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REACH AND ITS IMPACT ON MEDICINES AND MEDICAL DEVICES

In June 2007, the European Union's Regulation (EC) No. 1907/2006 on the Registration, Evaluation, Authorization and Restriction of Chemicals (the so-called "REACH Regulation")[1] entered into force. The REACH Regulation imposes sweeping requirements on all producers using substances in their goods and manufacturing processes.

The Regulation contains broad exemptions for pharmaceutical and medical device companies, but there remain important regulatory obligations. This memorandum summarizes the likely impact of the EU REACH Regulation on medicinal products and medical devices.

1. Medicinal Products

The REACH Regulation has a different impact on (i) medicinal products in finished state for the final user, (ii) medicinal products in bulk, (iii) active substances and excipients that are intended to be used in medicinal products (without any chemical transformation), (iv) intermediates that are used in the manufacture of active substances and excipients of medicinal products, and (v) investigational products used in clinical trials.

a. Medicinal Products in Finished State

- All substances contained in packaged medicinal products intended for final users are exempted from most of the REACH requirements, including registration, downstream user requirements, evaluation, information through the supply chain, and authorization. This is for the following two reasons:

  First, Article 2(5) of the Regulation exempts from registration, downstream user requirements, evaluation and authorization substances "used in" medicinal products for human or veterinary use within the scope of Regulation 726/2004, Directive 2001/82 and Directive 2001/83.

  Second, Article 2(6) of the Regulation exempts from the information through the supply chain requirements medicinal products for human or veterinary use within the scope of Regulation 726/2004, Directive 2001/82 and Directive 2001/83 if they are "in the finished state, intended for the final user." Substances contained in packaged medicinal products intended for final users are likely to be "in the finished state, intended for the final user."

[1] A copy of the Regulation is available at:

(http://eur-lex.europa.eu/LexUriServ/site/en/oj/2007/l_136/l_13620070529en00030280.pdf).

- However, any substance contained in medicinal products may be subject to the marketing and use restrictions of Title VIII and Annex XVII to the Regulation unless the specific entry for each restricted substance of Annex XVII specifies otherwise. This is because the Regulation does not contain any explicit exemption from its restriction provisions for substances used in medicinal products.

- Substances contained in medicinal products in finished state may also be subject to chemical classification reporting requirements. However, this is legally unclear, and the requirements may also change with the adoption of the future Regulation on the Global Harmonized System on the Classification and Labeling of Substances and Mixtures.

b. Medicinal Products in Bulk

- Substances contained in medicinal products (in their pharmaceutical form) but in bulk (*e.g.*, pills in bulk that are not yet placed in the final packaging) are also exempted from the REACH requirements of registration, downstream users, evaluation, and authorization. This is because medicinal products in bulk are considered as medicinal products within the scope of Regulation 726/2004, Directive 2001/82 and Directive 2001/83.

- However, substances in medicinal products in bulk will normally be subject to the information through the supply chain requirements of the Regulation. This is because the medicinal products are not in "finished state, intended for the final user." Thus, for example, the supply of medicinal products in bulk may have to be accompanied by safety data sheets (if the thresholds are met).

- Furthermore, the substances may also be subject to the restrictions of Title VIII and Annex XVII to the Regulation unless the specific entry for each restricted substance specifies otherwise.

- The substances may also be subject to the Regulation's classification and labeling reporting requirements, but this is legally unclear.

c. Active Substances and Excipients Intended to Be Used in Medicinal Products (Without Chemical Transformation)

- The current position of the European Chemicals Agency ("ECHA") is that substances intended to be used as active substances or excipients of medicinal products (and that are not already contained in the medicinal products) are also exempted from the REACH requirements of registration, evaluation, downstream user requirements, and authorization.

- In particular, the ECHA Guidance on Registration of February 2008 is clear in that the exemption from registration (and arguably from the other requirements) applies to substances even before they are present in the medicinal product, provided they are intended to be used in medicinal products. The Guidance argues that in order to benefit from the exemption the main criterion is the intended medicinal use of the substance and not whether the substance is already contained in the medicinal product.

- The ECHA Guidance exempts both active substances and excipients. It follows, however, from the general principles that this exemption only applies when there is no chemical transformation of the substances in question. In case there is such transformation, the substance can still qualify as an intermediate, provided it is intended for that use.

- Under the ECHA's interpretation, where a substance is manufactured or imported for use in a medicinal product and for other non-exempted uses, only the volumes of the non-exempted uses will be subject to registration.

- While the ECHA provides no guidance on this, past practice under EC chemicals law suggests that where a manufacturer or importer intends to benefit from the exemption for substances intended to be used in medicinal products, he may be required to submit documentary evidence proving that the substance will be used for medicinal purposes.

- The ECHA's interpretation exempting substances intended to be used in medicinal products (and not already contained in medicinal products), however, is not obvious and may change in the future. For example, while the REACH Regulation exempts from registration substances "used in" medicinal products, it also exempts from registration "active substances manufactured or imported for use in biocidal products." The latter suggests that when the Regulation intends to exempt a substance on the basis of its intended use, it explicitly provides so (for example, by stating "for use in").

- Furthermore, past practice on the notification requirements under the Dangerous Substances Directive (Directive 67/548/EEC, as amended) also suggests that European chemical authorities have been ambivalent on whether substances intended to be used in medicinal products (but not already contained in the medicinal product) are exempted from the chemical rules. In particular, the Commission's guidance on the status of these substances under EC chemicals rules has changed in the past.

- In addition, both active substances and excipients intended to be used in medicinal products are normally subject to the information through the supply chain requirements (*e.g.*, provision of safety data sheets). The substances may also be subject to the marketing and use restrictions of Title VIII and Annex XVII unless the specific entry of Annex XVII provides otherwise.

  The substances are also likely to be subject to the chemical classification reporting requirements of the Regulation, but this is legally unclear.

d. Intermediates

- The REACH Regulation defines an "intermediate" as a "substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance." The definition thus implies an intention for a specific use. If that intention is not present at the time of manufacturing in the EU/EEA or importation into the EU/EEA, the substance is in principle subject to the full REACH requirements.

- Intermediates that are used in the manufacture of active substances and excipients for medicinal products, but that are not themselves contained in the final medicinal product, are not likely to be exempted from the requirements of registration, downstream users, evaluation, information through the supply chain, and restrictions. This is because Articles 2(5) and 2(6) exempt substances "used in" medicinal products or "in" medicinal products in the finished state, and intermediates are not contained in the medicinal products.

  This interpretation is also confirmed by past guidance of EU chemical authorities under the Dangerous Substances Directive.

- However, intermediates may benefit from low registration requirements and may be exempted from authorization if they meet the specific technical conditions of Articles 3(15), 17, and 18 of the Regulation.

- Processing aids used in the manufacture of medicinal products (*e.g.,* ingredients for growth media used in the manufacturing of biotechnology medicines) are not exempted from the REACH requirements.

- Intermediates and processing aids may be subject to the marketing and use restrictions of Title VIII and Annex XVII to the Regulation unless the specific entry of Annex XVII for the substance specifies otherwise.

  Intermediates and processing aids are also subject to the chemical classification reporting requirements of the Regulation.

e. Substances Used in Investigational Medicinal Products

- There is a risk that substances used in investigational medicinal products do not benefit from the exemption for substances "used in" medicinal products. This is because investigational products in principle do not fall within the scope of Regulation 726/2004, Directive 2001/82 and Directive 2001/83. This interpretation seems to be confirmed by Article 9(7) of the REACH Regulation, which explicitly provides a temporary exemption from registration for substances "used exclusively in the development of medicinal products for human or veterinary use."

  It is not certain, however, that the authorities will adopt this stricter approach.

- Substances used in investigational products may, when not exempted, benefit from the temporary registration exemption for product and process oriented research and development ("PPORD"). This exemption is conditional upon the submission of a notification to the ECHA, payment of a fee, and an affirmative decision of the Agency. The exemption is for five years and may be extended up to a maximum of ten additional years.

  However, for the purposes of authorization, the decision on whether to exempt the use of the substance in investigational products, as PPORD, must be adopted on a case-by-case basis when the substance is listed as "subject to authorization." Thus, substances in investigational products may not always be exempted from authorization.

- Substances contained in investigational medicinal products are also likely to be subject to marketing and use restrictions and the chemical classification reporting requirements of the Regulation.

2. Medical Devices

The REACH Regulation provides only very limited exemptions for substances used in medical devices.

First, the risks to human health resulting from the use of substances in medical devices must not be considered when deciding whether to grant an authorization for the use of substances that are subject to authorization.

Second, medical devices in the form of preparations are not subject to information through the supply chain requirements (*e.g.*, safety data sheets) if (i) the medical devices are in finished state and intended for the final user, (ii) the medical devices are invasive or used in direct physical contact with the human body, and (iii) other EC legislation requires the classification and labeling of substances that are contained in medical devices.

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The REACH Regulation is technical in nature and many of its provisions are open to different interpretations. It is important to monitor how the rules are being implemented in more detailed provisions and guidelines.

The information in this memorandum is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein.

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