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Client Alert

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EUROPE – REVISION OF EU GENERAL PHARMACEUTICAL LEGISLATION: Shortages and Critical Medicines

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 Regulation, respectively.

This note explains the new rules on shortages and critical medicines. Several new obligations and requirements are introduced by the proposals to ensure continuity of supply and prevent shortages. Some are in line with the current national obligations and requirements.

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. In parallel, stakeholders should not lose sight of other ongoing EU initiatives that may lead to the same results as the new rules on shortages and critical medicines.

Current Regime - Ongoing EU Initiatives

EU General Pharmaceutical Legislation

- The marketing authorisation holder ("MAH") must notify the relevant competent authority (i.e., EMA or national competent authorities (collectively the "Authorities")) of any action to suspend the marketing of a medicinal product, withdraw a medicinal product, request the withdrawal of an MA, or not to apply for the renewal of an MA and the reasons therefor.
- When a medicinal product ceases to be placed on the market (either temporarily or permanently), the MAH must notify the Authorities at least 2 months before the interruption, unless exceptionally justified, and the reasons therefor.

EU Regulation 2022/123 on a Reinforced EMA Role in Crisis Preparedness and Management for Medicinal Products and Medical Devices

- EMA is responsible for preparedness (i.e., to address the impact of public health emergencies on medicinal products/medical devices through monitoring, preventing, and reporting of shortages).
- Creation of the EU platform for shortages.
- Establishment of the EMA Medicine Shortages Steering Group (MSSG), which is comprised by the Commission, EMA, and Member States representatives, and is responsible for: (i) the evaluation of information and recommendations on actions in relation to public health emergencies; and (ii) the establishment of the lists of critical medicinal products.
- Establishment of the Medicine Shortages Single Point of Contact (SPOC) Working Party, which is comprised by the national competent authorities' representatives who are the single national contact points for shortages.
- The MAH must provide information on critical medicinal products and relevant updates under specific deadlines. Failures and delays must be justified.

Public Information on Medicine Shortages

- EMA publishes information on shortages that affect or are likely to affect more than one of the Member States.
- EMA publishes information on critical shortages monitored by the SPOC Working Party at the EU level.
- Member States publish national shortages of medicines in national registers.

Health Emergency Preparedness and Response Authority (HERA)

- HERA was launched in 2021 as the EU Commission's Directorate-General responsible for preventing, detecting, and rapidly responding to health emergencies through intelligence gathering and building of necessary response capacities.
- Its role is to ensure the development, production, and distribution of medicines, vaccines, and other medical countermeasures in case of an emergency.

Proposals – Summary

- The Proposals supplement and develop the roles of the Authorities as set out in Regulation 2022/123 as well as HERA's mission beyond emergency situations.
- All provisions relevant to shortages/critical medicinal products are included in the Future Regulation (rather than the Future Directive) to achieve maximum harmonisation.
- Reporting of shortages (procedure/obligations) is harmonised for all Member States, and critical shortages are reported and monitored at the EU level.
- Earlier notifications of interruptions/shortages by the MAH.
- Increased obligations for the monitoring, management, and reporting of shortages by the MAH and other relevant entities/actors (e.g., wholesale distributors, patient organisations, HCPs, etc.).
- Authorities monitor shortages based on notifications from the MAH.
- Establishment of a list of EU critical medicinal products and a list of critical shortages of medicinal products.

- The MAH must offer the MA for transfer to another company before the withdrawal of a critical medicinal product.
- The MSSG provides recommendations on measures to be taken by the MAH, Member States, the EU Commission, and other entities to resolve any critical shortage or to ensure the security of supply of critical medicinal products.

Shortages of Medicinal Products

New Definitions

- "Shortage" means that the supply of a medicinal product that is authorised and placed on the market in a Member State does not meet the demand in that Member State.
- "Critical shortage in the Member State" means a shortage of a medicinal product for which there is no appropriate alternative medicinal product available on the market in that Member State, and that shortage cannot be resolved.
- "Critical shortage" means a critical shortage in the Member State for which coordinated Union level action is considered necessary to resolve that shortage.

Monitoring and Management of Shortages

- The MAH must notify the appropriate Authorities concerning the following:
  - Its decision to permanently cease/withdraw the marketing of a medicinal product - 12 months before the last supply.
  - Its decision to temporarily suspend the marketing of a medicinal product - 6 months beforehand.
  - A potential or actual shortage—temporary disruption in supply of a medicinal product (for more than 2 weeks and based on the demand forecast of the MAH) - 6 months in advance or, if it is not possible, a justification as soon as becoming aware.
- In addition, the MAH must notify the EMA of any action to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of an MA, or not to apply for the renewal of an MA and the reasons therefor. For withdrawals, the MAH must provide information on the impact on patients who are already being treated.
- In case of permanent withdrawal of a critical medicinal product, the MAH, before the withdrawal notification, must offer (under reasonable terms) to transfer the MA to a third party that has declared its intention to market that critical medicinal product or to use the MAH's pharmaceutical non-clinical and clinical documentation.

Shortage Prevention Plan ("SPP")

- The MAH must develop and update an SPP for any medicinal product on the market.
- The SPP must contain, among other information, shortage prevention measures and supply chain risk assessment (e.g., alternative marketed medicinal products, supply chain map, including supply chain vulnerabilities and shortage management measures).
- Specific SPP guideline will be developed by the EMA and the SPOC Working Party and the MSSG will develop recommendations per SPP updates.

Shortage Mitigation Plan ("SMP")

- The Authorities must continuously monitor any potential or actual shortage, and the MAH must cooperate with the Authorities and disclose any relevant information. In that context, the Authorities may request a shortage mitigation plan or an impact risk assessment of suspension, cessation, or withdrawal by the MAH and may set a specific deadline. Failure to provide any of the above must be justified.
- Commercially confidential information will be protected but should be identified and justified by the MAH.
- EMA will develop relevant guidance.

Obligations for Other Actors

- Wholesale distributors and other entities involved in the supply chain of nationally authorized medicinal products must report a shortage to the appropriate Authorities.
- All actors involved in the supply chain (e.g., other MAH, importers, manufacturers of medicinal products or active substances, relevant suppliers, wholesale distributors, stakeholder representative associations, etc.) must provide any relevant shortage information to the Authorities upon request.

Monitoring and Management of Critical Shortages

- Critical shortages in the Member States must be reported to the EMA, which may request additional information.
- The MSSG adopts a list of critical shortages for which a coordinated, EU-level action is necessary. The EMA and the SPOC Working Party will set the criteria to adopt and review that list.
- The MSSG provides recommendations on measures to resolve or mitigate critical shortages.
- Following a critical shortage, the EMA continuously monitors the situation and publishes relevant information until the MSSG considers it to be resolved.
- The MAH must: (i) provide relevant information to the EMA (upon request or not); (ii) take into account the MSSG recommendations; (iii) comply with relevant measures taken by the EU Commission or Member States; (iv) inform the EMA of any measures taken and their results; and (v) inform the EMA of the end date the critical shortage.

Critical Medicinal Products

The new rules on critical medicinal products will lead to the creation of a Union List, which will coexist with the national lists.

- "Critical medicinal product" is a medicinal product for which insufficient supply results in serious harm or a risk of serious harm to patients.
- National competent authorities must identify national critical medicinal products and inform the EMA.
- The EMA and the SPOC Working Party develop common criteria for the identification of critical medicinal products, including the vulnerability of the supply chain.
- The Authorities may request information from the MAH (e.g., the SPP) and all other actors involved. The MAH must provide the requested information in a set deadline and justify any delay/failure or request a justified deadline extension. The MAH must provide updates on relevant information.
- Based on this information, the MSSG proposes the Union List of Critical Medicinal Products for which coordinated, EU-level action is necessary. The EU Commission adopts and updates the Union List of Critical Medicinal Products, taking into account the MSSG proposal.
- Following the adoption of the list, the MSSG provides recommendations on the appropriate security of supply measures to the MAH, Member States, EU Commission, etc. (e.g., recommendations on diversification of suppliers and inventory management).
- The MAH of critical medicinal products must: (i) provide relevant information to the EMA; (ii) take into account the MSSG recommendations; (iii) comply with relevant measures taken by the EU Commission or Member States; and (iv) inform the EMA of any measures taken and their results.
- The EU Commission may take measures to improve the security of supply (e.g., imposing contingency stock requirements of active substances or finished dosage forms on the MAH, wholesale distributors, or other relevant entities).
- The EMA coordinates the monitoring and management of critical shortages as well as the identification and management of the Union List of Critical Medicinal Products. It supports the SPOC Working Party and the MSSG in their tasks.

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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.

ABOUT KING & SPALDING

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