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EUROPE – REVISION OF EU GENERAL PHARMACEUTICAL LEGISLATION: Marketing Authorization Procedures

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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 EMA ("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 focuses on the changes relating to regulatory procedures. Overall, more changes are proposed to the procedures under the Future Regulation than under the Future Directive because the centralized procedure is primarily dedicated to innovative products and more flexibility was necessary given the fast evolving technologies and science.

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.

Transitional Provisions

Future Directive

- The Future Directive must be transposed into national law within 18 months of its entry into force ("Date of Application").
- Transitional provisions:
  - The procedures concerning marketing authorization applications ("MAA") that were validated in accordance with the Directive before the Date of Application and were pending on the day before the Date of Application, will be completed in accordance with the Future Directive.
  - Procedures initiated based on Articles 29, 30, 31, and 107i of the Directive before the Date of Application and were pending on the day before the Date of Application, will be completed in accordance with Articles 32 to 34 or Article 107k, as appropriate, of the Directive as applicable on the day before the Date of Application.
  - The Future Directive generally applies to medicinal products authorized in accordance with the Directive before the Date of Application.
  - Medicinal products placed on the market in accordance with the Directive before the Date of Application may continue to be marketed until 5 years after the Date of Application, provided that they comply with the provision on labelling and package leaflets set out in the Directive as applicable on the day before the Date of Application.
  - Reference medicinal products for which the MAA has been submitted before the Date of Application, are subject to the provisions on data exclusivity periods set out in the Directive as applicable on the Date of Application until the Date of Application.
  - The obligation to report on public financial support does not apply to medicinal products authorized in accordance with the Directive before the Date of Application.

Future Regulation

- The Future Regulation applies within 18 months of its entry into force ("Date of Application").
- Marketing authorization ("MA") procedures validated under the Regulation must be completed in accordance with the Regulation.
- Article 117 (shortage prevention plan) does not apply to MA granted in accordance with the Regulation or the Directive before the Date of Application.
- The MAA procedures that have been validated in accordance with the Regulation before the Date of Application and were pending on the day before the Date of Application, are completed in accordance with the Regulation.
- Procedures concerning imposed post-authorization studies that were initiated in accordance with the Regulation before the Date of Application and were pending on the day before the Date of Application, are completed in accordance with the Future Regulation.
- The periods of regulatory protection do not apply to reference medicinal products for which an MAA has been submitted before the Date of Application. The Regulation continues to apply to them.

DOSSIER REQUIREMENTS

General Requirements

- The documents and information concerning the results of the pharmaceutical and non-clinical tests and the clinical studies must be accompanied by supportive raw data.

- The applicant must demonstrate (principle of replacement, reduction and refinement of animal testing) compliance with Directive 2010/63/EU with regard to any animal study conducted in support of the application.

MAA for Hybrid and Bio-Hybrid Medicinal Products

- A change to the active substance is removed from the "definition" of hybrid medicinal products and handled separately.
  - The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety or efficacy.
  - The applicant submits additional information to demonstrate that the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance do not differ significantly in respect of those properties.
  - Where there is a significant difference in properties, the applicant submits additional information to prove safety or efficacy in a hybrid application.
- Hybrid applications are now expressly allowed for biosimilars in case of changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product ('bio-hybrid').

Bibliographic MAA

- Two new conditions are added:
  - No reference medicinal product is or has been authorized for the active substance.
  - Well-established medicinal use for the same therapeutic use and route of administration.

Specific Requirements for Platform Technologies and Multi-Medicinal Product Packages

- Platform technology: Where justified for therapeutic purposes, a MA may, in exceptional circumstances, be granted for a medicinal product comprised of a fixed component and a variable component that is pre-defined in order to, where appropriate, target different variants of an infectious agent or, where necessary, to tailor the medicinal product to characteristics of an individual patient or a group of patients.
- A muti-medicinal product package means a package that contains more than one medicinal product under a single invented name and intended to be used in a medical treatment where the individual medicinal products in the package are for medical purposes simultaneously or sequentially administered.
- Where justified for public health reasons and when the active substances cannot be combined within a fixed dose combination medicinal product, a MA may, in exceptional circumstances, be granted to a multi-medicinal product package.
- An applicant that intends to submit a MAA for such a medicinal product must seek, in advance, the agreement concerning the submission of such MAA by the competent authority concerned.

Adapted Dossier Requirements

- Medicinal products listed in Annex VII to the Future Directive are subject to specific scientific or regulatory requirements when:
  - it is not possible to adequately assess the medicinal product or category of medicinal products applying the applicable requirements due to scientific or regulatory challenges arising from characteristics or methods inherent to the medicinal product; and
  - the characteristics or methods positively impact the quality, safety and efficacy of the medicinal product or category of medicinal product or provide a major contribution to patient access or patient care.
  - Annex VII currently includes "phage-containing medicinal products, in cases where the medicinal product has a variable composition depending on the specific clinical context".
  - The EU Commission is empowered to set out:

- detailed rules for the MA and supervision of the medicinal products that are proportionate to the risk and impact involved. These may entail adapted, enhanced, waived or deferred requirements. Any waiver or deferral is limited to the extent strictly necessary, proportionate and duly justified by the characteristics or methods inherent to the medicinal product, and is regularly reviewed and evaluated; and
- the technical documentation to be submitted by applicants.

VALIDATION AND EXAMINATION OF MAA

Validation of MAA

- Where EMA considers that the application is incomplete or contains critical deficiencies that may prevent the evaluation of the medicinal product, it informs the applicant and sets a time limit for submitting the missing information and documentation. That time limit may be extended once. If the applicant fails to provide the missing information and documentation within the time limit, the application is considered to have been withdrawn.

  The EMA will draw up scientific guidelines for the identification of critical deficiencies, in consultation with the European EU Commission and the Member States.

Examination of MAA

- Where within 90 days of the validation of the MAA and during the assessment, the CHMP considers that the submitted data are not of sufficient quality or maturity to complete the assessment, the assessment can be terminated. The CHMP summarizes the deficiencies in writing, and on this basis, the EMA informs the applicant and sets a time limit to address the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the EMA, the MAA is considered to be withdrawn.

CONDITIONS OF MA

- The list of conditions to which a MA may be subject is expressly expanded to the following:
  - to comply with stricter obligations on the recording or reporting of suspected adverse reactions;
  - to substantiate the clinical benefit, in case of medicinal products for which there is substantial uncertainty as to the surrogate endpoint in relation to the expected health outcome, where appropriate and relevant for the benefit-risk balance;
  - to conduct post-authorization environmental risk assessment studies, collection of monitoring data or information on use, where identified or potential concerns about risks to the environment or public health, including antimicrobial resistance, need to be further investigated after the medicinal product has been marketed;
  - to improve the safety and effective use of the medicinal product; and
  - where appropriate, to carry out medicinal product-specific validation studies to replace animal-based control methods with non-animal-based control methods.
- The MA sets deadlines for the fulfilment of the conditions, where necessary.

MA UNDER EXCEPTIONAL CIRCUMSTANCES AND CONDITIONAL MA

MA under Exceptional Circumstances

- New MAA and applications for a new therapeutic indication.
- Conditions:
  - The applicant has demonstrated, in the MAA, that there are objective and verifiable reasons not to be able to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, based on one of the grounds set out in Annex II to the Future Directive.
  - Except for these data, the MAA is complete and satisfies all the legal requirements.

- Specific conditions are included in the decision of the EU Commission or the national competent authority, in particular to ensure the safety of the medicinal product and that the MA holder ("MAH") notifies about any incident relating to its use and takes appropriate action where necessary.
- The reassessment of those conditions, which is conducted on the basis of an application by the MAH, occurs:
  - 2 years after the date of authorization; and
  - thereafter at a risk-based frequency specified in the MA.

Conditional MA

- Conditional MA or a new conditional therapeutic indication to an existing MA.
- The missing data may only be clinical data. However, in emergency situations, a conditional MA or a new conditional therapeutic indication may be granted also where comprehensive non-clinical or pharmaceutical data have not been supplied.
- The specific obligations are reviewed annually by the EMA for the first 3 years after granting the MA and every 2 years thereafter. Therefore, an initial conditional MA is valid for 1 year, on a renewable basis for the first 3 years and every 2 years thereafter.

VALIDITY AND RENEWAL OF MA

- A MA is now valid for an unlimited period subject to two exceptions:
  - MA under exceptional circumstances is only valid for 5 years.
  - The competent authority may decide to limit the validity of the MA to 5 years, on objectively and duly justified grounds relating to safety of the medicinal product.
- The MAH submits an application for renewal at least 9 months before the MA ceases to be valid.
- The MA is renewed for an unlimited period, following a re-evaluation of the benefit-risk balance.

DECENTRALIZED MA PROCEDURE (DCP)

- The competent authority of a Member State may request, for justified public health reasons, to enter the procedure. It informs the applicant and the reference Member State of its request within 30 days from the date of submission of the MAA. The applicant provides that competent authority with the MAA without undue delay.

MUTUAL RECOGNITION PROCEDURE (MRP)

- The competent authority of the reference Member State rejects the application for mutual recognition within 1 year from the granting of the MA, unless the competent authority of the Member State informs the competent authority of the reference Member State of its interest in this medicinal product.
- Like in the DCP, one or more Member States may request to be part of the procedure, for justified public health reasons.
- In case of referral, the Member States that have approved the assessment report and the product information, of the reference Member State may, at the request of the applicant, authorize the medicinal product without waiting for the outcome of the referral procedure. In that case, the national MA granted is without prejudice to the outcome of that procedure.

CENTRALIZED MA PROCEDURE (CP)

Scope of the Centralized Procedure

- The mandatory scope is extended to: any medicinal product with a new active substance, regardless of the disease, pediatric use MA ("PUMA"), and priority antimicrobials.

Duplicate marketing authorizations

- Only one MA may be granted for a specific medicinal product.
- The EU Commission authorizes the same applicant to submit more than one MAA for that medicinal product in either of the following cases:
  - If one of its indications or pharmaceutical forms is protected by a patent or a supplementary protection certificate in one or more Member States. As soon as the relevant patent or supplementary protection certificate expires, the MAH withdraws the initial or duplicate MA.
  - For reasons of co-marketing with a different company not belonging to the same group as the MAH of the medicinal product for which a duplicate is requested.

  Thus, duplicate MA are no longer granted for public health reasons, which is in line with the EU Commission's current practice.

Pre-Authorization Regulatory Support

Scientific advice

- Companies or not-for-profit entities may request scientific advice ("SA") from EMA.
- SA can also be requested for medicinal products addressing an unmet medical need or to be repurposed.
- The EPAR includes the key areas of the SA.

Parallel scientific advice

- Companies or not-for-profit entities established in the EU may request that the SA takes place in parallel to the joint scientific consultation carried out by the Member State Coordination Group on Health Technology Assessment in line with the HTA Regulation.
- In case of medicinal products involving a medical device, the applicant may request SA in parallel with the consultation of the MDR expert panels.

Enhanced scientific and regulatory support for priority medicinal products ('PRIME')

- EMA may offer enhanced scientific and regulatory support, including consultation with other bodies and accelerated assessment mechanisms, for certain medicinal products that, based on preliminary evidence submitted by the developer fulfill the following conditions:
  - are likely to address an unmet medical need;
  - are orphan medicinal products and are likely to address a high unmet medical need;
  - are expected to be of major interest from the point of view of public health, in particular as regards therapeutic innovation, taking into account the early stage of development; or
  - priority antimicrobials.

Scientific recommendation on regulatory status

- For products under development which may fall within the mandatory scope of the centralized procedure, a developer or a national competent authority may submit a request to the EMA for a scientific recommendation on whether the concerned product is potentially a 'medicinal product', including an 'ATMP'.
- When forming the recommendation, EMA consults, where appropriate, relevant advisory or regulatory bodies established in other Union legal acts in related fields. In the case of products that are based on substances of human origin, the EMA consults the Substances of Human Origin (SoHO) Coordination Board as established in the future SOHO Regulation.
- In the case of duly substantiated disagreement with the EMA's recommendation, a Member State may request the EU Commission to decide whether the product is a medicinal product. The EU Commission may initiate the procedure on its own initiative.

Rolling review

- EMA may offer a phased review of complete data packages for individual modules of particulars and documentation.
- Medicinal products that are likely to offer an exceptional therapeutic advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition.
- Upon advice of the CHMP regarding the maturity of the data related to the development.

Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products

- A not-for-profit entity may submit to EMA or to a national competent authority substantive non-clinical or clinical evidence for a new therapeutic indication that is expected to fulfill an unmet medical need.
- EMA may, on the basis of all available evidence, make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication that concerns an unmet medical need.
- In cases where the opinion is positive, the MAH of the medicinal product concerned submits a variation to update the product information with the new therapeutic indication.

Marketing Authorizations

- The European public assessment report ("EPAR") also includes:
  - a summary of the assessment report written in a manner that is understandable to the public;
  - a summary of environmental risk assessment studies and their results as submitted by the MA holder and the assessment of the environmental risk assessment; and
  - in the case of antimicrobials, an antimicrobial stewardship plan.

Regulatory Sandbox

A 'regulatory sandbox' is a regulatory framework during which it is possible to develop, validate and test in a controlled environment innovative or adapted regulatory solutions that facilitate the development and authorization of innovative products which are likely to fall in the scope of this Regulation, pursuant to a specific plan and for a limited time under regulatory supervision.

Regulatory sandbox

- The EU Commission may set up a regulatory sandbox pursuant to a specific sandbox plan, based on the EMA's recommendation, where all the following conditions are met:
  - it is not possible to develop the medicinal product (or category of products) in compliance with the requirements applicable to medicinal products due to scientific or regulatory challenges arising from characteristics or methods related to the product;
  - those characteristics or methods positively and distinctively contribute to the quality, safety or efficacy of the medicinal product (or category of products) or provide a major advantage contribution to patient access to treatment.
- The regulatory sandbox sets out a regulatory framework for the development and, where appropriate, clinical trials and placing a product on the market.
- The EMA is responsible for developing a sandbox plan based on data submitted by developers of eligible products and following appropriate consultations. The plan:
  - sets out clinical, scientific and regulatory justification for a sandbox, including the identification of the legal requirements that cannot be complied with;
  - a proposal for alternative or mitigation measures, where appropriate;
  - a proposed timeline for the duration of the sandbox;
  - measures in order to mitigate any possible distortion of market conditions as a consequence of establishing a regulatory sandbox, where appropriate.

- The EMA does not recommend setting up a regulatory sandbox for a medicinal product that is already advanced in its development program.

Products developed under a sandbox

- When authorizing a clinical trial application for products covered by a regulatory sandbox, Member States take the sandbox plan into consideration.
- A medicinal product developed as part of a regulatory sandbox must be authorized through the centralized procedure. The initial validity of the MA does not exceed the duration of the regulatory sandbox, but the MA may be prolonged at the MAH's request.
- In duly justified cases, the MA may include derogations from applicable legal requirements. Those derogations may entail adapted, enhanced, waived or deferred requirements. Each derogation is limited to what is apt and strictly necessary to attain the objectives pursued, duly justified and specified in the conditions to the MA.

EMA's Committees

- Only the CHMP and PRAC remain - the Paediatric Committee (PDCO), the Committee for Orphan Medicinal Products (COMP), and the Committee for Advanced Therapies (CAT) are abolished and replaced by CHMP's working parties.
  - The expertise is retained through the working parties.
  - The CHMP becomes competent for orphan and pediatric products.

Composition of CHMP and PRAC

- The composition of the CHMP now includes representatives of healthcare professionals and patient organizations.

OTHER CHANGES

- Electronic product leaflet
- MAH's obligation to report public funding of clinical trials
- Support to not-for-profit entities
- Non-interventional post-authorization safety study
- Temporary MA in case of health emergency ("temporary emergency MA")
- Recording and reporting of AR in case of compassionate use
- EMA's inspection powers
- EMA's collaboration with other EU bodies and with foreign authorities

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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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