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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 marketing authorisation holders of medicinal products 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 European Medicines Agency (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”), the Inspectors Working Group 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

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

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 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, IMPORTATION OF FINISHED PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS AND GMP AND GDP ISSUES

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-authorized 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 Regulation (EC) No 1234/2008 remains possible.⁵ The variation submission

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.

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.

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).

2.2. [NEW] Which measures will be taken in respect of GMP certificates and authorisations to manufacture/import in light of difficulties to conduct on-site GMP inspections due to restrictions linked to COVID-19 pandemic?

The COVID-19 pandemic has triggered national and international restrictions that may affect and/or prevent the conduct of certain on-site GMP inspections. In light of the severity of the current circumstances, measures should be put in place to ensure availability of GMP certificates and authorisations to manufacture/import to support regulatory submissions, as well as to maintain the validity of current GMP certificates and authorisations to manufacture/import.

Specifically, the validity of GMP certificates that support the manufacture and importation of medicinal products in the EEA should be extended to avoid disruptions in the availability of medicines. The validity of authorisations to manufacture/import should also be extended (in case they are time-limited). With a view to ensure the quality of medicines marketed in the EU/EEA, a distinct approach should be taken for sites that are located in the EEA and sites located outside the EEA that have never been inspected by an EEA supervisory authority.

Sites located in the EEA

The validity of GMP certificates for manufacturing/importing sites of active substances and/or finished products in the EEA should be extended until the end of 2021 without the need for further action from the holder of the certificate.⁶ This automatic extension does not cover changes in the scope of the GMP certificate (*e.g.* new buildings, new medicinal products).

⁶ An explanatory footer has also been introduced in EudraGMDP database.

The validity of time-limited authorisations/registrations to manufacture/import should also be extended until the end of 2021 without the need for further action from the authorisation/registration holder. This automatic extension does not cover changes in the scope of the authorisation/registration (e.g. new premises, new medicinal products).

For new sites/facilities in the EEA that have never been inspected and authorised, a distant assessment may be conducted in order to evaluate if the site could be authorised without a pre-approval inspection. In such cases, it should be indicated that the certificate has been granted on the basis of a distant assessment. Moreover, an on-site inspection should be conducted when circumstances permit. If the outcome of the distant assessment does not permit the granting of the GMP certificate, a clock-stop will be triggered until an on-site inspection is possible.

Sites located outside the EEA

The validity of GMP certificates for manufacturing sites of active substances and/or finished products located outside the EEA should be extended until the end of 2021 without the need for further action from the holder of the certificate, unless the issuing/supervisory authority takes any action that affects the validity of the certificate.

For new sites/facilities in third countries where an inspection is required, and where there is no operational mutual recognition agreement (MRA) or the scope is not covered by the MRA, a distant assessment by an EEA supervisory authority may be conducted. A GMP certificate may be granted depending on the outcome of the assessment. In such cases, it should be indicated that the certificate has been granted on the basis of a distant assessment. Moreover, an on-site inspection should be conducted when circumstances permit. If the outcome of the distant assessment does not permit the granting of the GMP certificate, a clock-stop will be triggered until an on-site inspection is possible.

Important remarks

Pre-approval or routine on-site inspections will resume as soon as COVID-19 restrictions are lifted,⁷ according to risk based inspection planning taking into account the date of the last inspection.

It is stressed that the obligation of manufacturers and importers to comply with GMP is not waived. It is incumbent upon manufacturers and importers to continue complying with GMP. Supervisory authorities will remain vigilant to ensure the quality of medicines that are made available to patients in the EEA. Inspections (including distant assessments) may be launched at any time and, in case of non-compliance, appropriate regulatory actions will be triggered.

⁷ Resumption of inspections will vary according to timing of the lifting of containment measures taken by each country and other factors such as restoration of transport links.

2.3. [NEW] Which measures will be taken in respect of GDP certificates and wholesale authorisations in light of difficulties to conduct on-site inspections due to restrictions linked to COVID-10 pandemic?

In light of difficulties to conduct on-site GDP inspections due to restrictions arising from the COVID-19 pandemic, the validity of GDP certificates should be extended until the end of 2021 without the need for further action from the holder of the certificate.

The validity of time-limited wholesale authorisations should also be extended until the end of 2021 without the need for further action from the holder of the authorisation.⁸ This automatic extension does not cover changes in the scope of the authorisation (e.g. type of medicinal products or authorised operations).

On-site inspections will resume as soon as COVID-19 restrictions are lifted,⁹ according to risk based inspection planning taking into account the date of the last inspection.

It is stressed that the obligation of distributors and wholesalers to comply with GDP is not waived. It is incumbent upon distributors and wholesalers to continue complying with GDP. Supervisory authorities will remain vigilant to ensure the quality of medicines that are made available to patients in the EEA. Inspections (including distant assessments) may be launched at any time and, in case of non-compliance, appropriate regulatory actions will be triggered.

2.4. [NEW] Which adaptations to the work of the QP are possible considering travelling and other restrictions arising from COVID-19 pandemic?

i. Remote batch certification

The remote batch certification is permissible under EU GMP rules, provided that the QP has access to all information necessary to enable them to certify the batch.

While in some Member States additional requirements have been introduced which may preclude remote certification, considering the current restrictions of travelling linked to the COVID-19 pandemic, the remote certification should be acceptable in all EEA Member States.

It is stressed that the obligations/responsibilities of the QP remain unchanged.

ii. Remote audits of the active substance manufacturer

Where on-site audits are not possible, the QP can rely on paper-based audits and also take into consideration the results of inspections from EEA authorities.¹⁰

⁸ An explanatory footer has also been introduced in EudraGMDP database.

⁹ Resumption of inspections will vary according to timing of the lifting of containment measures taken by each country and other factors such as restoration of transport links.

¹⁰ Guidance on good manufacturing practice and good distribution practice: Questions and answers. <https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers#eu-gmp->

Remote audits should provide confidence that the active substance is fit-for-purpose and will not negatively affect the safety and efficacy of the medicinal product. The QP is expected to justify the controls in place on a scientific basis and record a risk assessment on a product specific basis.¹¹

iii. Batch release of investigational medicinal products imported from third countries

In case of imports of investigational medicinal products from third countries, the QP should ensure that the quality of the batch is in accordance with the terms of the clinical trial authorisation (including compliance with the terms of the Product Specification File) and that it has been manufactured in accordance with quality standards at least equivalent to the GMP requirements applied in the EEA.

To make that assessment, where on-site inspections are not possible, the QP may rely on a variety of documents including, as appropriate: batch records, including in-process test reports and release reports, the validation status of facilities, processes and methods, examination of finished packs, the results of any analyses or tests performed after importation (where relevant), stability reports, the source and verification of conditions of storage and shipment, audit reports concerning the quality system of the manufacturer, *etc.*

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.

[guide-part-ii:-basic-requirements-for-active-substances-used-as-starting-materials:-gmp-compliance-for-active-substances-section](#)

¹¹ https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-template-qualified-persons-declaration-concerning-good-manufacturing-practice-gmp_en.pdf

4. PHARMACOVIGILANCE, INCL. ADVERSE REACTIONS REPORTING

4.1. [NEW] Is there any impact on reporting into EudraVigilance of Individual Case Safety Reports (ICSRs)?

According to Article 107 of Directive 2001/83/EC, MAHs shall submit electronically to the Eudravigilance database all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the MAH gained knowledge of the event. All non-serious suspected adverse reactions that occur in the Union shall be submitted within 90 days.

This includes adverse reactions that result from use outside the terms of the marketing authorisation (off-label use).

During the current pandemic the reporting of adverse events related to the widespread use of medicinal products for the treatment or prevention of the pathogen causing the pandemic may increase. At the same time, there is a risk that during a pandemic workforces in industry may be reduced due to high employee absenteeism.

These exceptional circumstances may force companies to activate business continuity plans and prioritise activities. Therefore, in case MAHs are for justified reasons relating to the pandemic unable to continue standard reporting operations, they should temporarily – until the pandemic is resolved – prioritise the reporting obligations as follows:

- Submission of serious ICSRs associated with medicinal products used for the treatment or prevention of the pathogen causing the pandemic;
- Submission of other serious ICSRs;
- Submission of non-serious ICSRs associated with medicinal products used for the treatment or prevention of the pathogen causing the pandemic;
- Submission of other non-serious ICSRs.

While in the present exceptional circumstances, some MAHs may have understandable difficulties complying with the relevant deadlines, it is essential that MAHs report all serious ICSRs within the 15 days set out in Directive 2001/83/EC. Where MAHs make use of prioritisation, they shall put a note in the pharmacovigilance system master file recording such practice.

For reports originating from compassionate use or named patient use, marketing authorisation holders should continue to follow the guidance in GVP Module VI Section VI.C.1.2.2.

5. PRODUCT INFORMATION AND LABELLING

5.1. 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.¹²

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
Directorate-General Health and Food
Safety

Heads of Medicines Agencies

European Medicines Agency

¹² 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).