de l'Institut national de la propriété industrielle*, *OJ* of 21 January 2019).

Confidentiality of EFSA conclusion on peer review of azadirachtin

A new action has been brought before the EU General Court against EFSA's confidentiality treatment of its conclusion on the peer review of the active substance azadirachtin (T-675/18, *Trifolio-M and Others -v- EFSA*, *OJ* of 21 January 2019).

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