King & Spalding
Client Alert

FDA and Life Sciences

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EUROPE – REVISION OF EU GENERAL PHARMACEUTICAL LEGISLATION: Relevant Miscellaneous

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

– 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 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 ("EU 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 some changes that are made here and there, are not part of key topics, and yet may have a significant impact for the pharmaceutical industry such as legal definitions or electronic patient leaflet. Those changes are more likely to be found in the Future Directive since it contains the basic rules applicable to all medicinal products.

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.

List of Topics

Legal definitions
Obligations and liability of MAH
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Future Directive

Compounding

- The Future Directive specifies that magistral preparations (medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient) may be prepared, in duly justified cases, in advance by a pharmacy serving a hospital, based on the estimated medical prescriptions within that hospital for the following seven days.

Legal Definitions

- '*Functional excipient'* means an excipient that contributes to or enhances the performance of a medicinal product or performs an action ancillary to that of the active substance but does not have a therapeutic contribution on its own;
- '*Entity not engaged in an economic activity'* means any legal or natural person that is not engaged in an economic activity and that: (i) is not an undertaking or controlled by an undertaking; and (ii) has not concluded any agreements with any undertaking concerning sponsorship or participation to the medicinal product development.

Obligations and Liability of MA Holders

- *New obligation to report on public financial support.* The MA holder ("MAH") must declare to the public any direct financial support received from any public authority or publicly funded body, in relation to any R&D activities of the medicinal product covered by a national or a centralized MA, irrespective of the legal entity that received that support. The MAH must publish an electronic report within 30 days after the MA is granted. The report must be updated annually.

Electronic Package Leaflet

- Member States may decide that the package leaflet must be made available in paper format or electronically, or both.
  - In the absence of such specific rules in a Member State, a package leaflet in paper format is included in the packaging of a medicinal product.
  - If the package leaflet is only made available electronically, the patient's right to a printed copy of the package leaflet is guaranteed upon request and free of charge, and it should be ensured that the information in digital format is easily accessible to all patients.
  - Where the package leaflet is made available electronically, the individual right to privacy is ensured. Any technology giving access to the information does not allow the identification or tracking of individuals, nor is it used for commercial purposes.
- The EU Commission may impose the electronic version of the package leaflet.

- National competent authorities may grant an exemption to the obligation that the mandatory information appear on the labelling and in the package leaflet in additional cases:
  - where there are space constraints due to the size of the packaging or of the package leaflet or in the case of multilingual packages or package leaflets;
  - in the context of a public health emergency;
  - to facilitate access to medicines in Member States.

MA Update related to Scientific and Technological Progress

- The MAH must, without undue delay, inform the national competent authority of:
  - any prohibition or restriction imposed on the MA holder or any entity in contractual relationship with the MAH by the competent authorities of any country where the medicinal product is marketed; and
  - any other new information that might influence the evaluation of the benefits and risks.

  The information includes both positive and negative results of clinical trials or other studies for all therapeutic indications and in all populations, whether or not included in the MA, as well as data on off-label use.
- The Future Directive regulates in detail non-interventional post-authorization safety studies that are initiated, managed or financed by the MAH and involve the collection of safety data from patients or healthcare professionals.
  - The studies must not be performed where the act of conducting the study promotes the use of a medicinal product.
  - Payments to healthcare professionals for participating in non-interventional post-authorization safety studies are restricted to the compensation for time and expenses incurred.

Advertising

- A new item is added to the express list of advertising: advertising related to medicinal products, that does not refer to specific medicinal products.
- New prohibitions are added:
  - Any form of advertising that aims to negatively highlight another medicinal product.
  - Advertising that suggests that a medicinal product is safer or more effective than another medicinal product, unless demonstrated and supported by the summary of product characteristics.

Specific provisions concerning Cyprus, Ireland, Malta and the United Kingdom in respect of Northern Ireland

Future Regulation

Compassionate use

- When compassionate use is envisaged by a Member State, the CHMP, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted.
- In the preparation of the opinion, the CHMP may:
  - request information and data from MA holders and from developers and may engage with them in preliminary discussions;
  - make use of health data generated outside of clinical studies, where available, taking into account the reliability of those data;
  - liaise with the third country agencies for medicinal products with respect to additional information and data exchanges;
  - may consult the Member State concerned and request that it provide any available information or data in its possession relating to the medicinal product concerned.

- Where a compassionate use program has been established, the applicant ensures that patients taking part also have access to the new medicinal product during the period between MA and placing on the market.

EMA Inspections

Inspection capacity of the EMA

- When an inspection is requested for a site located in a third country, the supervisory authority for this site may request the EMA to participate in the inspection or to carry out the inspection.
- The EMA may decide:
  - to lend its assistance by participating in a joint inspection with the supervisory authority of the site. In that case, the supervisory authority leads the inspection and the follow up thereof. After the completion of the inspection, the supervisory authority grants the relevant good manufacturing practice (GMP) certificate and enters it in the EU database; or
  - to carry out the inspection and the follow up thereof on behalf of the supervisory authority. After completion of the inspection, the EMA grants the relevant GMP certificate and enters the certificate in the EU database. Where the EMA decides to carry out the inspection, it may request other Member States to participate in the inspection and to be accompanied by a rapporteur or expert appointed by the CHMP.
- Where a follow-up inspection is required in view of a non-compliance GMP certificate issued by the EMA, the supervisory authority of the site will be in charge of its performance.
- Following a request by a Member State, the EMA inspectors may provide support to such Member State when it performs GCP inspections.
- The EMA ensures that (i) appropriate resources are made available for the performance of inspection tasks; (ii) the EMA inspectors possess expertise, technical knowledge, and formal qualifications equivalent to those of the national inspectors; and (iii) it participates as an inspectorate in the Joint Audit Program and be subjected to periodic audits.

International Inspections

- The EMA, in consultation with the European Commission, coordinates a structured cooperation on inspections in third countries between Member States, and as relevant, the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe (EDQM), the WHO and trusted international authorities, by means of international inspection programs.

Joint Audit Program

- The inspection working group endeavors to: (i) establish and develop the joint audit program ('JAP') and supervise it; (ii) monitor any measure taken by the Member State; and (iii) ensure cooperation with relevant international and EU level bodies to facilitate the work of the joint audit program.
- Each Member State (i) provides trained auditors; and (ii) accepts that the competent authority in charge of the implementation of GMP and GDP and related surveillance and enforcement activities applicable to medicinal products and active substances are audited regularly and where appropriate, according to the joint audit program.

Support to not-for profit entities

- For not-for-profit entities, the Commission shall adopt specific provisions clarifying the definitions, establishing waivers, reductions or deferrals of fees, as appropriate.

EU financial penalties

- The Commission may impose the financial penalties on a legal entity or legal entities other than the MA holder, provided that such entities form part of the same economic entity as the MA holder and that such other legal

entities: (i) exerted a decisive influence over the MA holder; or (ii) were involved in, or could have addressed, such failure to comply with the MA holder's obligation.

EMA's Internal and External Collaboration

Coherence of scientific opinions with other EU bodies

- The EMA takes the necessary and appropriate measures to monitor and identify at an early stage any potential source of divergence between its scientific opinions and the scientific opinions issued by other EU bodies and agencies carrying out similar tasks related to issues of common concern.
- The EU Commission may ask the EMA to conduct an assessment specifically regarding the use of the substance concerned in medicinal products. The EMA makes public its assessment, clearly stating the reasons for its specific scientific conclusions.
- To enable coherence between scientific opinions and to avoid the duplication of tests, the EMA makes arrangements with other bodies or agencies established under EU law for cooperation on scientific assessments and methodologies. The EMA shall also arrange for the exchange of data and information on relevant substances with the Commission, Member States' authorities and other EU Agencies, particularly for environmental risk assessments, non-clinical studies and maximum residue limits.

Scientific opinions in the context of international collaboration

- The EMA may give a scientific opinion, particularly in the context of cooperation with the WHO, for the evaluation of certain medicinal products for human use intended for markets outside the EU.
- The EMA may, after consulting the World Health Organization and as appropriate, other relevant organizations, draw up a scientific opinion.
- The EMA establishes specific rules for procedures and the provision of scientific advice.

International regulatory cooperation

- In so far as is necessary to achieve the objectives set out in the Future Regulation, and without prejudice to the respective competences of the Member States and the EU institutions, the EMA may cooperate with the competent authorities of third countries and/or with international organizations.
- To this end, the EMA may, subject to prior approval by the EU Commission, establish working arrangements with the authorities of third countries and international organizations, with regard to:
  - the exchange of information, including non-public information, where relevant jointly with the EU Commission;
  - the sharing of scientific resources and expertise, with a view to facilitating collaboration, while maintaining independent assessment in full compliance with the provisions of the Future Regulation and Future Directive and under conditions determined beforehand by the Management Board, in agreement with the EU Commission;
  - the participation in certain aspects of the EMA's work in agreement with the EU Commission.
- These arrangements do not create legal obligations incumbent on the EU and its Member States.
- The EMA ensures that it is not seen as representing the EU position to an outside audience or as committing the EU to international cooperation.

Interactions with Pricing and Reimbursement

- As a Directive, the Future Directive specifies that it does not affect the powers of the Member States' authorities regarding the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, based on health, economic and social conditions.

- The system set up for falsified medicinal purposes may be used for purposes of reimbursement:
  - Member States may extend the scope of application of the unique identifier to any medicinal product subject to prescription or subject to reimbursement.
  - Member States may use the information contained in the repositories system.

- The Future Directive indirectly ties data exclusivity prolongation to pricing and reimbursement.
  - Positive pricing and reimbursement decisions are equivalent to a confirmation by a Member State that a medicinal product has been launched in its territory within 2 or 3 years of the MA and thus may benefit from 2 additional years of data exclusivity.
  - Member States' representatives may request the EU Commission to discuss issues related to the practical application of data exclusivity prolongations in the Pharmaceutical Committee, and the EU Commission may invite bodies responsible for health technology assessment or national bodies responsible for pricing and reimbursement to participate in the deliberations of the Pharmaceutical Committee.

- The Bolar exemption expressly covers the use of a reference medicinal product for the purposes of health technology assessment (as defined in the HTA Regulation) and pricing and reimbursement.
- At the request of the EU Commission, the EMA, in respect of authorized medicinal products, may collect any available information on methods that national competent authorities use to determine the added therapeutic value that any new medicinal product provides.

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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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