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UPDATE: THE GERMAN *PLAVIX* CASE: LOOPHOLES IN EUROPEAN DATA PROTECTION?

Originators beware: The marketing authorization granted by the German authority for a generic formulation of Plavix and the subsequent decisions of the competent courts in preliminary proceedings to allow the marketing of the drug raise questions about the protection of data under the European regulatory framework. Business plans will have to allow for generic competition earlier than previously expected, and particular attention should be paid to the publication of preclinical and clinical data.

This is an update to our *Commentary* from September 2008, incorporating the decision of the court of appeals. Added sections are marked "UPDATE."

INTRODUCTION

In 2006, sales of Plavix, the blockbuster anticoagulant of the French pharmaceutical company Sanofi-Aventis, suffered a blow in the U.S., where it is distributed by Bristol-Myers Squibb, when the Canadian generics company Apotex launched a generic form of the drug. An injunction, upheld on appeal, subsequently barred Apotex from distributing the drug during the pending patent litigation. However, Apotex was not required to recall its significant shipments up to the injunction.

This summer, the French company had to fight for sales of the blood thinner on its own doorstep. In May 2008 the German regulatory authority granted a marketing authorization ("MA") for a blood thinner with a similar active pharmaceutical ingredient. On July 25, 2008, the administrative court of first instance granted the applicant the right to use the MA, in spite of the objections of Sanofi-Aventis and Bristol-Myers Squibb ("BMS"). The decision raises significant issues concerning the scope of the European generic marketing-authorization procedures and eventual limits on data protection with regard to bibliographic applications.

UPDATE: On September 26, 2008, the administrative court of appeals not only confirmed the decision of the court of first instance but, adding insult to injury, also ruled on the scope of data-protection rules with regard to generic applications in deviation of standing

practice and European law, throwing into question established European practice.

PLAVIX VS. CLOPIDOGREL YES

The anticoagulant Plavix with the active pharmaceutical ingredient ("API") clopidogrel hydrogen sulfate was granted an MA under the centralized procedure for the European Union on July 15, 1998. On the same day, the MA for Iscover was granted to BMS, which distributes the product in Europe under this name, alongside Sanofi-Aventis. As the applications for marketing authorization of Plavix and Iscover predated October 30, 2005 (the German cutoff date for the new data-protection period according to the "8+2+1" formula), they still enjoyed data protection under the old 10-year period. That is, applications for generic formulations according to European practice would not have been accepted by the national authorities until after July 15, 2008. Accordingly, taking into account the duration of the procedure for granting an MA, one would not have expected a generic version to obtain an MA in 2008—let alone before the expiration of the data-protection period.

However, on May 21, 2008, even before the expiration of the generic data-protection period, the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, "BfArM") granted three (identical) marketing authorizations for products designated "Clopidogrel YES 75 mg film-coated tablets" with the API clopidogrel besylate, *i.e.*, a different salt than the API of Plavix. Clopidogrel YES was authorized with a limited label compared to Plavix, namely for myocardial infarction, ischemic stroke, and established peripheral arterial disease, but not for acute coronary syndrome. The applicant was the German company YES Pharmaceutical Development Services GmbH ("YES Pharmaceutical"), acting for Switzerland's Cimex AG, part of the Schweizerhall Group (now trading under the name of Acino), which, based outside the EU, was prevented from filing an application itself. Two of the MAs have subsequently been transferred to Novartis's generic division Sandoz and the German generics company ratiopharm, respectively, which according to press releases are licensees of Cimex and distribute the product in Germany.

Sanofi-Aventis and BMS both objected to these MAs. Under German administrative law, this stayed the effect of the MAs and made it impossible to use them, *i.e.*, to place the products on the market. YES Pharmaceutical first requested the BfArM to set aside the staying effect, but in vain. It then applied to the competent court, the Cologne Administrative Court (Verwaltungsgericht Köln, the "Court"), in preliminary administrative proceedings.

THE COURT'S DECISION: LOOPHOLES IN EUROPEAN DATA PROTECTION?

The Court, in its decisions dated July 25, 2008 (Case Nos. 7 L 988/08 and others), granted the request for relief and set aside the staying effect. It held that the objections of Sanofi-Aventis and BMS were unfounded. It left open the question of whether the MAs had been granted legally. The Court found that no rights of Sanofi-Aventis and BMS had been violated. Therefore, they could not challenge the MAs, even if they were legally flawed.

The Court stated that YES Pharmaceutical had not filed a generic application, which requires only a bioequivalence study comparing the generic with the original product, and for the rest relies on the preclinical and clinical-trial data of the originator. Instead, it had filed a bibliographic application, in which the results of preclinical tests and clinical trials are replaced by appropriate scientific literature. The bibliographic application thus draws on data available in the public domain. This procedure is also known as the "well-established use" application under the European regulatory framework.

Under the European regulatory framework and its German equivalent, a bibliographic application is admissible if the applicant can demonstrate that the API of the medicinal product was in well-established medicinal use within the European Union for at least 10 years, with recognized efficacy and an acceptable level of safety. In that event, the preclinical and clinical-trial data normally required for an application may be replaced by appropriate scientific literature.

The Court did not discuss the first prerequisite at all, namely the identity of the API. The salt used by Clopidogrel YES differs from the salt used by Plavix (in order to circumvent the

patent protection). In a strict sense, clopidogrel besylate as the API of Clopidogrel YES so far has not been in medicinal use at all in the European Community. However, there exist precedents in which different salts used for oral formulations have been treated as the same API for purposes of a bibliographic application. This approach relies on the dissolution of the salt before resorption and disregards any differences in safety profiles that may result from different salts. Still, this issue should have been discussed by the Court.

Two points in the—brief—reasoning of the Court merit particular attention.

First, the Court held that the European Public Assessment Report ("EPAR") for Plavix, to which YES Pharmaceutical had referred in its application, did not belong to the protected data, as it was not part of the proprietary data filed by Sanofi-Aventis in the course of the application for marketing authorization. The Court erred on this point, taking a formalistic approach, instead of resorting to the object and purpose of the data-protection provision.

It is true that the EPAR is not filed by an applicant. According to the centralized procedure, it is drawn up by experts of the European Medicines Agency ("EMEA"). It is based on the application data and forms the basis for the opinion of the Committee for Medicinal Products for Human Use ("CMPH") of the EMEA, recommending (or not) the granting of an MA. The opinion of the CMPH in turn forms the basis for the decision of the European Commission on the application. The EPAR is continuously updated and could be called the scientific logbook of a granted MA. Initially, the EPAR under the European regulation was available from the EMEA on request, after the deletion of any commercially confidential information. Nowadays, the EPAR for any centralized MA can be retrieved from the EMEA web site, including the EPAR for Plavix. Accordingly, the EPAR is in the public domain.

However, it cannot be considered "scientific literature" for the purposes of a bibliographic application. It draws on, summarizes, and evaluates data of the applicant. If the data-protection period prevents applicants from drawing on such data, the same must be true for the EPAR summarizing and evaluating such data. It is of note that the equivalent expert report under the national German legislation is not published and thus not available in the public domain. Had Sanofi-Aventis, at the time, chosen to apply not for a centralized MA but for the respective national MAs, including a German one, YES Pharmaceutical would not have been in the position to submit the expert report.

As the Court did not hold that the reference to the EPAR could turn the application into a generic one, the Court did not have to review whether this reference was essential, *i.e.*, whether the further bibliographic data would have been sufficient in its own right to grant the MA. This, however, is of crucial importance. If the MA could not have been granted without the reference to the EPAR for Plavix, the application in substance relied on data of the originator, which turns the application at least partially into a generic one. A generic application, however, has been admissible only since July 15, 2008, which would have significantly delayed the granting of the MA.

The second point of interest is the Court's view on the 10-year period of well-established medicinal use required for a bibliographic application. The Court rejected the argument put forward by Sanofi-Aventis and BMS that an application might be accepted and evaluated only after the expiration of these 10 years, comparable to the data-protection period, which has to expire before the authority accepts an application for a generic formulation. The Court held that it is sufficient for the 10 years to have passed in substance, which means that the bibliographic application can be filed beforehand. It identified the beginning of this period as the granting of the MA for Plavix and Iscover—July 15, 1998, at the latest. Accordingly, the Court held that the 10-year period expired on July 15, 2008, which made it possible to use the MA for Clopidogrel YES beginning with this date.

Two comments on this view are in place. First, the date of the granting of an MA rarely coincides with the first placement of the product on the market. Not only does it take a couple of days for the decision to be served on the applicant, but although companies aim to reduce the time to market from the granting of a marketing authorization, there is usually a time lag for practical reasons; for example, the drafts for the packaging materials have to be verified against the final MA, and the MA number has to be included in all packaging materials. Therefore, the Court should have resorted

to the actual date of distribution in Europe. Second, and more important, the legal question is not as clear as the Court makes it out to be. The European legislation requires the applicant to demonstrate that the API has been in well-established use in the EU for 10 years. Also, the provisions of both the generic application procedure and the bibliographic application procedure are similarly worded. However, before the decision, it had been generally accepted that the generic applications are admissible only after the expiration of the data-protection period. It is therefore not clear why a distinction should be made between these procedures. This rather points to a bibliographic application equally being admissible only after the expiration of such period. The decision of the administrative court of appeals turned on this point.

UPDATE: Sanofi-Aventis and BMS appealed the decisions. The Administrative Court of Appeals (Oberverwaltungsgericht Münster, also known as Oberverwaltungsgericht Nordrhein-Westfalen, the "Court of Appeals") confirmed the decisions of the Court on September 26, 2008 (Case Nos. 13 B 1169/08 and others).

With regard to the data protection in relation to bibliographic applications, the Court of Appeals acknowledged that such protection awards a right to the originator and is not limited to a procedural provision. However, it relied on a European amendment from 1999. It therefore not only failed to notice that the earliest proposal for data protection of the European Commission dates back to 1984, it also missed out on Article 39 TRIPS, which has provided for data protection on a global scale since 1994.

From this wrong starting point, the Court of Appeals held that bibliographic applications are admissible even before the expiration of the 10-year protection period. It first drew on the wording of the German legislation. By contrast, the wording of the European legislation, which takes precedence, clearly points to the opposite. It also referred to the introduction of the "8+2+1" formula for generic applications in 2004 and held that a similar structure could have been introduced for bibliographic applications. However, bibliographic applications, according to the European Court of Justice, are supposed to remain an exception, which is why it was not deemed necessary in 2004 to amend the existing protection period for bibliographic applications. In addition, the Court of Appeals queried the additional period that would be awarded due to the time required for the BfArM to review the application. Because such additional period depends in no small measure on the workload of the BfArM and therefore cannot be exactly determined, the court held that the originator is not entitled to an unspecified protection for this additional period. Here, the court puts the cart before the horse. It may very well be that the period is difficult to determine. However, such factual questions cannot lead to a denial of a legal right in the first place.

With regard to the data protection in relation to generic applications, the Court of Appeals first acknowledged that a reference in the application of YES Pharmaceutical to the Summary Basis of Approval of the FDA for Plavix might trigger data protection against generic applications (the decision does not discuss the reference to the EPAR, for which the same would apply). However, it again held that the old 10-year protection period did not prevent an earlier filing and review of the application. It considered the wording of the provision inconclusive, which is again surprising, since both the German and the European legislation under the old rule require the applicant to demonstrate that the data-protection period has expired. This is obviously impossible before such expiration. The Court of Appeals did not find any conclusive evidence in the drafting history, either. This is not very surprising, given that the court took the wrong starting point. Had it referred to the initial proposal of the European Commission from 1984, it would have been clear that an application is admissible only after the expiration of the protection period. While Sanofi-Aventis and BMS referred to subsequent clarifications of the European Commission, the court dismissed them as nonbinding, which casts a shadow on European integration: obviously, clarifications of the European Commission are not binding, but they reflect the object and purpose of European legislation, and they should not be dismissed lightly. Last but not least, the Court of Appeals considered the introduction of the "8+2+1" formula inconclusive as to the interpretation of the previous rule. This is all the more surprising, as the court missed the major flaw in its argument in this respect: If, under the old rule, applications are admissible before expiration of the protection period, the old rule would have allowed for filing of generic applications the moment the original MA had been granted. This obviously was never the case.

UPDATE: OUTLOOK

While Sanofi-Aventis and BMS may still file for main proceedings, this would be futile. The clopidogrel products may now be marketed by the generic competition. It would, of course, be highly relevant for the industry to have the decision repealed, in particular regarding the data-protection period relating to generic applications, if necessary, by the Federal Administrative Court or the European Court of Justice. However, main proceedings would most likely last beyond 2015/2017, at which time the old rule on data protection will have been replaced by the "8+2+1" formula anyhow.

Originators may instead point out significant liability risks to the German authority. If, in contrast to the view of the two courts in preliminary proceedings, it violates European legislation on data protection if applications for bibliographic or generic applications are accepted and reviewed by the authority before the expiration of the protection period, this might result in a liability for according losses of the originators, which can be significant.

LESSONS LEARNED

Originators in any case should take these decisions as a warning.

First, careful attention should be paid to the strategy of publishing regulatory data. In particular, it must be borne in mind that the bibliographic application procedure, from its wording, requires only that the API be in well-established use for a period of at least 10 years. If the original drug relates to a new indication of an API that has been in well-established use for quite some time already, a bibliographic application could be filed shortly after the original MA is granted, if the originator publishes all regulatory data on this new indication shortly after (or even before) the granting of the MA for the original product. While it is accepted that the first, *i.e.*, original, application for a new indication may not be filed under the bibliographic application procedure, this is not necessarily true for the follow-on product. The wording of the European legislation allows for a wide interpretation. In an extreme example, if the API has already been in well-established use for 10 years and the originator's MA covers a new indication, a bibliographic application could be filed immediately afterwards, if all necessary data have been published (assuming that no patent or supplementary protection certificate still protects the original product).

Therefore, even if originators will not be able to withhold publication of preclinical and clinical data entirely, the scope of publications, and their subject matter, should be carefully evaluated. This process should start right at the beginning of product development, with regard to the publication of preclinical data, and should continue through clinical development. It is therefore of paramount importance that the regulatory department and the research and development department closely interact on this issue, as the regulatory department will have to monitor which data might open the doors to the bibliographic application of a competitor. This issue also has to be kept in mind by the marketing department when considering dissemination of medical information for the purposes of promoting the medicinal product.

UPDATE: With regard to generic competition, business plans of originators should be reviewed to identify the extent to which they include an additional protection period resulting from the processing of a generic application after the expiration of the old 10-year protection period (which, in Germany, on average amounts to 10 to 12 months, *i.e.*, almost an additional year of protection). Originators now need to prepare for generic competition earlier than expected.

In addition, originators may want to request their industry associations to take up this issue in the context of a pending amendment to the German Drug Act, requesting clarification in line with European legislation.

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