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AND FOOD SAFETY



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NOTICE TO STAKEHOLDERS

QUESTIONS AND ANSWERS ON REGULATORY EXPECTATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE DURING THE COVID-19 PANDEMIC

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INTRODUCTION

The current COVID-19 pandemic has a considerable impact on citizens, patients and businesses. It may force MAHs and regulatory authorities to operate under business continuity mode, impacting the standard way of working. Moreover, public health needs may require quick actions or re-prioritisation of operations.

The ultimate aim of the EU legislation on medicinal products is to ensure a high level of public health. The COVID-19 pandemic is posing unprecedented challenges and ensuring continuity of supplies of medicines is a priority for public health. Therefore, it is necessary to articulate appropriate measures to minimise risks of shortages while ensuring that the high standards of quality, safety and efficacy of medicines made available to patients in the EU are maintained.

This document provides guidance to marketing authorisation holders of medicinal products for human use (“MAH”) on regulatory expectations and flexibility during the COVID-19 pandemic. The document will be updated to address new questions and to adjust the content thereof to the evolution of the pandemic. For queries related to specific products that are not specifically addressed in this document, MAHs are invited to address the EMA (for centrally authorised products) or the relevant national competent authorities (for nationally authorised products).

This document remains valid until further notice. It has been developed in cooperation between the European Commission, the Coordination group for Mutual recognition and Decentralised procedures – human (“CMDh”) and the European Medicines Agency (“EMA”).

The ultimate responsibility for the interpretation of EU legislation is vested on the European Court of Justice and therefore the content of this document is without prejudice to a different interpretation that may be issued by the European Court of Justice.

A. LEGAL AND REGULATORY GUIDANCE

1. ISSUES RELATED TO MARKETING AUTHORISATIONS, MARKETING AUTHORISATION PROCEDURES

1.1. Can medicinal products intended for use in COVID-19 patients be marketed in the absence of a marketing authorisation?

A marketing authorisation is required before medicinal products can be marketed in the EU. A marketing authorisation granted by the European Commission is valid in all Member States (centralised marketing authorisation). A marketing authorisation granted by a National Competent Authority (“NCA”) in a Member State is valid only in that Member State (national marketing authorisation). Procedures exist to

facilitate the granting of national marketing authorisations of medicinal products that are authorised in another EU/EEA Member State.¹

The coordination group established under Article 27 of Directive 2001/83/EC (CMDh) has agreed to promote the use of zero-day mutual recognition procedure /repeat use procedure to expand national marketing authorisations to new Member States who need these medicinal products.

Member States may also authorise a medicinal product that has already been authorised in another EU Member State in accordance with Article 126a of Directive 2001/83/EC.

In cases where no centralised/relevant national marketing authorisation exists, Member States can make use of possibilities foreseen in Directive 2001/83/EC, including resorting to compassionate use, or authorisation of the distribution of an unauthorised medicinal product in accordance with Article 5(2) of Directive 2001/83/EC.

To permit prompt assessment of these requests, applicants are requested to identify any such communication to the relevant NCA with the message “CONCERNS COVID-19”.

1.2. Can I postpone my renewal application?

According to Article 14 of Regulation (EC) No 726/2004 and Article 24 of Directive 2001/83/EC the initial standard marketing authorisation is valid for five years. Such marketing authorisation may be renewed on the basis of a re-evaluation of the benefit-risk assessment. To this end, the MAH shall provide the Agency or the NCAs with a consolidated version of the file in respect of quality, safety and efficacy, at least 9 months before the marketing authorisation ceases to be valid.

MAHs facing difficulties to meet this deadline due to exceptional circumstances arising from the COVID pandemic, are invited to contact the EMA (for centrally authorised products) or the reference Member State (for products authorised under the MRP/DCP) before the foreseen deadline of the submission of the renewal application with a justified request to postpone the submission of the complete dossier to a later point in time. The reference Member State will consult with the concerned Member State(s) and advise the MAH on any further step to be taken before the foreseen deadline. In case of purely national marketing authorisations, the relevant national competent authority should be contacted.

The same considerations apply to conditional marketing authorisations granted in accordance with Article 14-a of Regulation (EC) No 726/2004.

1.3. Does the 'sunset clause' apply during a pandemic?

According to Article 24(4) to (6) of Directive 2001/83/EC and Articles 14(4) to (6) of Regulation (EC) No 726/2004, any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State or on the Union market will cease to be

¹ Mutual recognition procedure (“MRP”) and decentralised procedure (“DCP”) established by Directive 2001/83/EC.

valid. When an authorised product previously placed on the market in the authorising Member State or in the Union is no longer actually present on the market for a period of three consecutive years, the authorisation for that product will cease to be valid.

Due to the current pandemic, initial market launch plans may need to be adapted in a way that could trigger the sunset clause mechanism. MAHs are reminded of the possibility to request an exemption in view of exceptional circumstances and on public health grounds.

For centrally authorised products such request has to be submitted under Article 14(6) of Regulation (EC) No 726/2004 to the European Commission. During the pandemic, the Commission may accept sunset clause requests that refer to the pandemic as a reason without the need for any further justification.

For nationally authorised products such requests have to be submitted to the competent authorities of the Member State(s) concerned. It will be decided according to the national rules considering the pandemic situation.

2. MANUFACTURING AND IMPORTATION OF FINISHED PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS

2.1. How can changes in the manufacturing/supply chain be implemented swiftly to ensure continuity of supplies to the EU of crucial medicines for treatment of COVID-19 patients?

MAHs may experience supply chain/manufacturing disruptions due to manufacturing, distribution and trade restrictions arising from the COVID-19 pandemic. Ensuring continuity of supplies of medicinal products is a priority for public health.

It is therefore necessary to articulate regulatory tools that permit MAHs to swiftly source starting materials, reagents, intermediates or active substances from alternative suppliers, where that is necessary to ensure supplies to the EU of crucial medicines for treatment of COVID-19 patients. The addition of new manufacturing sites for part or all of the manufacturing process, as well as changes in the site(s) responsible for quality control should also be facilitated.

To reduce the risk of shortages or disruption of supply following from manufacturing and/or supply problems, an exceptional change management process (ECMP) is made available to MAHs of crucial medicines for treatment of COVID-19 patients. The ECMP will permit the swift implementation of changes to suppliers and/or manufacturing/control sites necessary to reduce the risks of shortages under certain conditions intended to ensure the quality of the medicinal product, while deferring the full assessment of the variation.

Under the ECMP, MAHs will be able to exceptionally source starting materials, reagents, intermediates or active substances from suppliers not specifically mentioned in the marketing authorisation if that is necessary to prevent/mitigate shortages of supplies in the EU. Likewise, MAHs will be able to use manufacturing sites or sites responsible for quality control that are not specifically mentioned in the

marketing authorisation in cases where the use of an alternative site is necessary to prevent/mitigate shortages of supplies in the EU.

Scope

The ECMP is only available for crucial medicines for use in COVID-19 patients.²

The ECMP cannot apply to changes classified as extensions of the marketing authorisation in accordance with Annex I of Commission Regulation (EC) No 1234/2008. In addition, it is only available for changes required to address supply chain/manufacturing challenges resulting from the current pandemic with a view to ensure continuity of supplies. Deviations from the requirements in the marketing authorisation or from GMDP³ (other than aspects intrinsically linked to the changes of suppliers and/or manufacturing/control sites) are excluded from the ECMP.

Procedure

MAHs that wish to rely on the ECMP must notify the relevant national competent authority that granted the marketing authorisation or EMA (in case of centrally authorised products). In the notification, the MAH should:

- Specify the intention to use the ECMP for the specific medicinal product.
- Commit to ensure that the quality of the finished product will not be compromised. To this end, the MAH should ensure that the new suppliers/sites abide by the quality standards applicable in the EU and, in particular, that the specifications (both for active substance(s) and finished product) in the marketing authorisation are respected. Where required by EU legislation, manufacturing/control site used under the ECMP should have an EU GMP certificate or have been certified by the authorities of a country with whom the EU has concluded a mutual recognition agreement.⁴ If the latter conditions are not met, a variation in accordance with Commission Regulation (EC) No 1234/2008 should be submitted.
- Commit to notify any changes to the relevant competent authorities within 48 hours after the change is implemented by the MAH. In the case of centrally-authorised products, notifications should be made to the EMA. The notification should indicate the medicinal product that is concerned as well a summary description of the change made.
- Commit to submit the corresponding variation application to the competent authorities no later than within 6 months following the implementation of the change. Grouping of relevant variations in accordance with Commission

² When in doubt whether a given medicinal product is a crucial medicine for treatment of COVID-19 patients, the MAH may contact the relevant competent authorities (EMA should be contacted for centralised marketing authorisations).

³ Good Manufacturing and Distribution Practices.

⁴ It is acknowledged that the GMP certificate for the site may not specifically cover the medicinal product at stake.

Regulation (EC) No 1234/2008 remains possible.⁵ The variation submission should provide all the data requirements provided for under the *Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.*

The relevant competent authority will assess the notification and specifically whether the application concerns crucial medicines for use in COVID-19 patients (in case of marketing authorisations granted under the mutual recognition or the decentralised procedure, the reference Member State will consult the concerned Member States). Within two working days, the MAH will be informed whether the relevant competent authority has agreed to the application of the ECMP. If within two working days following the submission date the relevant competent authority has not raised objections, the application of the ECMP shall be deemed accepted.

The agreed ECMP can cease to be valid in case one or more of the above-referred commitments are not fulfilled (including *e.g.* that critical findings in respect of the quality of the product are identified).

3. QUALITY VARIATIONS

3.1. Can quality requirements be waived/adapted for medicines intended to be used for the treatment of COVID-19 patients?

Without prejudice to the flexibilities afforded by the ECMP, the quality requirements foreseen in the marketing authorisation should be complied with for medicinal products marketed in the EU, including medicinal products that are administered to COVID-19 patients.

MAHs facing difficulties to perform the quality controls foreseen in the marketing authorisation, due to *e.g.* a significant increase of manufacturing capacity to meet the demands of patients in the EU or other circumstances related to the COVID-19 pandemic, are invited to contact the competent authorities and to present an adapted control scheme based on a risk-based approach. This request should be submitted as a variation in accordance with Commission Regulation (EC) No 1234/2008.

Other changes to the quality requirements foreseen in the marketing authorisations should also be processed in accordance with the Commission Regulation (EC) No 1234/2008.

To permit prompt assessment of these variation applications, applicants are requested to identify any such communication with the subject “CONCERNS COVID-19” next to the procedure number in the email heading.

⁵ Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

4. PRODUCT INFORMATION AND LABELLING

4.1. Is there any flexibility in the labelling and packaging requirements to facilitate the movement of medicinal products within the EU?

It is necessary to facilitate the movement of medicinal products within the EU so that they can be made available in the Member States where are needed the most. In the current exceptional circumstances, the regulatory flexibilities foreseen in the Directive 2001/83/EC should be fully utilised. Under Article 63(3) of Directive 2001/83/EC Member States may grant full or partial exemptions to certain labelling and packaging requirements to address severe problems in respect of the availability of medicinal products.

During the COVID-19 pandemic, Member States may therefore accept that the product information of products marketed in their territory may not be translated into the relevant official language if there are severe problems of availability of that medicinal product in the Member State.

In these exceptional circumstances, it may moreover be accepted that national specific information does not appear in the packaging/labelling, or that the presentation differs from the presentations authorised in the Member State where the product is marketed.

During the COVID-19 pandemic, the CMDh has agreed to apply the labelling and packaging flexibilities above-referred crucial medicines for use in COVID-19 patients.⁶

MAHs are required to notify the relevant national competent authorities in advance and should also provide a link to a website where the product information in the relevant official language may be obtained. Further guidance on specific national requirements/procedures will be developed by CMDh.

B. ADDITIONAL INFORMATION

The websites of the Commission (https://ec.europa.eu/health/human-use_en) and of the EMA (<https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19>) provide additional information. For products authorised in decentralised or mutual recognition procedures, additional information will be provided through the websites of the Coordination Group. These pages will be updated with further information, where necessary.

European Commission
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Heads of Medicines Agencies

European Medicines Agency

⁶ When in doubt whether a given medicinal product is a crucial medicine for treatment of COVID-19 patients, the MAH may contact the relevant competent authorities (EMA should be contacted for centralised marketing authorisations).