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EUROPE – REVISION OF EU GENERAL PHARMACEUTICAL LEGISLATION: Environmental Obligations and Risks

The European Union ("EU") General Pharmaceutical Legislation is the cornerstone of the EU regulatory system for medicinal products. It consists of:

– Directive 2001/83 that regulates, on the one hand, the placing on the market, manufacturing, import, export, supply, distribution, control, use, and advertising of all medicinal products and, on the other hand, the decentralized/mutual recognition of marketing authorization procedures and pharmacovigilance for medicinal products to be authorized at the national level ("Directive").
– Regulation 726/2004 that regulates the centralized marketing authorization procedure and pharmacovigilance for medicinal products to be authorized at the EU level and establishes the European Medicines Agency ("EMA") ("Regulation").

On April 26, 2023, the European Commission published legislative proposals for an updated: (i) Directive on the Union code relating to medicinal products for human use ("Future Directive"); and (ii) Regulation setting out the centralized procedure and establishing the EMA ("Future Regulation"), which will replace the current Directive and the Regulation, respectively.

The manufacturing and use of medicinal products has significant impact on the environment. The objective of the proposals is to limit that impact and to make medicinal products more sustainable without affecting their appropriate therapeutic use.

This note explains the main changes relating to environment and environmental risks. Overall, the proposals set ambitious environmental objectives and significantly increase requirements and sanctions for environmental risk assessments in order to address not only environmental risks but also the risks/issues related to antimicrobial resistance ("AMR") and genetically modified organisms ("GMOs"). The proposals could trigger a domino effect and influence other regulators at an international level.

The legislative process will likely be completed in 2025 at the earliest (as new European elections will take place in 2024). The legislative process will provide stakeholders with opportunities to impact the proposed changes.

Current Environment-Related Obligations

- An environmental risk assessment ("ERA") is required for all applications for marketing authorisation ("MAA").
  - No ERA requirement for MAs granted before October 30, 2005 or through the lifecycle of the medicinal product.
  - The EMA/national competent authorities ("Authorities") may request additional information related to the ERA.
- Scope of ERA is limited to the use and/or disposal of the medicinal product.
- Appropriate labelling provisions.
- Environmental risk connected to GMOs must also be addressed in the ERA.
- Environmental impact is not a criterion for refusal of a MA.

Extended ERA Scope

- Extension of the ERA definition: An ERA is the evaluation of risks to the environment, or risks to the public health, posed by the release of the medicinal product in the environment from the use and disposal of the medicinal product and the identification of risk prevention, limitation and mitigation measures.
- Broader definition of "risks related to use of the medicinal product":
  - Quality, safety or efficacy risk;
  - Environmental risk; and
  - Risk of undesirable effects on public health due to the release of the medicinal product in the environment, including AMR.
- AMR risk due to the manufacturing, use and disposal is added for antimicrobial medicinal products.

Increased ERA Requirements

- The MAA must indicate if the medicinal product/ingredients/constituents are (i) hazardous chemical substances (EU CLP Regulation). *[(a) persistent, bioaccumulative and toxic (PBT); (b) very persistent and very bioaccumulative (vPvB); (c) persistent, mobile and toxic (PMT), very persistent and very mobile (vPvM)];* or (ii) endocrine active agents.
- Risk mitigation measures must be included in the MAA to avoid/limit emissions to air, water and soil of pollutants.
- ERA for products authorised before October 30, 2005: MAH of MA granted before October 2005 (for which an ERA is not required) will have to submit an ERA if their existing products are evaluated as potentially harmful medicinal products.
  - The EMA prioritises the assessment of medicinal products concerned based on the risk posed by the medicinal product or active substance.
  - Collaboration/joint studies among MAH of same active substances are encouraged to minimise unnecessary data duplication and use of animals.
- Generics/Biosimilars/Hybrids: the ERA for these products can rely on the studies/data of the reference medicinal product.
- Additional scientific guidelines to be adopted by the EMA in consultation with the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA), and the European Environmental Agency (EEA) as appropriate.

Pre-Authorisation

- MA Refusal: Authorities may refuse granting a MA if:
  - the ERA is incomplete or insufficiently substantiated; or
  - the risks identified in the ERA have not been sufficiently addressed.

- Condition in MA: MA may include conditions, including to conduct post-authorisation ERA studies with specific deadlines.
- Prescription status: Antimicrobials or medicinal products containing an active substance which is hazardous (for human health or the environment) under the relevant EU chemicals legislation, must be subject to a medical prescription. National authorities are empowered to set additional conditions on the prescription of antimicrobials.

Post-Authorisation

- ERA updates: The ERA must be updated if new available information changes the conclusions of the ERA (through environmental monitoring, eco-toxicity studies, new available ERAs or environmental exposure data).
- Imposed post-authorisation ERA studies: Authorities may request post-authorisation ERA studies if new concerns emerge regarding the authorised medicinal product or other medicinal products containing the same/related active substance.
- Revocation/suspension/variation of MA: Authorities may suspend, revoke or vary a MA if a serious risk to the environment/public health has been identified and not sufficiently addressed.
- Prohibition of supply/withdrawal: Authorities may prohibit the supply or request the withdrawal of medicinal products if a serious risk to the environment or the public health (via the environment) has been identified and not sufficiently addressed.

Awareness on Environmental Issues

- Public assessment reports: Public assessment reports ("PAR") and European public assessment reports ("EPAR") published by the Authorities after the MA is granted must include a summary of ERA studies and their results after deletion of commercially confidential information.
- ERA Register: A register will be established to publish all ERAs. Commercially confidential information will be protected.
- ERA monographs: Establishment of an active substance-based monograph system, a database for related environmental information and risk assessments. This monograph system should be available to applicants for use when conducting an ERA for a new MAA.

Antimicrobial Resistance

One of the most important environmental risks related to medicinal products is the development of AMR. The proposals address the issue by introducing (i) increased and stricter environmental obligations for antimicrobial medicinal products and (ii) increased incentives for the development of new antimicrobials.

Stricter Requirements to Address AMR

- Definition: "antimicrobial" means any medicinal product with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals and antifungals.
- Increased ERA requirements: AMR risk due to manufacturing (in or outside the EU), use, and disposal of the product must be included in the ERA. A MAA may be refused if the Authorities consider that the AMR risks in the ERA are incomplete/insufficiently substantiated. The Authorities may impose post-authorisation ERA studies for AMR to MAH.
- Medical Prescription: antimicrobials are subject to medical prescription to reduce their use. Member States may adopt additional conditions such as restricting the validity of medical prescription and limiting the quantities prescribed to the amount required for the treatment. Additional conditions may also include submitting certain antimicrobial medicinal products to special medical prescription or restricted prescription e.g. mandatory use of diagnostic tests before prescription.

- Stewardship plan: Applicants must develop a stewardship plan for AMR that includes information on risk mitigation measures, monitoring and reporting of resistance to the medicinal product.
- Package size must correspond to the usual posology and duration of treatment.
- Special information requirements: information to HCPs and patients for the proper use, storage, and disposal of unused and expired antimicrobials.
    - MAH must provide educational materials to HCPs.
    - The packaging of antimicrobials must include an "awareness card" with specific information on AMR and on the appropriate use and disposal of antimicrobials.

Increased Incentives for New Antimicrobials – (See our client alert on Regulatory Exclusivities, Incentives, and the Bolar Exemption)

- Transferable Data Exclusivity Voucher (1 year of data exclusivity for one centrally authorised medicinal product) for priority antimicrobials.

GMO Provisions

Clinical Trials

- Currently, the procedure for clinical trials with investigational medicinal products containing or consisting of GMOs ("GMO medicinal products") is complex, long, and costly. Applicants must comply with EU GMO Directives and may have to obtain the consent/approval of national competent authorities (multiple requests are often required and MS have transposed the EU GMO Directives differently).
- The proposals amend the EU Clinical Trials Regulation so that applications for clinical trials for investigational GMO medicinal products may be submitted with a single, centralised application through the EU portal (CTIS). Such clinical trials are exempted from the relevant requirements set out by the Directive 2001/18/EC on the deliberate release into the environment of GMOs.
- Applicants for clinical trials for GMO medicinal products must submit an ERA with their clinical trial application. The ERA must include GMO aspects as described in the Directive 2001/18 and the relevant EMA guidelines.
- The EMA's Committee for Medicinal Products for Human Use (CHMP) will assess the ERA and issue a scientific opinion. The CHMP may request additional information from the sponsor.

ERA Requirement for GMO Medicinal Products

- MAA for GMO medicinal products must include an ERA addressing risks related to GMO.
- Unauthorised GMO medicinal products may be placed on the market without an ERA in exceptional circumstances: (i) named/individual patient needs, (ii) public health emergencies (in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm); or (iii) compassionate use.
- However, in these exceptional cases, Member States must implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the GMO medicinal products into the environment.

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King & Spalding's regulatory Life Sciences lawyers can help you better understand the changes that may result from the Revision, and anticipate their impact on the development and, in the future, marketing of products in Europe.

Companies involved in the development of orphan and pediatric medicinal products, as well as antibiotics, should closely follow future discussions around revision of the legislative framework and, whenever needed, be involved in those discussions.

Companies also should anticipate evolution of the EU legal framework and its impacts on current development and investment.

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