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The US Food and Drug Administration lifts the veil on biosimilar product labelling

On 31 March 2016, the US Food and Drug Administration (hereinafter, FDA) finally lifted the veil on its approach to biosimilar product labelling. Specifically, the FDA issued its '*Draft Guidance on Labeling for Biosimilar Products*' (hereinafter, the Draft Guidance), published in the Federal Register on 4 April 2016, thereby making it available for public comment. The publication of the Draft Guidance ends a period of uncertainty for interested parties in the pharmaceuticals industry and, in particular, biosimilar applicants and originators of the biologics, as well as patients and health care practitioners.

A biosimilar, or follow-on biologic, is a biologic medical product, which is an almost identical version of an original product that is manufactured by a different company. Section 351(i) of the Public Health Service Act (42 U.S.C. 262(k)) defines *biosimilarity* as when '*the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components*' and when '*there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product*'. The recently published Draft Guidance includes recommendations by the FDA and, as such, will not be binding for the industry. As the FDA puts it, an FDA Guidance merely describes the current thinking of the FDA on a certain topic and only provides suggestions or recommendations (unless otherwise specified by reference to regulatory or statutory requirements). In this case, the recommendations are intended to assist applicants in developing draft labelling for submission in applications for proposed biosimilar products under Section 351(k) of the Public Health Service Act. Further to that, FDA regulations shed some light on the general significance and purpose of the labelling content: the information included aims primarily at enabling health care practitioners to '*use the drug safely and for the purposes for which it is intended*' and thereby significantly reducing the likelihood of medication errors.

Key to understanding the Draft Guidance is the FDA's approach on biosimilars and their relation to the reference product (*i.e.*, the original product). According to the FDA, a demonstration of biosimilarity means, *inter alia*, that the FDA has determined that there are no clinically meaningful differences between the proposed product and the reference product as regards safety, purity, and potency. It follows that previous FDA findings on the safety and effectiveness of the reference product (as reflected in its FDA-approved prescribing information) may be relied upon as regards the proposed product. Therefore, it is only logical

that the FDA now recommends that, in the labelling of the biosimilar product, applicants incorporate relevant data and information from the reference product labelling, with appropriate product-specific modifications. This also explains why the FDA expressly takes the position that biosimilar labelling should not include a description of data from the clinical study of the proposed biosimilar product. However, such information may be included if the data from a clinical study does provide additional information regarding the safe and effective use by a health care practitioner. Additionally, the FDA recommends that a biosimilar product labelling should – based on the demonstration of biosimilarity – provide a description of the clinical data that supported safety and efficacy of the reference product in the FDA-approved product labelling for the original product. The Draft Guidance lays out in detail and with sample texts the recommended elements of the biosimilar product labelling. The point of departure remains the reference product and the reference product labelling, updated through appropriate product-specific modifications. The inclusion of such data is supposed to be limited to the relevant parts, in case the manufacturer of the biosimilar product only seeks approval for certain conditions of use, as compared to the reference product. Following on this path, the FDA expects that those sections of the biosimilar label that are based on the reference product label will be similar.

However, the labelling may not necessarily be identical, particularly because manufacturers are legally required to keep the labelling updated in case of new information. Further existing differences of the biosimilar product, as compared to the reference product, may also be included on the product labelling. This includes differences regarding administration, preparation, storage, or safety information that do not affect the overall demonstration of biosimilarity. In addition to this general approach, the FDA also includes recommendations on several other aspects of labelling. Firstly, there are very specific recommendation on product identification (*i.e.,* when to use which product name). Again, the FDA's approach demonstrates a clear logic, advocating for the use of the biosimilar name in the labelling text that refers to, or is specific to, the biosimilar product and to use the name of the reference product when the text refers to studies or data related to the reference product. Depending on the references, the use of both names may be appropriate in individual sections. Secondly, the FDA includes a list of recommendations relating to specific sections of the biosimilar labelling. This includes a general recommendation to include a so-called '*biosimilarity statement*' in the labelling and provides the suggested language and placement of said statement. Thirdly, information regarding the '*Indications and Dosage*' section should be specific to the biosimilar product. Finally, the Draft Guidance contains recommendations on the potential need to revise existing biosimilar product labelling and technical details on how to submit the labelling for approval.

Preliminary assessments of the Draft Guidance see it as an important signal for biosimilar manufacturers because the Draft Guidance takes up various aspects of generic product labelling. Additionally, it does not embrace – as laid out above – the argumentation put forward by brand-name manufacturers that clinical trial data, used to prove a certain drug is in fact a biosimilar, should be included on labels. This approach and the recommendation regarding the '*biosimilarity statement*' have been, not surprisingly, lauded by the *Generic Pharmaceutical Association* (GPhA) and its *Biosimilars Council.* According to a statement by the *Biosimilars Council*, the Draft Guidance '*is a positive step to assure patients, providers and others that these products are just as safe and effective as their brand biologic counterparts*'. Arguably, the labelling is particularly important because it is the primary source for doctors to determine which product, the original or the biosimilar, to prescribe.

The Draft Guidance deals with a significant question surrounding the increasingly important issue of biosimilars. This is, naturally, not limited to the US, and is instead an issue that resonates around the world. Issues relating to generics and biosimilars remain strongly debated with respect to a wide range of legal questions, including intellectual property rights, competition law aspects and international trade rules. A balance must be achieved to protect

the competitive position of the manufacturers of original products, while at the same time enabling the development of biosimilars and thereby improving the public's access to competitive products. During the last several years, the inclusion of dedicated rules on generics and biosimilars in preferential trade agreements has stirred significant debate (see *Trade Perspectives,* Issue No. 10 of 15 May 2015). Most recently, negotiations of the Trans-Pacific Partnership Agreement took up various issues relevant to biosimilars. Many aspects, however, like labelling, remain domestically regulated. Considering the high costs of different packaging and labelling, the issue of labelling looks poised to be raised in future trade negotiations and should aim at progressive international harmonisation.

Ending the aforementioned period of uncertainty is a crucial step for all involved stakeholders and should also lead to an important increase in transparency for health care practitioners and patients. The publication of the Draft Guidance in the US Federal Register on 4 April 2016 marks the beginning of a comment period of 60 days. A representative of the Office of New Drugs at the FDA expressly noted that the Draft Guidance had been issued in order to provide an opportunity for public comment – in particular by the various stakeholder communities, namely industry, health care providers and patients. While US law allows comments on any guidance at any time, comments on the Draft Guidance on biosimilar labelling should be submitted either electronically or in writing by 3 June 2016, to ensure that the FDA will consider the comments before it begins its work on the final version of the future guidance. All interested stakeholders should, therefore, carefully analyse the Draft Guidance well before 3 June 2016 and make use of the opportunity to comment on this proposal. A final version of the proposal can be expected to be unveiled in the fall of 2016.

The WTO issues the Panel Report in *European Union – Anti-Dumping Measures on Biodiesel from Argentina*

On 29 March 2016, the WTO circulated the Panel Report in *European Union – Anti-Dumping Measures on Biodiesel from Argentina*. The dispute concerns anti-dumping measures imposed by the EU against imports of biodiesel from, *inter alia*, Argentina. The panel's findings were mixed, but the Report is effectively a victory for Argentina. The panel's findings may also signal a similar outcome in the related dispute filed by Indonesia against the EU.

In August 2012, following a complaint lodged by the European Biodiesel Board, the EU Commission launched anti-dumping proceedings against '*fatty-acid mono-alkyl esters and/or paraffinic gasoils obtained from synthesis and/or hydro-treatment, of non-fossil origin, in pure form or as included in a blend*' (*i.e.*, biodiesel) from Argentina and Indonesia. The EU eventually adopted definitive anti-dumping duties on Argentina and Indonesia in November 2013, through *Council Implementing Regulation (EU) No. 1194/2013 of 19 November 2013 imposing a definitive anti-dumping duty and collecting definitively the provisional duty imposed on imports of biodiesel originating in Argentina and Indonesia*. In December 2013, Argentina requested WTO consultations with the EU regarding: (1) rules on the adjustment or establishment of costs associated with the production and sale of products under investigation in the determination of dumping margins contained in the EU's Basic Anti-Dumping Regulation (*i.e.*, *Council Regulation (EC) No. 1225/2009 of 30 November 2009 on protection against dumped imports from countries not members of the European Community*); and (2) the actual anti-dumping measures imposed on biodiesel originating in, *inter alia*, Argentina, and their underlying investigation (see *Trade Perspectives*, Issue No. 2 of 24 January 2014). That is to say, Argentina made '*as such*' claims against the EU's Basic Anti-Dumping Regulation and '*as applied*' claims against the anti-dumping investigation and the measures imposed. In particular, Argentina claimed that the EU's measures are inconsistent with the WTO Agreement on Implementation of Article VI of the General Agreement on Tariffs and Trade 1994 (commonly referred to as the WTO Anti-Dumping

Agreement, and hereinafter AD Agreement) and the General Agreement on Tariffs and Trade 1994 (hereinafter, GATT).

Argentina's '*as such*' challenge of the EU's Basic Anti-Dumping Regulation claimed that the second subparagraph of Article 2(5) of said regulation is inconsistent with Article 2.2.1.1 of the AD Agreement. The second subparagraph of Article 2(5) of the EU's Basic Anti-Dumping Regulation provides that "*[i]f costs associated with the production and sale of the product under investigation are not reasonably reflected in the records of the party concerned, they shall be adjusted or established on the basis of the costs of other producers or exporters in the same country or, where such information is not available or cannot be used, on any other reasonable basis, including information from other representative markets*". Argentina argued that, therefore, such language requires EU authorities to conclude that the records do not reasonably reflect the costs associated with the production and sale of the product under consideration, where they find that the costs of the inputs reflect prices that are "*abnormally or artificially low*" in comparison to other markets. However, the panel rejected Argentina's argument, instead agreeing with the EU, in particular, that the provision is clear and prescribes what EU authorities must do after having determined that a producer or exporter's records do not reasonably reflect the costs of production, pursuant to the first subparagraph of Article 2(5) of the EU's Basic Anti-Dumping Regulation.

Argentina's '*as applied*' challenges of the EU's anti-dumping determinations also dealt with, *inter alia*, Article 2.2.1.1 of the AD Agreement, where Argentina claimed that the EU acted inconsistently with said agreement, as well as the GATT, when it failed to calculate the cost of production of biodiesel on the basis of the records kept by the producers or exporters under investigation. During the EU's investigation, its authorities concluded that domestic prices of soybeans in Argentina were distorted due to the difference in the export taxes imposed by Argentina on soybeans and those imposed on biodiesel, and thus EU authorities replaced the costs reported in the records of Argentinean producers and exporters for soybeans with reference prices published by Argentina's Ministry of Agriculture. The panel sided with Argentina, finding that the conclusion of the EU authorities did not constitute a legally sufficient basis under the AD Agreement to replace reported costs with reference prices. Notably, the panel rejected the EU's argument that "*the notion of dumping is not limited to situations that arise out of producer/exporters' '*voluntary*' pricing behaviour, but rather, it also covers situations that are created by the action of the governments*". In this regard, the EU was claiming that export taxes imposed by Argentina amounted to currency manipulation. However, the panel stated that the second Ad Note to Article VI:2 and Article VI:3 of the GATT is limited to "*multiple currency practices*" and indicates that it should be treated as an exceptional and specialised provision. As such, the panel saw no reason to find that the concept of '*dumping*' covers distortion arising from government action. The use of reference prices by EU authorities, instead of the prevailing costs in Argentina (*i.e.*, the country of origin) also led the panel to find that the EU had acted inconsistently with Article 2.2 of the AD Agreement. Lastly, the panel also upheld Argentina's claim that the EU acted inconsistently with Article 9.3 of the AD Agreement and Article VI:2 of the GATT 1994 by imposing anti-dumping duties in excess of the margin of dumping that should have been established under Article 2 of the AD Agreement. The panel found that EU authorities acted inconsistently with their obligations in their establishment of the dumping margin, due to the use of surrogate input prices in the establishment of each investigated Argentinean producer's normal value.

Following the issuance of the Panel Report by the WTO, the European Biodiesel Board published a press release reiterating its position and the effects of Argentina's export tax mechanism, and called upon the EU to file an appeal. Pursuant to the procedural rules of the WTO Dispute Settlement Body, Argentina and the EU have up to 60 days to notify the Dispute Settlement Body of their decision to appeal. As noted above, the Council Implementing Regulation imposing the definitive anti-dumping duties against Argentina also

imposed anti-dumping duties on Indonesia. A similar dispute, initiated by Indonesia against the EU, is pending, with its panel having been composed on 4 November 2015. In 2012, Argentina and Indonesia accounted for 90% of the biodiesel imported into the EU, but reports indicate that since the measures were implemented, Argentina has lost USD 1.6 billion in sales annually. It appears likely that appeals are forthcoming in the dispute at hand, as well as in Indonesia's dispute against the EU, regardless of the outcome. Interested parties should continue to monitor the disputes, as their final outcomes are sure to have a significant impact on trade.

Glyphosate renewal process: MEPs urge the EU Commission not to renew authorisation

On 22 March 2016, the EU Parliament's Committee on the Environment, Public Health and Food Safety (hereinafter, ENVI Committee) adopted with 38 votes to 6 (with 18 abstentions) a motion for a non-binding resolution calling on the EU Commission not to renew the authorisation of the active ingredient glyphosate, as long as serious concerns remain about its eventual carcinogenicity and endocrine disruptive properties. Instead, MEPs demand the EU executive to commission an independent review and to disclose all the scientific evidence that the European Food Safety Authority (hereinafter, EFSA) used to assess glyphosate.

Glyphosate is an active ingredient patented in the early 1970s and widely used in herbicides. Glyphosate-containing herbicides were introduced to the consumer market in 1974 as broad-spectrum herbicides and quickly became best sellers (in particular *Monsanto*'s RoundUp). Since the patent expired in 2000, glyphosate-containing herbicides have been marketed by various companies and several hundred plant protection products containing glyphosate are currently registered in Europe for use on crops. Glyphosate-containing herbicides are applied to the leaves of plants to eradicate both broadleaf plants and grasses. For example, glyphosate may be used to kill weeds in a field before a crop is sown, before it germinates, or after it has been harvested. Glyphosate-containing products are also sprayed onto crops before they are harvested to make them dry out, or to make them easier to harvest (this practice is called desiccation). Glyphosate is used as a desiccant on cereals, oilseed rape, maize and sunflowers. Other approved uses for glyphosate-based herbicides in the EU include weed control in vineyards, olive groves and fruit orchards. Glyphosate is also used on grass pastures, in forestry, in urban and garden applications and for clearing railway lines. It should be noted that there are glyphosate-tolerant GM crops, which permits its use (where authorised) on wide areas of land.

The approval of the active ingredient glyphosate in the EU expires on 30 June 2016. It originally ran until 31 December 2015, but was extended by six months in order to have enough time for a comprehensive and thorough re-evaluation of the active substance. A re-approval of glyphosate would likely be for 15 years. The approval of active substances can always be checked as soon as there are indications that an active substance is no longer safe. EU Member States' experts in the EU Commission's Standing Committee on Plants, Animals, Food and Feed (Phytopharmaceuticals Section, hereinafter SCoPAHF) are currently debating a draft *Commission Implementing Regulation renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No. 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Implementing Regulation (EU) No. 540/2011*. The examination of an active ingredient in the EU is carried out jointly by all EU Member States, EFSA and the EU Commission. The review of an application is first performed by an EU Rapporteur Member State, which produces a comprehensive evaluation report. In the case of the re-registration of glyphosate, in December 2013, the German Federal Institute for Risk Assessment (BfR) proposed to classify glyphosate as '*non-carcinogenic*'. Other EU Member States and EFSA commented on this evaluation report as part of the peer review. The peer

review concluded in November 2015 that glyphosate is "*probably not genotoxic*" (*i.e.*, DNA damaging), nor does it represent a carcinogenic threat to humans and, therefore, recommended that glyphosate not be classified as carcinogenic. In particular, the experts from the EU Member States, with the exception of Sweden, agreed that neither the epidemiological data (*i.e.*, those with respect to humans), nor the evidence from animal studies, showed a causal association between glyphosate exposure and cancer in humans. On request of the EU Commission, EFSA also reviewed a report of March 2015 of the International Agency for Research on Cancer (IARC), an agency of the World Health Organisation, which classified glyphosate as "*probably carcinogenic to humans*" and created some controversy. It can be observed that both EFSA and IARC are blamed for disregarding studies and being opaque as to the origin of scientific findings included in their respective reports.

From a legal point of view, two points relating to the scope of the assessment are particularly relevant. First, under current EU legislation (in particular Regulation (EC) No. 1107/2009), the assessment of, or re-assessment of, active ingredients takes into account only the active ingredient, in this case glyphosate. However, the IARC report looked at both glyphosate, the active ingredient *per se*, and glyphosate-containing formulations. This is important, as studies suggest that certain glyphosate-containing mixtures could be genotoxic, while others that consider only the active ingredient glyphosate, do not show this effect. EFSA looked at glyphosate alone and concluded that glyphosate is unlikely to cause cancer while IARC assessed its use in combination with other chemicals in glyphosate-containing formulations, and deemed the chemical to be probably carcinogenic in humans. It is, therefore, possible that the observed genotoxic effect in some glyphosate-based mixtures does not relate to glyphosate, but to other ingredients. On that basis, EFSA recommends in its assessment that the competent authorities of EU Member States take into account in greater detail the eventual toxicity of each plant protection product, and in particular its genotoxic potential. In the EU, Member States are responsible for the evaluation of plant protection products placed on the market in their respective territories. The EU Commission has already proposed, as a condition in the draft regulation on glyphosate, that EU Member States must ensure that plant protection products containing glyphosate do not contain the co-formulant *POE-tallow amine*, a surfactant that enhances the activity of herbicides. Second, there is another important difference in the risk assessment performed by the IARC and EFSA. The IARC considered in its assessment the extent of possible damage (hazard potential), while EFSA goes beyond and assesses how likely it is that this damage may occur (*i.e.*, what the risk is). The latter is, for example, dependent on the extent to which one is exposed to a potential '*hazard*'. Accordingly, '*hazard*' includes anything that can potentially cause damage, while the '*risk*' assessment aims at determining the actual '*risk*'.

The motion for a non-binding resolution by the ENVI Committee calls on the EU Commission to table a new draft. MEPs want the EU Commission and EFSA to "*immediately disclose all the scientific evidence that has been a basis for the positive classification of glyphosate and the proposed re-authorisation, given the overriding public interest in disclosure*".

From a scientific point of view, what appears to be true is that glyphosate is not completely metabolised by the human body. The question is to what extend its presence is harmful. A study analysing the level of glyphosate contamination in urine samples by the German Heinrich Böll Foundation called on the German Government to introduce a *moratorium* on the use of glyphosate until further research has been carried out. The researchers reported that some 75% of their target group displayed levels of glyphosate contamination that were five times higher than the legal limit of drinking water. It has been said that the German Government should be concerned enough by this report to initiate "*further and more profound and precise studies*" on the issue of glyphosate contamination and its health consequences. The Böll Foundation calls for further and sounder results on this issue, specifically concerning contamination of ground and drinking water.

Commercially, glyphosate-containing products are important worldwide. Reportedly, in the UK, the top ranked herbicides in arable crop production and in commercial fruit orchards contain glyphosate. In Denmark, 35% of all pesticides used in agricultural production contain glyphosate. In Germany, it has been estimated that glyphosate is used on 4.3 million hectares (39%) of agricultural land each year, with nearly two thirds applied to just three crops (oilseed rape, winter wheat and winter barley). It is estimated that 50% to 60% of sunflower crops in France, Romania and Hungary are treated before harvest with glyphosate-containing products. Worldwide, around 825,000 tonnes of glyphosate products were reportedly used in 2014, and sales were worth around USD 6.5 billion in 2010, more than the value of all other herbicides combined. And its use appears to be increasing, in large part because of the production of GM crops.

On 5 April 2016, the Committee of Professional Agricultural Organisations and the General Confederation of Agricultural Cooperatives (jointly referred to as Copa-Cogeca) urged the EU Commission and MEPs to keep glyphosate on the EU market, saying that "*[a]fter EFSA confirmed its safety, we expect the EU Commission to extend the authorization in June. Glyphosate is widely used in herbicides in all EU Member States and a key part of farmers tool box due to its availability and cost-effective price. Without this, cereal crops as well as vineyards, fruit and olive production across Europe would be seriously threatened. This would be unacceptable given the current agricultural crisis and the need to meet growing world food demand. Not approving this active substance would consequently benefit non-EU countries that export to the EU, as it would still be part of farmers tool box in these countries*".

The motion for a non-binding resolution will most likely be put to a vote at the 11-14 April 2016 plenary session of the EU Parliament in Strasbourg. The EU needs a decision over the coming weeks to prevent a legal vacuum when the existing approval of glyphosate expires at the end of June. The national experts sitting in the SCoPAF will presumably vote to adopt or reject the EU Commission's proposal by qualified majority in May 2016. If there is no such majority, it will be up to the EU Commission to decide. According to press reports, EU sources said they no longer expected a decision after the French, Swedish and Dutch Governments indicated that they would oppose extending approval, while EU diplomats said Germany planned to abstain.

The outcome of the glyphosate re-assessment in the EU is uncertain. The current debates on the safety of glyphosate appear to be carried out in a very emotional way. Perhaps the scientific findings and their legal consequences must be communicated in a better way. Risk communication is a part of risk analysis. *Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety* defines '*risk communication*' as "*the interactive exchange of information and opinions throughout the risk analysis process as regards hazards and risks, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, feed and food businesses, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions*". This must be the objective of the ongoing re-assessment of glyphosate.

Recently Adopted EU Legislation

Food and Agricultural Law

- *Commission Implementing Regulation (EU) 2016/535 of 5 April 2016 amending Annex II to Regulation (EU) No. 206/2010 as regards the entry of Singapore in*

the list of third countries, territories or parts thereof from which the introduction into the Union of fresh meat is authorised

- *Commission Regulation (EU) 2016/479 of 1 April 2016 amending Annex II to Regulation (EC) No. 1333/2008 of the European Parliament and of the Council as regards the use of steviol glycosides (E 960) as a sweetener in certain energy-reduced or with no added sugars beverages*

- *Commission Implementing Regulation (EU) 2016/459 of 18 March 2016 amending Regulation (EC) No. 1235/2008 laying down detailed rules for implementation of Council Regulation (EC) No. 834/2007 as regards the arrangements for imports of organic products from third countries (Text with EEA relevance)*

- *Regulation (EU) 2016/429 of the European Parliament and of the Council of 9 March 2016 on transmissible animal diseases and amending and repealing certain acts in the area of animal health ('Animal Health Law')*

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