August 2015

NON-COMPLIANCE OF THE FRENCH RULES ON OFF-LABEL USE OF MEDICINES (*RECOMMANDATIONS TEMPORAIRES D'UTILISATION*) WITH THE UNION *ACQUIS*

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COMPLAINT IN THE CONTEXT OF ARTICLE 258 TFEU

The European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Association for BioIndustries (EuropaBio) and the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) hereby submit a complaint against measures adopted by the French Republic in 2014 and 2015 in relation to the use (and reimbursement) of medicinal products outside the terms of the marketing authorisation. These rules envisage official recommendations on off-label use, called *Recommandations Temporaires d'Utilisation* or RTUs. The RTUs are issued by the French Medicines Agency (ANSM).

The general measures were adopted in August and December 2014 and allow for RTUs even when there are alternative medicines with a marketing authorisation that covers the therapeutic use in question. In addition, there are clear indications that the RTU regime also has an economic purpose and is intended to be used in certain cases to save costs in the healthcare system.

An example of such use is the RTU that was issued in June 2015 for the medicine Avastin, for the off-label treatment of neovascular age-related macular degeneration. That use requires handling and compounding so that the product can be injected into the eye. The RTU thus expressly envisages reformulation that renders it a new and unapproved medicinal product, which goes against the terms of the Union marketing authorisation. This decision is also covered by the complaint.

The RTU regime infringes and undermines the Union marketing authorisation system that specifically protects public health -- and in particular patients -- by setting detailed standards for the quality, safety and efficacy of medicines and by operating clear procedures for assessing medicines against these standards and for monitoring products on the market. In addition, the RTU regime is in part also based on budgetary considerations that should never overrule the protection of public health.

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Executive Summary

This complaint is submitted in the context of Article 258 of the Treaty on the Functioning of the European Union (TFEU).

The complaint is addressed against the adoption and the application by the French Republic of the regime of *Recommandations Temporaires d'Utilisation* or RTUs, in particular when there are authorised alternative medicines available. The RTU regime is laid down in the following legislative provisions:

- Article L. 5121-12-1 of the Public Health Code (*Code de la Santé Publique*), as last amended by the law no. 2014-892 of 8 August 2014 (*Loi de financement rectificative de la sécurité sociale pour 2014 (1)*). Copy of the article as currently in force is enclosed as Attachment 1 and copy of the law of 8 August 2014 is enclosed as Attachment 2.

  Article L. 5121-12-1 starts with the following general provision:

  "*I.- Une spécialité pharmaceutique peut faire l'objet d'une prescription non conforme à son autorisation de mise sur le marché en l'absence de spécialité de même principe actif, de même dosage et de même forme pharmaceutique disposant d'une autorisation de mise sur le marché ou d'une autorisation temporaire d'utilisation dans l'indication ou les conditions d'utilisation considérées, sous réserve qu'une recommandation temporaire d'utilisation établie par l'Agence nationale de sécurité du médicament et des produits de santé sécurise l'utilisation de cette spécialité dans cette indication ou ces conditions d'utilisation et que le prescripteur juge indispensable le recours à cette spécialité pour améliorer ou stabiliser l'état clinique de son patient.*"

- Articles R. 5121-76-1 to R. 5121-76-9 of the Public Health Code, implementing Article L. 5121-12-1. They were last amended by decree no 2014-1703 of 30 December 2014.[1] A copy of the articles as currently in force are enclosed as Attachment 3 and a copy of the decree of 30 December 2014 is enclosed as Attachment 4.

[1] *Décret no 2014-1703 du 30 décembre 2014 modifiant les règles relatives à l'élaboration de recommandations temporaires d'utilisation établies en application du I de l'article L. 5121-12-1 du code de la santé publique.*

On 24 June 2015, the French Medicines Agency (ANSM) issued an RTU for the use of Avastin to treat neovascular age-related macular degeneration. The decision enters into effect on 1 September 2015. This is the first RTU issued notwithstanding the availability of authorised alternative medicines and apparently for economic reasons. A copy of the decision and the related patient follow-up protocol are enclosed as Attachments 5 and 6. This covers not only an off-label use of Avastin, but also requires reformulation of the product.

The reimbursement of products used under an RTU is covered by Article L. 162-17-2-1 of the Social Security Code (Attachment 7). In July 2015, the *Haute Autorité de Santé* (HAS) adopted a recommendation for reimbursement of Avastin under the RTU (Attachment 8). A decision providing for reimbursement was adopted in August and enters into effect on 1 September 2015 (Attachment 8 bis).

Articles L. 5121-12-1 and R. 5121-76-1 to R. 5121-76-9 of the *Code de la Santé Publique*, and the ANSM decision of June 2015 (and the related reimbursement principles and decision) are hereinafter also referred to as the "contested measures."

These provisions infringe European Union law for the following reasons:

- Through these provisions, France actively promotes the off-label use of the medicines covered by an RTU, also when there are authorised alternative medicines and also for economic reasons. This is incompatible with the EU marketing authorisation regime for medicines, and in particular Directive 2001/83 and Regulation 726/2004,[2] which excludes exceptions to the marketing authorisation principle based on other than purely therapeutic reasons, such as economic considerations, as well as official recommendations on off-label use.

- The official promotion of off-label use also infringes the duty of loyalty of France towards the EU marketing authorisation rules (and with regard to the contested ANSM decision, the European Commission decisions authorising Avastin) and its obligation to guarantee their practical effectiveness (*effet utile*).

- The measures also infringe fundamental Union rights, in particular the right to protection of public health and the freedom to conduct a business.

The complainants do not specifically seek action against the RTUs that have been issued by the ANSM in cases where there are concrete patient needs because of the absence of authorised treatments and where there are no apparent economic considerations. Also in those cases, however, the RTU regime should be revised so as to ensure compliance with Union law. Examples of such RTUs are those granted in 2015 for Velcade, Thalidomide Celgene and Circadin.[3]

The complainants respectfully request the European Commission to take action to ensure the termination of France's failure to comply with its obligations under Union law.

[2] See Annex A (List of Key Union Legislation and Court Decisions) for the full titles of the legislation.

[3] For details, see http://ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Liste-des-specialites-faisant-actuellement-l-objet-d-une-RTU/%28offset%29/1.

This complaint is subject to additional arguments that may be submitted at a later moment.

Union Action is Important and Urgent

This action is important and urgent for the following reasons:

(i) The contested measures seriously undermine the EU system of marketing authorisation for medicinal products, which is fundamental for ensuring adequate protection of patient health.

- The measures promote off-label use of medicines without ensuring full compliance with the standards for quality, safety and efficacy of Directive 2001/83 and Regulation 726/2004 and without following the assessment and supervision procedures laid down in that legislation, without a clear medical need.

- The measures are at least in part inspired by budgetary reasons, while the EU principles clearly require that the protection of public health takes precedence over financial considerations.

- The measures also undermine the incentives for innovation under the EU pharmaceutical rules. Article 10 of Directive 2001/83 and Article 14 of Regulation 726/2004 provide for regulatory exclusivity for new medicines in general and Regulation 141/2000[4] grants specific market exclusivity for orphan medicines. These incentives are granted for developing new medicines and ensuring that they meet the Union standards of quality, safety and efficacy. The new medicines can consist of existing active ingredients that are used for a new therapeutic indication, and this is very often the case for orphan medicines. National measures that stimulate off-label use of approved medicines (and sometimes of reformulated and thus unapproved medicines), in particular when authorised alternatives are available, risk undermining these incentives for developing new uses of existing active ingredients.[5]

- In addition, the measures may ultimately also affect the availability of generic or biosimilar medicines. If the commercial position of an innovative medicine is undermined by national measures supporting the off-label use of other, less expensive, medicines for economic reasons, this may jeopardise the market entry of generic or biosimilar versions of the innovative medicine when the relevant exclusivity period expires.

- These infringements go to the heart of the EU pharmaceutical regime and undermine patient protection in the short term (by promoting off-label use without the same guarantees as for a marketing authorisation, also when authorised alternatives are available) and in the long term (by undermining the effectiveness of the pharmaceutical regime and the incentives for new developments).

[4] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

[5] The General Court recently stressed the importance of preserving the full effectiveness of the orphan exclusivity, also in light of possible off-label use of other medicines: "*It must be held that if the effectiveness of Article 8(1) of Regulation No 141/2000 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 provision should not be facilitated*." (decision in *CTRS v Commission*, Case T- 452/14, par. 78).

(ii) The contested measures risk being followed by similar actions in other Member States, which would further undermine the EU pharmaceutical regime. Italy already adopted somewhat similar measures, and discussions are ongoing in other Member States. The Commission has ordered a study on off-label use of medicines, but the results of that study and the policy measures based on the results risk coming too late to prevent a fundamental erosion of the marketing authorisation system.

(iii) Private legal action before the national French courts is expected to be time consuming, requiring proceedings before the *Conseil d'Etat* and quite possibly referrals to the EU Court of Justice.

(iv) National litigation in different Member States on similar measures may result in contradictory decisions throughout the Union on a matter that affects a core aspect of the EU pharmaceutical regime.

Original Language Versions and Translations

For the sake of clarity and simplicity, this complaint makes direct reference to the French versions of the official texts. This facilitates the analysis, especially where the specific nuances of the wording used are important. The complainants can, of course, provide English translations of texts where needed.

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1. Complainants

This complaint is submitted in the context of Article 258 TFEU by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Association for BioIndustries (EuropaBio) and by the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE).

- EFPIA is a non-profit organisation representing the interests of the R&D-based pharmaceutical industry in Europe. EFPIA is established under the laws of Luxembourg, with a permanent office at Rue du Trône/Troonstraat 108, B-1050 Brussels, Belgium registered under BE0418762559. For more details, see the website www.efpia.eu.

- EuropaBio is the European Association for BioIndustries, located in Avenue de l'Armée 6, 1040 Brussels and was created in 1996 as an international association with a scientific purpose as governed by Belgian Law. For details, see the website www.europabio.org.

- EUCOPE is an international non-profit association established under Belgian law with primarily pharmaceutical companies as members. For details, see the website www.eucope.org.

EFPIA's mission is to promote the technological and economic development of Europe's pharmaceutical industry, leading to researching, developing and bringing to patients new medicines that will improve health and the quality of life in Europe and around the world. EFPIA considers that healthcare bodies promoting economic driven off-label use when

licensed alternatives exist, undermine the European regulatory framework, potentially compromise patient safety and create legal uncertainty. This will discourage pharmaceutical companies from undergoing the costly and time-consuming authorisation process for new indications if public authorities favour off-label use of other, cheaper medicines which have not undergone the same stringent safety and efficacy assessment.

EuropaBio's mission is to create an innovative and dynamic biotechnology-based industry in Europe. The membership is composed of 61 corporate members, 17 associate members and Bio regions, and 16 national biotechnology associations, who in turn represent more than 1800 small and medium sized biotech companies in Europe. Members of EuropaBio are involved in research, development, testing, manufacturing and commercialisation of biotechnology products and processes. Corporate members have a wide range of activities: human and animal health care, diagnostics, bioinformatics, chemicals, crop protection, agriculture, food and environmental products and services. EuropaBio believes that the promotion of off-label use for economic reasons when approved alternatives are available creates an unpredictable and unfavourable environment for the development and growth of the European biotech industry and will ultimately reduce the attractiveness of Europe as a location for non-European companies to invest and grow.

EUCOPE has an interest in bringing this matter to the attention of the Commission because its corporate purpose includes, amongst other activities, enhancing the opportunities for interfacing with the EU Institutions, other organisations and national and regional governments. EUCOPE also has many mid-sized innovative pharmaceutical companies among its members and the robustness of the EU pharmaceutical regime is of significant importance to them (as it is to the entire pharmaceutical industry).

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The complainants authorise the Commission to disclose their identity in the contacts with the French authorities.

2. Brief Historical Overview of the RTU Rules in France

The RTU regime was first put in place in late 2011, but has undergone some significant changes over the years. It is helpful to provide a brief historical overview as background to the complaint.

- The original RTU provisions were adopted in December 2011 (by Article 18 of Law no. 2011-2012 of 29 December 2011). Article L. 5121-12-1 of the Public Health Code, as then adopted, envisaged RTUs when there was no appropriate alternative medicine that was covered by a marketing authorisation or a temporary use authorisation (*autorisation temporaire d'utilisation* or ATU[6]). A copy of Article L. 5121-12-1, as then adopted, is enclosed as Attachment 9.

  This was implemented by Decree no. 2012-742 of 9 May 2012, inserting more detailed provisions in Article R. 5121-76-1 to 9 of the Public Health Code. A copy of these articles, as then in force, is enclosed as Attachment 10. Decree no. 2012-740 of 9 May 2012 also laid down the conditions for reimbursement of medicines used under an RTU.

  This regime is often referred to as the "therapeutic RTU" as it only allowed an RTU when there was no appropriate alternative medicine covered by a marketing

[6] An ATU is an authorisation for named patient use ("nominative ATU") or for compassionate use ("cohort ATU").

authorisation or ATU for the specific therapeutic use in question. The rules also allowed the doctor to prescribe a medicine off-label outside an RTU when this was indispensable to treat the patient.

Based on these principles, RTUs were granted for Lioresal and Baclofène Zentiva (March 2014), Roactemra (April 2014) and Remicade (July 2014).

- Article 57 of the social security financing law no. 2012-1404 of 17 December 2012 inserted a new paragraph V in Article L. 5121-12-1, allowing for, on an exceptional basis, an RTU also when there is an appropriate authorised alternative medicine (see Attachment 11). This possibility was given either to address a demonstrated public health risk ("*un risque avéré pour la santé publique*") or to avoid expenses with a significant impact on the financing of the health insurance regime ("*d'éviter des dépenses ayant un impact significatif sur les finances de l'assurance maladie*"). The latter use is typically referred to as the "economic RTU."

  The same law also amended the reimbursement conditions for medicines covered by an RTU.

  During the adoption of the law, the *Conseil Constitutionnel* reviewed specific complaints, also against Article 57. These complaints were dismissed, but did not entail any review of the compliance of the article with EU law.[7]

- In March 2014, the French government submitted a first draft decree implementing the revised Article L. 5121-12-1 to the *Conseil d'Etat*. Opinions of the *Conseil d'Etat* are not binding, but have high authority. They are confidential and the complainants are not aware of the details of the opinion on the draft decree, but press statements indicate that the opinion was negative and concluded that the draft decree infringed EU law principles. Copies of the press statements are enclosed as Attachment 13.

  In May 2014, the government prepared a new draft decree. A comparative table with the texts of the two draft decrees is enclosed as Attachment 14. The complainants are not aware of a *Conseil d'Etat* opinion on the second draft decree.

- In light of the circumstances, the French government apparently decided to abandon the draft decrees and instead in June 2014 proposed an amendment to the then pending draft corrective social security financing law ("*loi de financement rectificative de la sécurité sociale pour 2014*"). This is illustrated by press reports that quote the Member of the French Parliament Gérard Bapt (acting as rapporteur in the *Assemblée*) as stating that "the draft decree does not seem to be getting anywhere at the *Conseil d'Etat*" and referring to "legal obstacles" (see Attachment 15).

  The corrective social security financing law was promulgated on 8 August 2014. Its Article 10 amended Article L. 5121-12-1 of the Public Health Code and this version is

[7] Decision no. 2012-659 DC of 13 December 2012 (enclosed as Attachment 12). The *Conseil Constitutionnel* can review the implementation of EU legislation into national law, but held that the RTU rules do not constitute an implementation of Directive 2001/83 (see par. 56 of the decision). The decision thus did not review the new RTU rules against EU law.

still in force (see Attachments 1 and 2). It also amended the rules governing the reimbursement of medicines used under an RTU.[8]

- In parallel with the legislative amendment, the French government also prepared a new draft implementing decree. The draft was notified to the European Commission under the TRIS regime in August 2014.[9] This was the only RTU related measure that was notified under the TRIS regime.[10]

  The TRIS review focuses on restrictions on the free movement of goods within the Union. It is not directly relevant for the current complaint, which is based on an infringement of the EU marketing authorisation regime and fundamental principles of EU law.

  The draft decree as notified to the Commission is enclosed as Attachment 17. Decree no 2014-1703 was adopted on 30 December 2014 (Attachment 4) and Attachment 19 provides a comparison of the draft decree as notified and the final text of the decree.

3. Key aspects of the RTU Regime in France

The RTU regime as currently laid down in the Public Health Code has the following key characteristics:

Nature of the RTU

- The RTU is a formal recommendation by the French Medicines Agency, intended to ensure the safety of off-label prescription ("*sécuriser la prescription d'un médicament non conforme à son autorisation de mise sur le marché*" - Article R. 5121-76-1).

- The RTU can be granted even when there is an authorised alternative medicine for the treatment in question. This follows implicitly but clearly from the wording of the first sentence of Article R. 5121-76-1. It is also confirmed by the contrast in the wording between the first and second part of Article L. 5121-12-1 I. The latter allows a doctor to prescribe a medicine off-label without RTU but only when there is no alternative medicine ("*qu'en l'absence d'alternative médicamenteuse*"), which makes it clear that that restriction does not apply to an RTU.

- The RTU should not be granted when there is a medicine with the same active ingredient, same dosage and same pharmaceutical form, covered by a marketing authorisation or ATU[11] (Article L. 5121-12-1 I -- see also Article R. 5121-76-1, first par.). The law is not clear on whether that condition should be checked by the prescribing doctor or by the ANSM. In the context of the TRIS review for the draft decree, the French government indicated that the condition should be checked by both and thus also applies to the adoption of an RTU (see Attachment 18, page 23).

[8] Two complaints to specific provisions of the law were submitted to the *Conseil Constitutionnel*, which held some provisions to be unconstitutional (Decisions no. 2014-698 and 2014-699). The decisions do not relate to the RTU rules in article 10 of the law.

[9] The notification and the correspondence on the notification between the French Republic and the Commission (obtained pursuant to Regulation 1049/2001) are enclosed as Attachments 16 to 18.

[10] The Commission made critical remarks on that point during the TRIS review.

[11] A nominative ATU, however does not prevent an RTU (Article R. 5121-76-1, fifth par.).

The reference to situations where there is no "authorised"[12] medicine with the same active ingredient, same dosage and same pharmaceutical form is derived from the case law of the Court of Justice, in particular the decisions in cases *Novartis v Apozyt* (C-535/11) and *Commission v Poland* (Case C-185/10). This is confirmed by the brief explanation accompanying the government proposal for the revision of Article L. 5121-12-1:

> *"La Cour de justice de l'union européenne a récemment précisé sa doctrine sur les prescriptions de produits en dehors de leur autorisation de mise sur le marché.*
>
> *Sa jurisprudence autorise désormais la prescription d'un médicament en dehors de son autorisation de mise sur le marché, même dans le cas où une alternative thérapeutique existe, dès lors que cette alternative n'a pas la même substance active, ni le même dosage, ni la même forme pharmaceutique que le produit que le médecin estime devoir prescrire pour soigner son patient."*[13]

It is also confirmed by the brief statement of grounds accompanying the TRIS notification of the draft decree:

> "*In this regard, the draft Decree supplements the provisions of Article R. 5121-76-1 of the French Public Health Code in order to clarify, firstly, that the RTU mechanism falls within the provisions of paragraph 1 of Article 5 of Directive No 2001/83/EC of the European Parliament and of the Council of 6 November 2001 and, secondly, to take into account the consequences of the Ruling of the European Court of Justice of 11 April 2013 in case C-535/11.*"[14]

As shown below, however, the mentioned rulings of the Court of Justice are not correctly referenced and are wrongly interpreted. They actually prohibit the RTU regime as adopted in 2014.

- The RTU mentions the therapeutic indication, posology, method of administration, undesirable effects and the prescription status of the medicine covered by it. It must be accompanied by a reasoning ("*argumentaire*") supporting the assumption that the benefits outweigh the risks and specify how patients are followed and data concerning safety and efficacy are gathered (Article R. 5121-76-1).

  The standard for issuing an RTU is that the evaluation of available safety and efficacy data allow to assume that the expected benefit outweighs the undesirable effects ("*évaluation permet de présumer que le rapport entre le bénéfice attendu et les effets indésirables encourus est favorable*" - Article R. 5121-76-6). The French government has confirmed during the TRIS discussions on the draft decree that this evaluation is very incomplete. It stated that the RTU "sheds light on the risk profile and brings the

[12] Under a marketing authorisation or (cohort) ATU.
[13] See the *Exposé sommaire* to Amendment 219 of 30 June 2014, Attachment 20.
[14] TRIS notification of 7 August 2014, Attachment 16. Par. 46 of the decision in *Novartis v Apozyt* (Case C-535/11) refers to the earlier decision in *Commission v Poland* (Case C-185/10) holding that "Article 5(1) cannot be relied on where medicinal products having the same active substances, the same dosage and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market."

first elements of efficacy" of the company's product ("*un éclairage … sur le profil de risque et les premiers éléments d'efficacité de son produit*" - Attachment 18, page 24).

- The cost for the patient follow-up has to be borne by the pharmaceutical company[15] (Article R. 5121-76-7).

Procedure

- The RTU is issued by the ANSM (Article L. 5121-12-1 I and R. 5121-76-6). It is accompanied by a patient follow-up protocol (Article L. 5121-12-1 IV *in fine* and R. 5121-76-6 *in fine*). The law assumes that the ANSM can take the initiative for preparing an RTU and Article R. 5121-76-3 entitles the Minister of Health, the Minister of Social Security, the *Haute Autorité de Santé*, the sickness fund union, the national cancer institute, rare disease research and competence centres, and recognised patient organisations to suggest the preparation of an RTU.

- When preparing an RTU, the ANSM asks the pharmaceutical company for relevant information (Article R. 5121-76-4) and later on provides a draft of the recommendation and the protocol to the company for comments (Article R. 5121-76-6).

  When the RTU is envisaged in the area of cancer or rare diseases, the input of specialised bodies is also requested (Article R. 5121-76-5).

- The RTU is valid for up to three years and can be renewed (Article L. 5121-12-1 II). It can also be amended, suspended or withdrawn (Article R. 5121-76-8).

Use of the RTU

- The pharmaceutical company must make the RTU available to the prescribing doctors ("*mises à la disposition des prescripteurs*" - Article L.5121-12-1 II). This must be done through active dissemination ("*diffuse auprès des prescripteurs la recommandation temporaire d'utilisation initiale et chacune de ses mises à jour*") but in a non-promotional way (Article R. 5121-76-9).

  The ANSM also publishes the RTU on its website (Article R. 5121-76-9).

  In addition, the decision of 24 June 2015 provides that Roche must post the RTU for Avastin on its own website (Attachment 5, art. 4).

- The prescribing doctor relying on an RTU must be of the opinion that the use of the medicine is indispensable to treat the patient ("*juge indispensable le recours à cette spécialité pour améliorer ou stabiliser l'état de son patient*") and justify the prescription in the medical file (Article L. 5121-12-1 I and III). He must do this to respond to the patient's needs ("*pour répondre aux besoins spéciaux du patient*") and based on therapeutic considerations specific to the patient ("*en se fondant sur les considérations thérapeutiques qui lui sont propres*") (Article R. 5121-76-1, first par.). The draft decree, as notified under TRIS, required the decision to be based on purely

[15] The holder of the marketing authorisation or the person marketing the product in France (the "*exploitant*").

therapeutic considerations ("*considérations purement thérapeutiques*") but the word "purement" was omitted in the final text, which must have been a deliberate amendment.

The prescribing doctor must also inform the patient of the risks and benefits and the reimbursement status of the product covered by the RTU (Article L. 5121-12-1 III).

4. Infringement of Directive 2001/83, Regulation 726/2004 and Commission Decisions on Marketing Authorisations

The contested measures infringe the Union marketing authorisation regime and in particular Directive 2001/83 and Regulation 726/2004, as they:

(i) Constitute an official decision "recommending" the use of an authorised medicine for a therapeutic indication that is not covered by the marketing authorisation without respecting the conditions for granting an exemption from the marketing authorisation requirement under Article 3 and Article 5(1) of Directive 2001/83[16] and because they are also based on cost containment considerations (see below, section (b)).

(ii) Undermine the practical effectiveness (*effet utile*) of the marketing authorisation rules; and in the case of the ANSM decision on Avastin, of the European Commission decisions authorising Avastin in accordance with Regulation 726/2004 (see below, section (c)).

Before discussing this in detail, section (a) provides a brief overview of the core aspects of the Union marketing authorisation regime.

a. The Union Marketing Authorisation Principles

The cornerstone of the Union pharmaceutical regime is the requirement of a marketing authorisation before a medicine can be placed on the market (now contained in Article 6(1) of Directive 2001/83 and in Article 3(1) of Regulation 726/2004). This requirement is imposed to protect the safety of patients, who must have adequate guarantees of the quality, safety and efficacy of the medicines they use; and as recital 2 of Directive 2001/83 states "[t]he essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health."[17]

The exceptions to the marketing authorisation requirement are expressly listed in Articles 3, 5 and 7 of Directive 2001/83 and in Article 83 of Regulation 726/2004.[18]

Article 3 of Directive 2001/83 states:

[16] Or under Article 83 of Regulation 726/2004.

[17] See also recital 13 to Regulation 726/2004: "In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations."

[18] They cover magistral formulas; officinal formulas; products used in clinical trials and other R&D testing; special products, such as certain radiopharmaceuticals (covered by Article 7); blood and certain blood components; hospital preparations of advanced therapy medicines; named patient supplies and medicines used in compassionate use programmes (under Article 5(1) of the Directive and Article 83 of the Regulation); and temporarily authorised products to fight infections by pathogens, toxins, chemical agents or nuclear radiation.

"This Directive shall not apply to:
1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).
[…]"

Article 5(1) of Directive 2001/83 states:

> *"A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility."*

Article 83 of Regulation 726/2004 applies this exemption to compassionate use programmes for medicines governed by the Regulation, subject to specific limitations laid down in paragraph 2.

Marketing Authorisation Procedures

A marketing authorisation (MA) is granted on the basis of an application by the future MA holder and can only be granted provided the application dossier meets the standards of Directive 2001/83 and Regulation 726/2004.[19] Annex I to Directive 2001/83 specifies what data the application dossier must contain and very extensive Commission and EMA guidelines further implement these principles. This ensures a harmonised regulatory regime that allows the quality, safety and efficacy of medicines to be assessed on the basis of common criteria throughout the Union and the EEA.

As a rule, a MA cannot be granted by the competent authorities at their own initiative.[20]

Variations to marketing authorisations

Variations to a marketing authorisation require approval (or in some limited cases only notification) in accordance with Commission Regulation 1234/2008. An application for such approval must be made by the MA holder, although exceptionally the public authorities can also unilaterally impose certain variations for public health reasons.

Variations are classified based on their significance and need for detailed review. Minor

[19] Articles 8 and following and Article 26 of Directive 2001/83; Articles 4, 6 and 12 of Regulation 726/2004.

[20] Since 2004 only one exception exists, which, however, only applies with regard to national MAs and not to centrally granted MAs. In order to ensure better availability of medicines in certain smaller Member States, Directive 2001/83, as amended, provides in Article 126a that Member States can authorise medicines at their own initiative, but only based on an existing approval in another Member State and subject to certain conditions: (i) the product has a valid MA in another Member State; (ii) there is no MA or pending application for an MA for the product in that Member State; (iii) there are "justified public health reasons;" and (iv) the Member State must request a copy of the assessment report for the product from the authorities in the Member State that granted the existing MA. This Article was added to Directive 2001/83 at the initiative of the Council of the EU, which stated in its Common Position of 29 September 2003: "*To improve availability of medicines - particularly in smaller markets - a new article 126a has been introduced that will allow a Member State for public health reasons and under certain circumstances to grant an authorisation for a medicinal product authorised in another Member State.*" This exceptional provision obviously only applies to national MAs and not to centrally approved medicines (as Article 126a presupposes an MA in another Member State). It is also a special form of mutual recognition procedure and does not allow for a new product or a new therapeutic indication to be approved.

variations of types Ia and Ib are subject to simplified procedures, based on a notification. Major variations of type II require a more in-depth review. In addition, "certain changes which have the highest potential impact on the quality, safety or efficacy of medicinal products require a complete scientific assessment, in the same way as for the evaluation of new marketing authorisation applications" (recital 4 to the Regulation). These variations are called "extensions."

Extensions are defined in Annex I to the Regulation and include, for instance, changes to the pharmaceutical form or to the route of administration. Major or type II variations are defined in Annex II and include, for instance, the addition of a new therapeutic indication (or the modification of the existing indication), substantial changes to the manufacturing process and changes in the fill weight of certain sterile medicines. These specific variations cannot be unilaterally imposed by the authorities.

National and Union Procedures

Marketing authorisations can be granted and varied by the national competent authorities under a purely national procedure or under the decentralised or mutual recognition procedures (governed by Directive 2001/83). For certain medicines, the applicant has the option to go through the centralised procedure under Regulation 726/2004, involving a review by the EMA and a final decision by the European Commission. The centralised procedure is mandatory for products listed in the Annex to the Regulation, including medicines developed by means of recombinant DNA technology, orphan medicines and new active substances for treatment of cancer and certain other serious conditions.

Summary of Product Characteristics

The marketing authorisation includes a summary of product characteristics (SmPC), which is a core reference document for the product and provides guidance to healthcare professionals and others who wish to consult it. The Commission Guideline on Summary of Product Characteristics of September 2009 states:

> *"The SmPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process. As such the content cannot be changed except with the approval of the originating competent authority.*
> *The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively."*

Key parts of the SmPC include the qualitative and quantitative composition, pharmaceutical form, therapeutic indications, posology, method of administration, contraindications, and special warnings and precautions for use.

All advertising must also comply with the particulars in the SmPC.[21]

Off-label Use

There are no specific Union rules on off-label use of medicines, but such use is subject to the general framework of the EU legislation and to the principles expressed by the Court of

[21] Article 87(2) of Directive 2001/83 provides that "*All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics*."

Justice. Off-label use is recognised as legitimate, based on the professional rules governing the practice of medicine and the understanding that a medicine is only prescribed when it is a preferable way of treating the patient. The Court of Justice held in *Novartis v Apozyt*, that this must happen for an individual patient, under the doctor's "direct personal responsibility", and "solely on therapeutic considerations specific to his patients" (Case C-535/11, par. 48-49). Public health authorities must respect these principles. In particular, they must not take actions -- such as disseminating statements on the efficacy and safety of off-label use -- that attenuate the direct personal responsibility of the treating doctor (decision of the General Court in *CTRS v Commission*, Case T- 452/14, par. 82).

Public Health Takes Precedence Over Economic Considerations

A fundamental principle underlying the Union pharmaceutical regime is that public health considerations take precedence over economic considerations. The EU Court of First Instance confirmed the general principle of precedence of public health over economic considerations in the so-called Anorectics case (*Artegodan a.o.*, joined Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00) and applied it to the suspension and revocation of marketing authorisations:

> *"173. The aforementioned conditions for withdrawal of an authorisation must be interpreted in accordance with the general principle, identified in the case-law, that protection of public health must unquestionably take precedence over economic considerations (see, in particular, order in Case C-180/96 R United Kingdom v Commission [1996] ECR I-3903 paragraph 93, and the judgment in Case C-183/95 Affish [1997] ECR I-4315, paragraph 43).*
>
> *174. In the context of the grant and management of marketing authorisations of medicinal products, that principle requires, first, the taking account exclusively of considerations relating to the protection of public health; second, the re-evaluation of the benefit/risk balance of a medicinal product where new data give rise to doubts as to its efficacy or safety and, third, the application of rules of evidence in accordance with the precautionary principle, which is implicitly relied on by the Commission (see above, paragraph 165) and is, in particular, the corollary of the principle that the requirements of the protection of public health are to prevail over economic interests."*

b. The RTU Regime, Especially When Applied Where Therapeutic Alternatives Are Available, and the RTU Decision on Avastin Infringe Directive 2001/83 and Regulation 726/2004

The French RTU rules, especially when applied in cases where authorised therapeutic alternatives are available, and the ANSM decision issuing an RTU for Avastin clearly infringe the EU marketing authorisation rules. An RTU is an official recommendation for a specific use of a medicine outside the terms of its marketing authorisation. It operates as a *quasi*-marketing authorisation and actively supports the use in question, but without following the procedures and the standards laid down in Directive 2001/83 and Regulation 726/2004. It is also not covered by the exemption under Article 5(1) of Directive 2001/83.

The rules allowing an RTU also when therapeutic alternatives are available were adopted for budgetary reasons and even allow the reformulation of a medicine into a new product. They infringe the basic principle that public health goes above financial considerations and undermine the EU marketing authorisation regime.

i. The RTU is a quasi-marketing authorisation

The French RTU rules constitute a direct infringement of Article 6(1). RTUs are formal recommendations that are *quasi*-marketing authorisations:

- The RTU is adopted by the French Medicines Agency ANSM, which is the main competent authority in charge of medicines in France.

- The RTU is by nature a recommendation for a certain use of a medicine not covered by the marketing authorisation. In that respect, the RTU is even stronger than a marketing authorisation, which is a condition for placing a medicine on the market but does not, as such, constitute an official recommendation.

- The relevant provisions of the Public Health Code show that the RTU has characteristics that are similar to those of a marketing authorisation (see above under section 3 for details on these characteristics):
    - It is issued by the ANSM, as official medicines agency.
    - It is issued for a specific period[22] and can be renewed, apparently many times.
    - It contains key elements (therapeutic indication; posology and method of administration; and undesirable effects) that are similar to those contained in the SmPC of an authorised medicine and defines the prescription status of the product.
      In addition, the patient follow-up protocol for the Avastin RTU covers other elements that are also included in SmPCs, such as special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, pregnancy and lactation, and effects on ability to drive and use machines (see Attachment 6, pages 6-7).
    - The RTU is based on an assessment of the benefits and risks of using the product in the specific off-label setting and an assumption of a positive risk-benefit balance.
    - That assessment must be summarised in the patient follow-up protocol. This is to some extent similar to a public assessment report.

- The pharmaceutical company must actively disseminate the RTU to healthcare professionals and the ANSM posts the RTU on its website (see above, section 3). This automatically implies that the medicine in question is placed on the market not only under the relevant marketing authorisation, but also under the terms of the RTU. The RTU thus directly enables (and forces) the placing on the market of a medicine in a manner that goes beyond the terms of the marketing authorisation.

- The basic rule on prescribing under an RTU (under Article L. 5121-12-1, par. I) provides that a doctor can prescribe a medicine off-label when the use is covered by an RTU and when the doctor deems that it is necessary to improve or stabilise the clinical condition of the patient ("… *le prescripteur juge indispensable le recours à cette spécialité pour améliorer ou stabiliser l'état clinique de son patient*"). The latter requirement is, however, very similar to the general requirement that a doctor must always, also when prescribing a medicine in-label, "limit his prescriptions and acts to what is necessary for the quality, safety and efficacy of the medical care"

[22] Up to three years, while marketing authorisations are (initially) valid for five years.

(Article R. 4127-8 of the Public Health Code: "*…limiter ses prescriptions et ses actes à ce qui est nécessaire à la qualité, à la sécurité et à l'efficacité des soins.*").[23]

There is thus no real difference between the standard for prescribing in-label (under the marketing authorisation) or off-label under an RTU. On the other hand, an off-label prescription without an RTU is only permitted when there is no authorised therapeutic alternative[24] (Article L. 5121-12-1, par. I, *in fine*).

Consequently, in essence, the French Public Health Code puts an RTU at an equivalent level to a marketing authorisation.

- The RTUs go beyond mere off-label use and may also envisage reformulation of an existing and approved medicine. This is confirmed by Article L. 162-17-2-1 of the Social Security Code (Attachment 7), as amended in August 2014, which provides that the price for the product can also take into account the "preparation, splitting, change in packaging or change in presentation" of the product.[25] A change in presentation can, for instance, be a different pharmaceutical form.[26]

  The same provision also expressly envisages that the reformulated product can be dispensed at the retail stage ("… *en vue de sa délivrance au détail*") and thus that reformulated medicines are placed on the market.

- The RTU decision for Avastin expressly envisages reformulation (see Attachment 6, page 2 and pages 37-38) so as to make a preparation for injection into the eye. This handling and compounding results in a new and unapproved medicinal product that is distinct from Avastin and the endorsement by ANSM of its preparation and use is manifestly a derogation from to the marketing authorisation principle. The changes made to Avastin[27] include, for instance, the following:
  - The pharmaceutical form of Avastin is "concentrate for solution for infusion" (par. 3 of the SmPC and par. 4 of the outer package labelling). The pharmaceutical form of the off-label monodoses will be "solution for injection."
  - The route of administration of Avastin is "intravenous use after dilution" (par. 5 of the outer package labelling). The route of administration of the off-label monodoses is "intravitreal use."

[23] This obligation is directly imposed by law (the Public Health Code) and applies to all doctors (Article R. 4127-1), but is also enforced by the professional organisations (*ibid.*).

[24] Either under a marketing authorisation or under a cohort temporary authorisation for use ("ATU"), which is the French mechanism for named patient sales and compassionate use programmes.

[25] "*Lorsque la spécialité a fait l'objet d'une préparation, d'une division ou d'un changement de conditionnement ou d'un changement de présentation en vue de sa délivrance au détail, le prix est fixé par décision des ministres chargés de la santé et de la sécurité sociale, en tenant compte du prix ou du tarif de responsabilité en vigueur pour les indications remboursées, du coût lié à cette opération et de la posologie indiquée dans la recommandation temporaire d'utilisation.*"

[26] See also the summary of reasons for the Government proposal that resulted in article 10 of Law nr. 2014-892 (Attachment 20) "*Par ailleurs, il précise les conditions de tarification des médicaments utilisés hors de leur AMM lorsque cet usage nécessite un reconditionnement ou une préparation spécifique qui justifie la fixation d'un prix différent de celui qui a cours dans les indications de l'AMM.*" (emphasis added).

[27] For the SmPC, package leaflet and labelling of Avastin, see: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf .

- The off-label monodoses must be prepared as pre-filled syringes or small vials, intended for intraocular injection. This deviates from par. 6.5 of the SmPC for Avastin, which refers to 4 ml or 6 ml solution in a vial. The off-label monodose will be presented in a syringe as opposed to a vial, or at least in a vial with a much lower content than 4 ml.
- The SmPC for Avastin contains an express precautionary warning against repeated use of the same vial:

  "6.6 Special precautions for disposal and other handling

  …

  Avastin is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed in accordance with local requirements."[28]

  This is automatically disregarded when different monodoses are prepared for intravitreal administration.
- The final manufacturing of the off-label monodoses will be done by hospital pharmacies and not by the manufacturer identified in the package leaflet of Avastin.

All these differences are of significant relevance from a public health point of view. The first two are expressly recognised as being fundamental by Commission Regulation 1234/2008 on variations. Annex I to the Regulation classifies a change of pharmaceutical form and a change of route of administration as "extensions", which require evaluation "in accordance with the same procedure as for the initial marketing authorisation" (Article 19(1)). This is because "certain changes which have the highest potential impact on the quality, safety or efficacy of medicinal products require a complete scientific assessment, in the same way as for the evaluation of new marketing authorisation applications" (recital 4).

- The notification under TRIS of the draft decree also expressly accepted that the legality of the regime must be assessed under the marketing authorisation rules. Indeed, the Brief Statement of Grounds for the notification provides:

  "In this regard, the draft Decree supplements the provisions of Article R. 5121-76-1 of the French Public Health Code in order to clarify, firstly, that the RTU mechanism falls within the provisions of paragraph 1 of Article 5 of Directive No 2001/83/EC of the European Parliament and of the Council of 6 November 2001 and, secondly, to take into account the consequences of the Ruling of the European Court of Justice of 11 April 2013 in case C-535/11." (Attachment 16)

  As demonstrated below, however, Article 5(1) does not exempt the RTUs.

[28] In addition, the special precautions for storage (par. 6.4 of the SmPC and par. 9 of the outer package labelling) are based on the specific formulation of the product and cannot be extrapolated to off-label monodoses. Similarly, the shelf life specified (in par. 6.3 of the SmPC) will not apply to the off-label monodoses.

ii. The RTU is not granted in accordance with the Union marketing authorisation rules.

It is obvious that RTUs are not granted in accordance with the EU marketing authorisation procedures.

- The RTU process does not follow the procedures prescribed by Directive 2001/83 and Regulation 726/2004.

- The RTU process does not respect the mandatory scope of the centralised procedure under Regulation 726/2004.

- Marketing authorisations are granted based upon an express request by the pharmaceutical company.[29] The RTU procedure, on the other hand, is started by the ANSM itself and the Public Health Code grants various public institutions and patient organisations the right to suggest the preparation of an RTU (see above under section 3). Thus, the RTU can clearly be granted against the wish of the marketing authorisation holder.

In addition, the RTU process does not at all respect the standards for quality, safety and efficacy of medicines, which aim at protecting public health.

- The standards for review of the safety and efficacy for an RTU under the Public Health Code are very loose. Article L. 5121-12-1, par. I merely provides that the RTU must ensure the safety of ("*sécuriser*") the use of the medicine in the off-label indication or conditions of use. Article R. 5121-76-6 similarly merely provides that an evaluation of available safety and efficacy data allows an assumption that the expected benefit outweighs the undesirable effects. This is very different from the specific approval and refusal criteria for marketing authorisations.

  As mentioned, the French government also confirmed during the TRIS discussions that the evaluation under an RTU is very incomplete as it only "sheds light on the risk profile and brings the first elements of efficacy" of the company's product ("*un éclairage … sur le profil de risque et les premiers éléments d'efficacité de son produit*" - Attachment 18, page 24).

- The rules do not define what scientific and medical data must be available to allow an RTU. On the contrary, the approach is basically one of reviewing any data that are available (which are data the pharmaceutical company has and must supply under Article R. 5121-76-4; or other "available scientific knowledge" under Article R. 5121-76-6), without setting a specific standard for non-clinical and clinical evidence. This is very different from the precise standards laid down in Annex I to Directive 2001/83, so as to guarantee appropriate quality, safety and efficacy of medicines that receive a marketing authorisation.

- The rules envisage possible reformulation, but do not set any quality standard.

[29] Article 126a of Directive 2001/83 provides for a very narrow exception (see above, footnote 20).

- The standard is also deliberately loose because Article R. 5121-76-1 provides that one RTU can cover different medicines, even with different active ingredients, provided that they have a "similar mode of action."

iii. The RTU regime does not comply with Article 5 of Directive 2001/83

The TRIS notification of the draft decree in June 2014 claimed that "the RTU mechanism falls within the provisions of paragraph 1 of Article 5 of Directive No 2001/83/EC" (Attachment 16, page 2). This is clearly not correct.

The Court of Justice held that the exemption under Article 5(1) is exceptional. It must be limited to situations where the following cumulative conditions are met:

- it "must remain exceptional in order to preserve the practical effect of the marketing authorisation procedure"
- it should only be used when it "is necessary, taking account of the specific needs of patients"
- it only applies to "individual situations justified by medical considerations"
- the medicine must be supplied "in response to a 'bona fide unsolicited order'", which requires a prescription by a doctor as a result of an "actual examination of his patients and on the basis of purely therapeutic considerations"
- there is "no authorised equivalent" medicine available.

(Case C-185/10, *Commission v Poland*, par. 32-36).[30]

This requires that when there are authorised medicines, the prescribing doctor must reach the professional judgment that for the individual patient in question the unauthorised medicine is therapeutically better than the authorised alternatives. This is expressly confirmed by the Court in *Novartis v Apozyt*, in the context of using Avastin instead of Lucentis for treating patients with neovascular age related macular degeneration:

> "*… since the active ingredients of Avastin and Lucentis are different, a doctor, when faced with a particular condition and relying solely on therapeutic considerations specific to his patients, including considerations pertaining to how the medicine is administered, may take the view that a treatment not covered by the marketing authorisation, in accordance with the pharmaceutical form and the dosage which he considers appropriate and using Avastin which has a Community marketing authorisation, is preferable to treatment with Lucentis.*" (par. 48, emphasis added)

In addition, the Court of Justice held that Article 5(1) cannot be relied upon for economic or financial reasons.

> *"Financial considerations cannot, in themselves, lead to recognition of the existence of such special needs capable of justifying the application of the derogation provided for in Article 5(1) of that directive."* (*Commission v Poland*, par. 38)

[30] The Court of Justice also referred to this in *Novartis v Apozyt*: "It should be borne in mind in that regard that Article 5(1) of Directive 2001/83 is a specific derogating provision, which must be interpreted strictly, applicable in exceptional cases where it is appropriate to meet special medical needs, in circumstances in which a doctor, following an actual examination of his patients and on the basis of purely therapeutic considerations, prescribes a medicinal product which does not have a valid marketing authorisation in the European Union and for which there is no authorised equivalent on the national market or which is unavailable on that market (see, to that effect, Case C 185/10 *Commission v Poland* [2012] ECR I 0000, paragraphs 35, 36 and 48)." (par. 46).

The RTU regime clearly does not meet these requirements. Several aspects of the regime disregard the principles governing Article 5(1) and each on its own constitutes an infringement of EU law:

- First, the RTU regime in general contradicts the exceptional nature of the scope of application of Article 5(1):
  - The RTU is a formal recommendation that has the effect of a *quasi*-marketing authorisation (see above, section 4.b.i).
  - The RTU is not only published on the website of the ANSM, but it must also be actively disseminated by the pharmaceutical company towards prescribing doctors (see above, section 3).

- Second, the RTU regime disregards the need for a medical conclusion that the use of a medicine outside the terms of the marketing authorisation is therapeutically better for the individual patient than the use of the authorised alternative.

  The relevant provisions are:
  - An RTU can be adopted whenever there is no medicine with the same active substance(s), same dosage and same pharmaceutical form, authorised for the same therapeutic indication. (Art. L. 5121-12-1 and art. R. 5121-76-1 of the Public Health Code).
  - When using the RTU (by prescribing a medicine under the terms of an RTU) the doctor must consider that the medicine is necessary for treating the patient. See art. L. 5121-12-1: "*le prescripteur juge indispensable le recours à cette spécialité por améliorer ou stabiliser l'état clinique de son patient*"; and art. R. 5121-76-1: "*pour répondre aux besoins spéciaux du patient*").

  Adoption of the RTU

  The RTU rules do not require an assessment of what therapeutic benefits the off-label use may provide to patients when authorised therapeutic alternatives are available. They only require that there is no medicine with the same active substance(s), same dosage and same pharmaceutical form authorised for the same therapeutic indication. This is a clear reference to the decision of the Court of Justice in *Commission v Poland*, where the Court held that Article 5(1) could not be relied upon "[w]here medicinal products having the same active substances, the same dosage and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market" (par. 37). This passage is also referred to in *Novartis v Apozyt* (par. 46).

  The RTU regime is based on the assumption that the Court rulings imply that as soon as there is no authorised medicine with the same active substance(s), dosage and pharmaceutical form, the use of an unauthorised medicine is possible under Article 5(1). This was also expressly stated by the French Government in the legislative proposal that resulted in the current wording of article L. 5121-12-1. The first two sentences of the summary of reasons state:

  > "*La Cour de justice de l'union européenne a récemment précisé sa doctrine sur les prescriptions de produits en dehors de leur autorisation de mise sur le marché.*

Sa jurisprudence autorise désormais la prescription d'un médicament en dehors de son autorisation de mise sur le marché, même dans le cas où une alternative thérapeutique existe, dès lors que cette alternative n'a pas la même substance active, ni le même dosage, ni la même forme pharmaceutique que le produit que le médecin estime devoir prescrire pour soigner son patient."[31]

This is a complete misrepresentation of the decisions of the Court. The wording in question in *Commission v Poland* was based on the specific provision of Polish law that formed the subject matter of the dispute and allowed the use of unauthorised medicines with the same active substance, dosage and form as authorised medicines (see par. 5 of the decision). There can indeed be no medical need for such products.

Nowhere, however, did the Court decide that Article 5(1) can automatically be invoked whenever there is no authorised medicine with the same active substance, dosage and pharmaceutical form. On the contrary, as stated above it clearly held that in such a case the use of the unauthorised medicine must be shown to bring a therapeutic benefit over the authorised therapy. That assessment is completely missing in the RTU regime. Article L. 5121-12-1 and Article R. 5121-76-1 and following of the Public Health Code do not require any assessment of the therapeutic benefit of the off-label use over authorised therapies.

This is also illustrated by the RTU for Avastin. Three medicines are expressly authorised for the treatment of neovascular age related macular degeneration under the centralised procedure, namely Macugen (marketing authorisation of January 2006), Lucentis (marketing authorisation of January 2007) and Eylea (marketing authorisation of November 2012).

Nowhere in the assessment by the ANSM in preparation of the RTU decision for Avastin is there an evaluation of the possible benefits of Avastin over the use of the approved alternatives. On the contrary, the assessment is, with regard to efficacy, expressly based on a finding of non-inferiority of Avastin versus Lucentis. So the two other approved products are essentially disregarded and the review expressly does not examine what specific benefits Avastin might possibly bring compared to Lucentis. In addition, the safety assessment acknowledges that the information is very limited. For the details, see Attachment 6, pages 11 and following, with a synthesis on page 24.

As demonstrated below (section 5.a.) the advisory committee assisting the ANSM in the assessment also stressed the uncertainties and safety risks and indicated that there was only an economic benefit, and thus no therapeutic benefit, in using Avastin.

This is further confirmed by the HAS recommendation for reimbursement of Avastin under the RTU. The recommendation does not evaluate any potential therapeutic benefit of Avastin for certain individual patients over the authorised medicines, and concludes:

"*Considérant l'ensemble des informations suivantes :*

- *la dégénérescence maculaire liée à l'âge (DMLA), première de cause de malvoyance après 65 ans dans les pays occidentaux.*

[31] See the *Exposé sommaire* to the amendment of 30 June 2014, Attachment 20.

- *l'absence de spécialité remboursable de même principe actif, de même dosage et de même forme pharmaceutique ;*
- *le fait que le bevacizumab ait un intérêt thérapeutique pour les patients atteints de dégénérescence maculaire liée à l'âge exsudative néovasculaire choroïdienne rétrofovéolaire,*

le Collège de la HAS considère que la spécialité AVASTIN 25 mg/ml, solution à diluer pour perfusion peut faire l'objet d'une prise en charge dérogatoire dans le traitement de la dégénérescence maculaire liée à l'âge exsudative néovasculaire choroïdienne rétrofovéolaire dans les situations où le prescripteur juge son utilisation indispensable pour améliorer l'état de santé des patients ou éviter leur dégradation." (Attachment 8, page 14 of the recommendation)

The HAS recommendation is the basis for the decision of 19 August 2015 on reimbursement of Avastin under the RTU (as shown by the fourth recital to the decision, Attachment 8 bis).

Use of the RTU

The RTU rules require that the doctor must consider that the medicine is necessary for treating the patient. This is worded in vague terms and fails to clearly require that the doctor makes a medical judgment that for the individual patient in question the off-label use is therapeutically better than the use of any of the authorised alternatives. This is, however, as shown above a necessary condition for invoking Article 5(1).

This infringement of the principles governing Article 5(1) is clearly illustrated by the RTU for Avastin. The patient follow-up protocol provides detailed instructions for the prescribing doctors:

"*Le médecin prescripteur :*

- *Vérifie les critères de prescription ;*[32]
- *Vérifie l'absence de contre-indication au traitement ;*
- *Identifie et prend en compte les facteurs de risques individuels cardio-vasculaires et hémorragiques ;*
- *Informe son patient, son représentant légal ou la personne de confiance qu'il a désignée, du cadre hors AMM de la prescription, des risques encourus et des contraintes et bénéfices susceptibles d'être apportés par AVASTIN®, ainsi que des conditions de prise en charge par l'assurance maladie, et s'assure de la bonne compréhension de ces informations ;*
- *Remet au patient, à son représentant légal ou à la personne de confiance qu'il a désignée la note d'information destinée au patient (cf. Annexe II), la liste des médecins à contacter en cas d'effet indésirables*

[32] The criteria are laid down on page 4 of the protocol: "*Critères de prescription*
Sujets :
- âgés de 18 ans est plus ;
- présentant une forme néovasculaire (humide) de la dégénérescence maculaire liée à l'âge (DMLA) ;
- ayant été informés de l'usage hors AMM du produit et des risques potentiels (cf. Annexe III : note d'information au patient) ;
- ayant une contraception efficace pour les femmes en âge de procréer."

et le formulaire de signalement-patient d'effet(s) indésirable(s) lié(s) à un médicament (cf. Annexe II) .

- *Etablit une ordonnance d'AVASTIN® en portant sur l'ordonnance la mention « Prescription sous RTU » ainsi que l'identification du patient, la date d'injection, la posologie d'AVASTIN, l'identification du prescripteur et l'œil traité (droit ou gauche) ;*

- *Motive sa prescription dans le dossier médical patient ;*"

(Attachment 6, page 8 of the protocol)

This clearly omits the crucial step of determining that for the specific patient the off-label use of Avastin is therapeutically better than the use of the medicines specifically authorised for this treatment.

- Third, the French government apparently expressly decided to deviate from the key principle laid down in *Commission v Poland* and *Novartis v Apozyt* that the exception applies when based on "purely therapeutic considerations." While the draft decree attached to the TRIS notification provided that the off-label prescription had to be based on "purely therapeutic considerations", the final version of the decree (and the current Article R. 5121-76-1) merely states that it must be based on "therapeutic considerations." It thus implicitly allows other considerations to be taken into account as well.

- Fourth, the RTU regime as put in place in 2014 was adopted for economic reasons.

  The TRIS notification of the draft decree in June 2014 alleges that "[t]he purpose of an RTU is to ensure safety when doctors prescribe a medicine outside the parameters of its marketing authorisation (AMM) on the basis of purely therapeutic considerations relating to the specific needs of their patients, as identified by examination,…" (Attachment 16).

  The facts, however, demonstrate that the RTU regime as established under Law no. 2014-892 is based on financial considerations:

  - Law no. 2014-892 of 8 August 2014 is entitled "corrective law on the financing of the social security for 2014" (*Loi n° 2014-892 du 8 août 2014 de financement rectificative de la sécurité sociale pour 2014*). The main objective of the law is thus to regulate the financing of the social security system.

  - The amendments to the RTU rules (under both the Public Health Code and the Social Security Code) made by Law no. 2014-892 are contained in its Article 10. This article is included in the second part of the law, which is entitled "Provisions on costs" ("*Dispositions relatives aux dépenses*") (see Attachment 2).

  - The summary of reasons for the Government proposal that resulted in Article 10 of Law no. 2014-892 (Attachment 20) states:

"*Or, le dispositif de RTU tel qu'il a été instauré dans la loi médicament interdit aujourd'hui toute prescription hors AMM dès lors qu'il existe une alternative thérapeutique, ce qui proscrit par exemple l'usage de l'Avastin® dans le traitement de la DMLA à la place du Lucentis®, alors même que les deux molécules ne sont pas rigoureusement identiques …*"

- During the discussions in Parliament, the Minister of Health stated:

> "*Pour résumer très abruptement cet amendement, je dirais qu'il renvoie au débat suscité par deux médicaments désormais bien connus des membres de la commission des affaires sociales : l'Avastin et le Lucentis. Depuis que je suis au Gouvernement, j'ai mené plusieurs actions pour permettre la prescription de l'Avastin dans le traitement de la dégénérescence maculaire liée à l'âge au lieu du Lucentis. Aujourd'hui, seul ce dernier a une autorisation de mise sur le marché pour traiter la DMLA ; or, il coûte beaucoup plus cher que l'Avastin.*
>
> *Or des études et des essais cliniques ont montré que l'Avastin pourrait remplir le même objectif. Je tiens à rappeler que cette préoccupation financière est significative puisque plus de 430 millions d'euros ont été dépensés en 2013 pour le seul remboursement du Lucentis.*
>
> *Il y a donc bien un enjeu financier, mais le dossier est juridiquement complexe.*" (emphasis added)[33]
>
> and
>
> "*Tout en garantissant la sécurité sanitaire, l'adoption de cet amendement permettra de réaliser des économies, puisque des spécialités moins coûteuses mais présentant la même efficacité pourront être prescrites – par exemple, l'Avastin dans le traitement de la dégénérescence maculaire liée à l'âge, la DMLA.*" (emphasis added)[34]

- Press articles also confirm that the purpose behind the rules is an economic one (see Attachment 23).

- As mentioned, the final decree dropped the "purely" in the reference to therapeutic considerations.

- As also mentioned, the rules also provide that the Minister of Social Security and the sickness funds union can request the ANSM to envisage an RTU.

- The economic considerations were also highlighted during a March 2015 meeting of the advisory committee[35] when the RTU for Avastin was being prepared. The minutes of the meeting state:

> *"Isabelle DEBRIX s'étonne que le volet économique du dossier ne soit pas traité alors qu'Avastin® est bel et bien proposé car il est plus économique que Lucentis®.*

[33] See Attachment 21, page 44.
[34] See Attachment 22, page 6122.
[35] The *Commission d'évaluation initiale du rapport bénéfice risque des produits de santé*.

> *Cécile DELVAL rappelle que la question est posée car il existe un usage hors AMM. La question posée à la Commission est de savoir s'il faut encadrer cet usage hors AMM et selon quelles modalités.*
>
> *Isabelle DEBRIX maintient que la question économique anime ce dossier.*
> *Willy ROZENBAUM indique, avant tout, que la question est de déterminer si les deux produits peuvent être proposés pour la même indication, s'il est admis qu'ils sont équivalents.*
>
> *Albert TRINH-DUC estime que la raison pour laquelle le prescripteur choisit ce médicament plutôt qu'un autre est sans doute économique, alors même qu'il existe aujourd'hui un produit équivalent ayant une AMM."*
>
> Dr. Debrix, Prof. Rozenbaum and Dr. Trinh-Duc are members of the committee. Dr. Delval is head of evaluation of the ANSM (see Attachment 24, pages 10-11).

The Court of Justice held very clearly in *Commission v Poland* that Article 5(1) cannot be relied upon for economic or financial reasons.

It follows from the above that the RTU regime infringes Article 5(1) of Directive 2001/83 in four different ways:

- By giving formal recommendations in the form of an RTU, the regime disregards the exceptional nature of the provisions of Article 5(1).
- By allowing an RTU whenever there is no authorised medicines with the same active substance(s), dosage and pharmaceutical form (for the same therapeutic indication), the regime infringes the need to determine that the non-authorised use is therapeutically better for the patient than the use of the authorised alternatives. The regime does not expressly require the prescribing doctor to make such assessment either.
- The regime deliberately allows for other than purely therapeutic considerations to be taken into account when prescribing a medicine under an RTU.
- The regime is based on economic considerations when used in cases where authorised therapeutic alternatives are available.[36]

iv. The RTU regime infringes the off-label principle expressed in CTRS v Commission

In *CTRS v Commission*, the General Court held that:

> *"The point must also be made that off-label prescribing is the sole responsibility of the prescribing physician (see, to that effect, judgment of 11 April 2013 in Novartis Pharma, C-535/11, ECR, EU:C:2013:226, paragraph 48). 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."* (Case T-452/14, par. 82)

That case concerned statements in the SmPC and the EPAR on the efficacy and safety of the medicine in therapeutic indications other than those for which it was officially approved. *A fortiori*, the same principle applies to formal recommendations by the competent national

[36] Similarly, the exception under Article 83 of Regulation 726/2004 does not apply. In addition, the conditions under Article 83(2) are not fulfilled.

authority to use a medicine off-label that are actively disseminated to all prescribing doctors, like an RTU.

v. RTUs with reformulation are not covered by the magistral formula exemption

RTUs that involve reformulation, such as the Avastin RTU, also do not qualify for the magistral preparation exemption for intrinsic reasons:

- The Court of Justice recently confirmed in *Abcur v Apoteket and Apoteket Farmaci* (Cases C-544/13 and C-545/13) that the magistral formulation exemption must be interpreted strictly:

  > *"… it must be taken into account that, generally, provisions which are in the nature of exceptions to a principle must, according to settled case-law, be interpreted strictly (see in particular, to that effect, Erotic Center, C 3/09, EU:C:2010:149, paragraph 15, and Commission v Poland, C 185/10, EU:C:2012:181, paragraph 31 and the case-law cited)."* (par. 54)

  In line with this, magistral formulas must not be promoted through an official recommendation and cannot be motivated by economic considerations.[37]

- By its nature, the magistral formula exemption relies on the professional responsibility of the pharmacist (and the prescribing doctor) and cannot be steered by official "recommendations", and especially not by a systematic process of encouraging and promoting off-label use (as also confirmed by the General Court in its *CTRS* ruling).

- Finally, a magistral preparation is made on the basis of active substances and excipients, but not by reformulating existing medicines.

These restrictions are needed to preserve the fundamental objective of Directive 2001/83 and Regulation 726/2004 to protect public health; and as demonstrated above are not met by the contested measures.

vi. RTUs with reformulation are not covered by the considerations in Novartis v Apozyt

The derogation put in place with the contested measures is also not covered by the following considerations by the Court of Justice in *Novartis v Apozyt*, related to the supply by a manufacturer of reformulated Avastin and Lucentis to pharmacies:[38]

> *"42 In such circumstances, provided that the referring court does in fact find that the processes in question do not result in any modification of the medicinal product and that they are carried out solely on the basis of individual prescriptions making provision for them, there is no ground for considering that the activity thus carried out can be equated with a new placing on the market of a medicinal product included in point 1 of the Annex to Regulation No 726/2004; accordingly, the*

[37] The *Abcur* decision also reviewed when magistral preparations fall within the scope of Directive 2001/83 as being "prepared industrially or manufactured by a method involving an industrial process." This issue does not arise here as Avastin is clearly an industrially prepared medicine and is approved under Regulation 726/2004. This also follows implicitly but very clearly from the Court's ruling in *Apozyt*.

[38] The exact scope of this consideration is unclear as the Court does not base it on a specific article in the legislation.

company concerned is, in that respect, not subject to the obligation to hold a marketing authorisation granted by the Community pursuant to Article 3(1) of the regulation." (emphasis added)

First, the transformation into off-label monodoses under the RTU for Avastin does imply a modification of the product. These changes are described above (section 4.b.i) and include:

- a different pharmaceutical form,
- a different route of administration,
- a different dosage and immediate packaging, and
- an additional manufacturer.

Similarly, in the *Novartis v Apozyt* case, following the Court of Justice decision, the German national court held that the reformulated products (in pre-filled syringes) implied a modification and required a marketing authorisation.[39]

Second, and more importantly, the consideration by the Court of Justice was expressed in the context of a private initiative of a manufacturer in Germany. In the present case, the contested measures constitute an official act by the national legislator and the national competent authority, formally "recommending" the off-label use of the products covered by an RTU. Consequently, independently from possible modifications to the product, the consideration by the Court in *Novartis v Apozyt* cannot apply in the current context.

vii. Infringement of Article 3 of Regulation 726/2004

In addition to infringing the basic marketing authorisation requirement under Article 6 of Directive 2001/83, the RTU regime also infringes Article 3 of Regulation 726/2004 which requires biotechnology and many high-technology medicines to be reviewed under the centralised procedure. Recital 7 of the Regulation states that "it is necessary to create a centralised authorisation procedure that is compulsory for high-technology medicinal products, particularly those resulting from biotechnical processes, in order to maintain the high level of scientific evaluation of these medicinal products in the European Union and thus to preserve the confidence of patients and the medical professions in the evaluation."

The RTU regime is worded in general terms and does not exclude medicines that are subject to the mandatory scope of the centralised procedure. On the contrary, as indicated above, the amendments introduced in August 2014 were in particular intended to allow the off-label use of the recombinant monoclonal antibody product Avastin; and Articles R. 5121-76-3, 5 and 6 of the Public Health Code expressly envisage RTUs for orphan medicines and for cancer treatments. However, all biotechnology medicines (such as Avastin), orphan medicines and cancer medicines that contain active ingredients that were not yet authorised in late 2005 must be reviewed under Regulation 726/2004. By having this general scope of application the RTU rules also infringe Article 3 of the Regulation.[40]

[39] LG Hamburg, decision of 14 January 2014 (416 HKO 78/11), referring to the differences between the reformulated products and the authorised Avastin and Lucentis, including those listed above. The case is currently pending on appeal.

[40] Article 83 of Regulation 726/2004 also does not apply (see above, footnote 36).

viii. Infringement of the Commission decisions granting and varying marketing authorisations

The RTU regime, when applied to centrally approved medicines, also infringes the Commission decisions granting and varying the marketing authorisations. These decisions define the exact scope of the authorisation and contain the approved SmPC in attachment. By officially recommending in a structured way the use of authorised medicines in other indications or under other conditions than those specified in their marketing authorisation, the RTU rules infringe the Commission decisions -- in this case the Commission decisions issuing and varying the marketing authorisation for Avastin.

ix. Policy considerations with regard to generics and biosimilars

In addition, the RTU regime, when applied in cases where authorised alternative medicines are available, undermines the general balance struck by the EU pharmaceutical regime between innovative products and their generic (or biosimilar) versions. When France, through the RTU regime, seeks to make cheaper alternative medicines available so that they can compete with innovative medicines that are expressly authorised for the therapeutic use in question, it also undermines the potential for generic companies to seek the approval of generic or biosimilar versions of these innovative medicines when the exclusivity period expires.

This goes against the express purpose of the EU regime to also stimulate generic products. Recital 14 to Directive 2004/27,[41] amending Directive 2001/83, states: "Since generic medicines account for a major part of the market in medicinal products, their access to the Community market should be facilitated in the light of the experience acquired."

c. The RTU Regime Undermines the Practical Effectiveness of Directive 2001/83, Regulation 726/2004 and Commission Decisions Granting and Varying Marketing Authorisations

Section b demonstrates that the RTU regime directly infringes Article 6 of Directive 2001/83, Article 3 of Regulation 726/2004 and the Commission decisions granting and varying marketing authorisations under the Regulation.

In case such direct infringement were not accepted, the RTU regime still clearly undermines the practical effectiveness (*effet utile*) of these rules and decisions. Member States have a duty of loyal collaboration with Union rules and policies. Article 4(3) of the Treaty on European Union (TEU) provides as follows:

> *"Pursuant to the principle of sincere co-operation, the Union and Member States shall, in full mutual respect, assist each other in carrying out tasks which flow from the Treaties.*
>
> *The Member States shall take any appropriate measure, general or particular, to ensure fulfilment of the obligations arising out of the Treaties or resulting from the acts of the institutions of the Union.*

[41] Directive 2004/27/EC of The European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

The Member States shall facilitate the achievement of the Union's tasks and refrain from any measure which could jeopardise the attainment of the Union's objectives."

Pursuant to this duty, Member States must "take all measures necessary to guarantee the application and effectiveness of Community law" (joined Cases C-36/97 and C-37/97 *Hilmar Kellinghusen v Amt fur Land- und Wasserwirtschaft Kiel* and *Ernst-Detlef Ketelsen v Amt für Land- und Wasserwirtschaft Husum*, par. 30).

By officially recommending the off-label use of medicines (especially when there are alternative treatments and done in light of economic considerations), France undermines the practical effectiveness of the Union marketing authorisation system and it puts the safety and health of patients and users of medicines at risk.

5. Infringement of Fundamental Rights

a. Protection of Public Health

Article 35 of the Charter of Fundamental Rights of the EU provides that:

"A high level of human health protection shall be ensured in the definition and implementation of all the Union's policies and activities."[42]

In accordance with Article 51 of the Charter, its principles also apply to Member States "when they are implementing Union law." As the EU courts have laid down principles related to the exemptions to the EU marketing authorisation rules and to the off-label use of medicines, Member States have to respect the principle of Article 35 also in this context.

When the RTU regime is applied when authorised alternative medicines are available, it undermines the high level of human health protection that is required. This is *a fortiori* the case when an RTU is granted also for economic reasons.

The ANSM documents related to the Avastin RTU also illustrate this. The minutes of the March 2015 meeting of the ANSM advisory committee expressly identify concrete areas of uncertainty and safety concerns.

First, the ANSM director of neurological medicines (Dr. Philippe Vella) indicated:

"En conclusion, l'ensemble de ces travaux montrent une efficacité d'Avastin® utilisé en IVT dans le traitement de la DMLA exsudative et une non infériorité d'Avastin® à Lucentis® en termes d'efficacité fonctionnelle sur l'acuité visuelle. En revanche, sur les critères morphologiques rétiniens, l'évolution pourrait être un peu moins favorable chez les patients traités par Avastin®, mais les conséquences cliniques sont, à ce stade, difficiles à appréhender et restent du domaine de la recherche clinique. Concernant la tolérance, les effets oculaires observés d'Avastin® sont des effets attendus des anti-VEGF utilisé en IVT. Le risque d'infection est principalement lié au mode de préparation d'Avastin® en IVT, qui serait donc à encadrer par des recommandations de préparation très strictes. Il n'a pas été démontré l'existence d'une différence significative pour les EIG systématiques avec Avastin® par rapport à Lucentis®, excepté pour les EIG gastro-intestinaux. Il faut noter que l'évaluation des données de tolérance se base sur des études randomisées conçues pour évaluer l'efficacité d'Avastin® et non son profil de sécurité. Par conséquent, il est difficile de

[42] The same principle is laid down in Article 168 TFEU.

déterminer de façon certaine la sécurité d'Avastin® administré en IVT. Il semble aussi nécessaire de prendre en compte les facteurs de risque cardiovasculaires et hémorragiques. Il semble donc nécessaire de collecter des données en vie réelle pour consolider le profil de sécurité." (see Attachment 24, page 14)

Second, two of the committee members stated:

Stéphane TELLEZ s'enquiert de l'intérêt de prescrire Avastin® sur Lucentis® compte tenu des contraintes de préparation associées. Hormis l'aspect économique, il voit mal le bénéfice d'Avastin® sur Lucentis®. De plus, aucune information n'est donnée sur le possible relais de l'Avastin® s'il est noté que l'effet de Lucentis® s'émousse.

Albert TRINH-DUC estime que, vu du patient, le Lucentis® présente un avantage ne serait-ce par le fait qu'il ne nécessite pas de préparation. De même, en termes de santé publique, pourquoi faire prendre des risques au patient alors qu'il existe une alternative thérapeutique non inférieure." (see Attachment 24, page 18)

On the other hand, three medicines are expressly authorised for the treatment of neovascular age related macular degeneration under the centralised procedure, namely Macugen, Lucentis and Eylea. These are clear therapeutic alternatives that make the recourse to the reformulated use of Avastin unnecessary. During the March 2015 meeting of the advisory committee it was stated that the French ophthalmologists may not yet be that familiar with Eylea but the use of Lucentis is established:

"Jean-Christophe ZECH rappelle que Lucentis® est utilisé depuis 7/8 ans, les médecins bénéficient d'un certain recul. Alors qu'Eylea® est disponible depuis peu sur le marché." (see Attachment 24, page 8)[43]

In addition, the entire assessment of Avastin by the advisory committee is based on a comparison with Lucentis (as illustrated by the two passages quoted above but also by the entire report). There is thus no doubt that there is a valid therapeutic alternative with a marketing authorisation covering the treatment of neovascular age related macular degeneration.

b. Infringement of the Fundamental Freedom to Conduct a Business

Under Article 16 of the Charter "[t]he freedom to conduct a business in accordance with Union law and national laws and practices is recognised."

An RTU implies a serious restriction on the commercial freedom of the pharmaceutical company in question:

- The RTU is unilaterally imposed and cannot be refused.
- The company has to carry the cost of the patient follow-up.
- The company must actively make the RTU available to prescribing doctors.
- The company is subject to broader pharmacovigilance obligations because of the additional use, possibly (like is the case for Avastin) in a very different therapeutic area.

[43] Macugen may in practice be rarely used (see the HAS assessment of July 2015, Attachment 8, page 8 of the recommendation).

- The product liability exposure of the company is significantly widened. The use of a medicine under an RTU will normally be a use "to which it could reasonably be expected that the product would be put" under Article 6(1) of the Product Liability Directive 85/374/EEC.[44] This may even apply in other Member States than France as it is possible that French RTUs are also taken into account by prescribing doctors in other countries. On the other hand, the defence for compliance with mandatory regulations under Article 7 of the Product Liability Directive may not be available.
- The RTU can last for more than three years as there is no limitation on the renewals.

In addition, Article L. 162-17-2-1 of the Social Security Code (Attachment 7) provides that the decision on the reimbursement of the medicine under an RTU may impose an obligation on the pharmaceutical company to seek a marketing authorisation (or possibly a variation) for the therapeutic indication in question.[45] This obligation can be enforced through an annual financial penalty of up to 10% of the turnover of the concerned medicine in France (Article L. 162-17-2-1, fifth indent). This is not only in contradiction with the above mentioned principles of the EU marketing authorisation regime but also a significant restriction on the commercial freedom of the company.

When there is an authorised medicine available for the therapeutic use in question, there is no public health need that could justify these very serious restrictions on the company's commercial freedom.

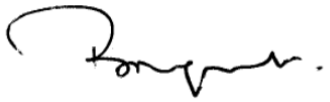
6. Earlier Discussions and Actions at the National and European Union Level

Industry representatives have had various interactions on the French RTU regime with the European Commission. The French pharmaceutical industry association (LEEM) raised concerns about the earlier RTU regime with the Commission in December 2013 and submitted a "summary note" outlining the different violations of EU law. This was followed by a meeting with officials of the Pharmaceutical Unit in February 2014 and a written submission in July 2014. The LEEM and EFPIA also made submissions to the Commission in the context of the TRIS procedure related to the draft RTU decree.

At the national level, the LEEM filed an action for annulment of the RTU Decree, as adopted on 30 December 2014, before the *Conseil d'Etat* on 11 February 2015.

31 August 2015

On behalf of the complainants,



Peter Bogaert, Advocaat, Covington & Burling LLP
pbogaert@cov.com

[44] Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products.

[45] The decision on reimbursement of Avastin under the RTU does not impose such obligation. Article 3 imposes patient follow-up in accordance with the RTU protocol (Attachment 8 bis).

Attachments

Contested measures[46]

1. Article L. 5121-12-1 of the Public Health Code (*Code de la Santé Publique*), as currently in force.

2. Law no. 2014-892 of 8 August 2014 (*Loi de financement rectificative de la sécurité sociale pour 2014 (1)*)- in particular Article 10.

3. Articles R. 5121-76-1 to R5121-76-9 of the Public Health Code (*Code de la Santé Publique*), as currently in force.

4. Decree no. 2014-1703 of 30 December 2014 (*Décret no 2014-1703 du 30 décembre 2014 modifiant les règles relatives à l'élaboration de recommandations temporaires d'utilisation établies en application du I de l'article L. 5121-12-1 du code de la santé publique*).

5. Decision of 24 June 2015 of the ANSM, issuing an RTU for Avastin.

6. Patient follow-up protocol (*Protocole de suivi des patients*) referred to in Article 4 of the ANSM decision of 24 June 2015.

Other

7. Article L. 162-17-2-1 of the Social Security Code (*Code de la Santé Publique*), as currently in force.

8. Recommendation of the HAS (*Haute Autorité de Santé*) for the reimbursement of Avastin of 8 July 2015.

8 bis. *Arrêté* of 19 August 2015 holding reimbursement of Avastin under the RTU.

9. Article L. 5121-12-1 of the Public Health Code (*Code de la Santé Publique*), as adopted in December 2011.

10. Articles R. 5121-76-1 to 9 of the Public Health Code (*Code de la Santé Publique*), as in force in May 2012.

11. Law no. 2012-1404 of 17 December 2012 (*Loi de financement de la sécurité sociale pour 2013*).

12. Decision of the *Conseil Constitutionnel* no. 2012-659 DC of 13 December 2012.

13. Press statements on the opinion of the *Conseil d'Etat* on the first draft decree implementing the revised Article L. 5121-12-1.

[46] See also document 8 bis.

14. Comparative table with the texts of the draft decrees implementing the revised Article L. 5121-12-1.

15. Article quoting MP Gérard Bapt.

16. TRIS notification of the draft decree amending the rules relating to the creation of temporary recommendations for use established pursuant to point I of Article L. 5121-12-1 of the French Public Health Code.

17. Draft decree amending the rules relating to the creation of temporary recommendations for use established pursuant to point I of Article L. 5121-12-1 of the French Public Health Code, as notified under TRIS.

18. Correspondence between the French Republic and the European Commission on concerning the TRIS notification.

19. Comparison of the draft RTU decree as notified under TRIS and the final decree adopted.

20. Amendment 219 to the draft *Loi de financement rectificative de la sécurité sociale pour 2014*, tabled on 30 June 2014.

21. Minutes of the discussion on Amendment 219 within the *Assemblée Nationale* of 2 July 2014.

22. Minutes of the discussion on Amendment 219 within the *Sénat* of 15 July 2014.

23. Press articles on the economic purpose of the RTU regime.

24. Minutes the meeting of the Commission for the Initial Evaluation of the Benefit-Risk Ratio of Health Products (*Commission d'évaluation initiale du rapport bénéfice risque des produits de santé*) of 19 March 2015.

Annex A

List of Key Union Legislation and Court Decisions
Referred to in the Complaint

Union legislation infringed by the contested measures

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28 November 2001, p. 67), as amended

  Referred to as "Directive 2001/83"

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30 April 2004, p. 1), as amended

  Referred to as "Regulation 726/2004"

- The Charter of Fundamental Rights of the European Union (OJ C 83, 30 March 2010, p. 389)

  Referred to as "Charter of Fundamental Rights" or "Charter"

Other Union legislation referred to in the complaint

- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7), as amended

  Referred to as "Commission Regulation 1234/2008"

- Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22 January 2000, p.1), as amended

  Referred to as "Regulation 141/2000"

- Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products (OJ L 210, 7 August 1985, p. 29), as amended

  Referred to as "Product Liability Directive"

Main Union case law on the marketing authorisation regime, referred to in the complaint

- *Artegodan and Others v Commission*, Joined Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00, EU:T:2002:283 ("Anorectics case")

- *Commission v Poland*, C-185/10, EU:C:2012:181

- *Novartis Pharma GmbH v Apozyt GmbH*¸ C-535/11, EU:C:2013:226

- *Laboratoires CTRS v Commission*, T 452/14, EU:T:2015:373.

- *Abcur v Apoteket AB and Apoteket Farmaci* (Cases C-544/13 and C-545/13), EU: EU:C:2015:481.