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NOTICE TO STAKEHOLDERS

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

Contents

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 advice 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 is only available for the following changes:

- Changes in the manufacturing and/or control sites that are necessary to prevent/mitigate shortages of supplies in the EU.

- Changes in suppliers of starting materials, reagents, intermediates or active substances where that is necessary to prevent/mitigate shortages of supplies in the EU.

It is stressed that the ECMP cannot cover:

- Changes classified as extensions of the marketing authorisation in accordance with Annex I of Commission Regulation (EC) No 1234/2008.

- Deviations from the requirements in the marketing authorisation or from GMDP[3] (other than the changes of suppliers and/or manufacturing/control sites above-referred).

- Changes to the dossier other than changes of suppliers or manufacturing/control sites.

Procedure

Step 1:

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.

- State the medicinal product concerned.

- Provide a summary description of the changes that will be implemented. A notification should be submitted for each supplier and/or manufacturing/control site that is implemented under the ECMP.

- 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

[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.

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 the implementation of the changes made 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.

- Commit to submit the corresponding variation application to the competent authorities no later than within 6 months following the implementation of the change.

Step 2:

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.

Step 3:

Within 48 hours after the change is implemented by the MAH, a notification is submitted to the competent national authorities or EMA (in the case of centrally-authorised products). The notification should indicate the medicinal product that is concerned as well a summary description of the change made.

Step 4:

Within 6 months after the implementation of the respective changes, a variation is submitted. 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.*

Grouping of relevant variations in accordance with Commission Regulation (EC) No 1234/2008 remains possible.[5]

[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.

Important remarks

The ECMP does not cover changes other than those specifically foreseen in the scope thereof (*see* above). Other changes should be notified as a variation. Absence of the submission of the relevant variation constitutes a breach of the obligations of the MAHs.

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. [UPDATED] 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 2021without 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).

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

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

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. This automatic extension does not cover changes in the scope of the GMP certificate (e.g. new buildings, new medicinal products).

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.

2.3. Which measures have been put in place to mitigate the suspension of on-site inspections of plasma collection centres?

i. EEA or third country sites that have been previously inspected

The supervisory authority will implement a control measure in line with EMA recommendation EMA/INS/GMP/534269/2018 "Application of inspection and control measures". Supervisory authorities will issue Statements of Next Inspection (SONIs) which will state the recommended date of the next inspection.

ii. EEA or third country sites that have not been previously inspected

If the centre is operated by a parent company that already operates other centres that are included in the manufacturers' PMF then Supervisory authorities should carry out a distant assessment for individual centres. Supervisory authorities will issue

[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.

Statements of Next Inspection (SONIs) which will state the recommended date of the next inspection.

A clarifying remark will be made in the SONI:

"Due to the restrictions caused by COVID-19, the period of validity of the SONI in effect at the time of declaration of the pandemic by WHO is extended applying inspection and control measures in line with EMA recommendation EMA/INS/GMP/534269/2018 "Application of inspection and control measures...". On-site inspections will resume as soon as there is a consensus that the period of the public health crisis has passed. The clarifying remark section of individual SONIs will indicate any exceptions. Competent authorities reserve the right to inspect a blood establishment should the need arise".

If the outcome of the distant assessment does not permit the approval of the establishment, a clock-stop will be triggered until an on-site inspection is possible.

If the Centre is operated by a parent company that has never previously been inspected or where the parent company is in a compliance management programme then an on-site inspection will be required.

2.4. 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.

[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.

2.5. 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]

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*.

[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-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

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[12].

4. PHARMACOVIGILANCE ACTIVITIES

4.1. 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,

[12] For electronic submissions made to EMA, COVID-19 related applications should be indicated by selecting YES to 'COVID19 related' flag in the eSubmission Gateway XML delivery file user interface.

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.

4.2. [NEW] Is there any impact on corrective and preventive actions management under the pharmacovigilance provisions?

According to Article 11(1)(e) of Commission Implementing Regulation (EU) No 520/2012, Marketing Authorisation Holders (MAHs) shall put in place specific quality system procedures and processes in order to ensure the effective communication with the national competent authorities and the Agency on corrective and preventive actions.

During the pandemic situation MAHs might activate business continuity plans and prioritise activities. Therefore, in case MAHs are unable to continue standard management of corrective and preventive actions, for justified reasons relating to the pandemic, they should temporarily prioritise the deviations by applying risk-based approach taking into account relative criticality of the deviation to risks impacting the pharmacovigilance system, processes and parts of processes.

Any deviation from the processes and procedures, due to the prioritisation of activities during the pandemic, should be duly recorded as soon as identified, limited in time and should be addressed and closed when the circumstances permit so, taking into consideration the management of backlogs.

4.3. [NEW] Is there any flexibility in the planning and conduct of pharmacovigilance system audits?

According to Article 13(1) of Commission Implementing Regulation (EU) No 520/2012, MAHs shall perform risk-based audits of the quality system at regular intervals to ensure that the quality system complies with the quality system requirements set out in Articles 8, 10, 11 and 12 and to determine its effectiveness. Those audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited. According to Article13

(2) of the Regulation, corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary. A report on the results of the audit shall be drawn up for each audit and follow-up audit and sent to the management responsible for the matters audited.

During the current pandemic MAHs may need to activate business continuity plans and prioritise activities. This may have an impact on planned audits. Any adaptation in the planning and conduct of audits should be based on a risk-based approach with all decisions clearly justified and duly documented as part of a prioritisation strategy. For cause audits should be prioritised and planned audits should be conducted as soon as possible and without undue delay.

Before considering to delay a planned audit, alternative approaches, such as remote audits may need to be considered in the short-term. Where a decision has been made to conduct remote audits, the MAH should consider how these audits will ensure the independent and objective evaluation of the fulfilment of pharmacovigilance requirements by the auditee. This would typically involve a mixture of interview sessions (e.g. via telephone or video conferencing) and document review. Utilising questionnaires alone, without supporting evidence, would not be accepted as audits[13]. Partners should be kept informed on the overall risk-based strategy. In case of uncertain results, a follow up audit shall be performed as soon as possible.

4.4. [NEW] Which measures will be taken in light of difficulties to conduct on-site pharmacovigilance inspections during the COVID-19 pandemic?

During the COVID-19 pandemic, on-site inspections may not be possible due to multiple factors including difficulties and restrictions related to travelling between and within the countries, restrictions to accessing facilities and additional health risks for inspectors and inspectees. Regulatory authorities also may need to prioritise, reduce or postpone certain activities and look for alternative ways of supervision using a risk-based approach. For pharmacovigilance inspections that are part of pharmacovigilance inspection programmes and cannot be conducted on-site, a remote inspection may be considered, if appropriate and feasible. Decision on "for cause" inspections should be considered on a case-by-case basis by inspectors and concerned assessors, as applicable, to determine whether a remote inspection is feasible and it could fulfil the purpose of the requested inspection.

Remote inspections should follow, where applicable, the guidelines that already exist for the conduct of pharmacovigilance inspections but should also take into consideration the limitations imposed by using a remote process. It is fundamental to ensure that the inspectee meets the technical requirements to provide remote access to electronic systems, as well as maintains communication with and provides support to inspectors. During the remote inspection initiation phase, the inspectee should provide detailed information as requested by the inspectors to allow a feasibility assessment by the inspection team[14].

[13] See footnote 3 of the Guideline on Good Pharmacovigilance practices, Module IV.

[14] See also related information: Good pharmacovigilance practice Module III– Pharmacovigilance inspections (see section GVP Module III.B.1.7. Remote inspections and Distant/virtual pharmacovigilance inspections of MAHs during a crisis situation- Points to consider.

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.[15]

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.

6. ADDITIONAL TEMPORARY GMP AND GDP FLEXIBILITY

6.1. Introduction

To help manufacturers and distributors of pharmaceutical products to cope with the consequences of the pandemic and ensure availability of medicinal products to respond to increased demand, following provisions have been made to allow for some extraordinary GMP and GDP flexibility.

In case national legislation in EEA member states already provides legal tools for such extraordinary situations, these national tools need to be triggered before applying parts of the proposed measures.

Member States are encouraged to facilitate appropriate implementation of this harmonised guidance in order to minimise the disruption of manufacturing and supply of crucial medicines in EEA during the public health crisis.

[15] 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).

At the same time, holders of marketing authorisations, manufacturing and import or wholesale distribution authorisations need to take into account that national legislation and derogations cannot be superseded.

The potential implication of simultaneous use of multiple regulatory/GMP flexibilities should be appropriately assessed as part of a comprehensive risk management process.

GMP Flexibilities

6.2. When new lines or re-purposed facilities are to be used to ensure continuous availability of crucial medicines for treatment of COVID-19 patients (e.g. through use of ECMP), is it possible to:

i. Introduce premises and/or equipment into use following limited prospective qualification?

Yes, when relocation or extension of production is deemed necessary to ensure continuous availability of these crucial medicines it may be possible that the premises and/or equipment could be introduced into use following limited prospective qualification, providing that:

- Formal application of Quality Risk Management is used to determine the required scope and extent of the limited prospective qualification in order to proceed to the next level of qualification/validation.

- Additional risk mitigation measures are adopted, as required, to verify acceptable ongoing performance and ensure product quality.

- All decisions are documented within the pharmaceutical quality system (PQS) and approved by authorised personnel, including the Qualified Person.

- Regular qualification tasks are resumed as soon as COVID-19 restrictions are lifted.

- The results of the limited prospective qualification together with the experience from usage of the premises / equipment is reviewed against routine qualification expectations and a programme put in place to address any gaps identified.

ii. perform concurrent validation of a manufacturing process?

Yes, for crucial medicines for treatment of COVID-19 patients and where delay in supply may affect those treatment , it is acceptable to conduct process validation concurrently rather than prospectively.

The use of a concurrent validation approach according to the provisions given in Annex 15[16] should be documented within the pharmaceutical quality system (PQS) and approved by authorised personnel including the QP. It should also be supported

[16] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10_annex15.pdf

by application of quality risk management principles using an appropriate approach such as described in ICH Q9[17] within Part III of the GMP Guide[18].

Where a concurrent process validation approach is employed, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria.

All related equipment and testing methods should be appropriately qualified and validated prior to commencing concurrent process validation.

For sterile medicinal products, the processes that assure sterility must be prospectively validated. This would include any sterilisation process for a terminally sterilised product, sterilisation of equipment used in aseptic processing and completion of aseptic process simulations for an aseptically produced medicine.

The manufacturing process and quality control requirements for the medicinal product must reflect the details as approved under the Marketing Authorisation. Without prejudice to any flexibilities available through the exceptional change management process (ref Q&A 2.1), any changes to the manufacturing process itself or the quality requirements (ref Q&A 3.1) must be approved in advance through the existing variation process under Commission Regulation (EC) No 1234/2008.

6.3. Is it possible to implement temporary changes to certain scheduled quality related tasks in order to free resources for ensuring continued supply of crucial medicines used for treatment of patients infected with Covid-19?

Yes, where necessary temporary changes in elements of the quality system may be introduced to enable redirection of resources to focus on supply of crucial medicines, provided that the changes do not adversely impact quality, efficacy and safety of medicinal products manufactured on the site.

Such temporary changes should be managed transparently within the pharmaceutical quality system (PQS) and documented according to GMP Guideline Chapter 4.

Quality risk management should be employed using an appropriate approach such as described in ICH Q9 to assess the impact of the temporary change.

The Qualified Person should be made aware of any planned changes and these temporary changes cannot be used to facilitate certification of batches affected by non-compliance with registered specifications.

If appropriately justified, temporary changes could apply to deferral of certain routine operations such as:

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[17] ICH Q9 specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions in the context of the crisis.

[18] https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf

- Maintenance, requalification, revalidation, recalibration,
- Periodic review of PQS documents,
- On sites re-audits of suppliers, and replacement by remote audits,
- Periodic re-trainings,
- Deferral of stability testing, where justified, to focus resources on product release testing.

6.4. What temporary flexibilities can be employed to address imminent market shortage of imported medicines, which are crucial for treatment of COVID-19 patients?

i. Postponing or waiving the testing in the third country?

In order to make such medicinal products, more rapidly available, it may be justified for the QP to temporarily postpone or, if necessary waive the testing in the third country and receive the product under quarantine in the EU without a certificate of analysis. This should be recorded as a deviation from the normal process. The batch should be fully tested in the EEA in accordance with the requirements of the marketing authorisation prior to decision on certification of the batch by the Qualified Person.

ii. Postponing certain testing in the EEA?

In certain situations, due to the extraordinary circumstances emerging from the COVID-19 pandemic, it may be necessary in justified cases to deviate from the requirement for importation testing in the EEA, prior to QP certification in order to prevent immediate shortage of crucial medicines for treatment of COVID-19 patients. Where there is imminent shortage, the QP may give consideration to certification of specified batch(es) of crucial medicines based on testing performed in a third country where it has been ascertained that:

a) The product has been deemed crucial for treatment of COVID-19 patients and is in short supply in the EEA market(s). Shortage in supply must be stated/confirmed by the relevant competent authority in the market concerned;

b) All the batch release tests specified in the marketing authorisation have been performed at the third country site and the results obtained comply with the finished product specification;

c) All of the testing in the third country has been conducted in facilities which have been GMP certified by an EEA supervisory authority or MRA partner;

d) Review of the testing history in the third county laboratory shows results consistent with the EU test results;

e) Identity testing of all the active substance(s) for each batch as described in the marketing authorisation, has been carried out in the EEA;

f) For biological products, specialist analyses, notably vaccine inactivation tests, continue to be performed in the EEA before batch certification;

g) The decision to certify the batch prior to completing full importation testing in the EEA has been recorded as a deviation in the pharmaceutical quality system and all supporting rationale for the decision included.

Any tests described in the marketing authorisation which had been postponed, should be carried out in the EU after certification. The relevant supervisory authority should be notified immediately if any test results subsequently obtained in the EEA for a released batch are found to be out-of-specification.

Any decision to postpone importation testing in the EEA should be notified in advance to the relevant supervisory authority, in order to enable the authority to take supervisory action, as appropriate.

GDP Flexibility

6.5. Which adaptations to the work of the Responsible Person (RP) are possible considering travelling, absenteeism and other restrictions arising from COVID-19 pandemic?

i. Remote working of the RP

If a regional or national government authority has implemented quarantine measures such as stay-at-home restrictions for entire regions or the whole country resulting in cancellation or prohibition of travelling, then remote working of the RP is permissible, limited to the duration of the restrictions, provided that :

- the RP has timely access to all information necessary to ensure that the wholesale distributor can demonstrate GDP compliance and that public service obligations are met.
- the RP can fulfil responsibilities specified in chapter 2.2 EU GDP Guidelines.

ii. Delegation of duties and responsibilities of an RP to another RP?

In case of comparable size, structure and complexity of distributor's activities and with prior approval by the competent authority, it could be acceptable for a RP designated by a wholesale distributor to temporarily take over the duties and responsibilities of another RP designated by a wholesale distributor in:

- Another branch(es) of the same group / company.
- Another company within the same group of companies.

When temporarily designated to the role, the RP should fulfil his responsibilities of the role personally. After a risk assessment has been performed to determine that the person has the resources and capacity to take on the additional responsibilities, a written job description should define those responsibilities and the authority to make decisions relevant to the role, in compliance with the principles of and guidelines of GDP.

iii. Delegation of duties of an RP to a person who is not a RP

When necessary, it is acceptable for a RP to delegate duties to an appropriately trained person designated by a wholesale distributor according to paragraph 2.3 of the GDP Guide. However, responsibilities for the correct execution of the duties remain with the RP.

iv. Replacement of the RP at short notice

It is recognised that under exceptional circumstances, like quarantine measures travel restrictions or longer absence due to sickness, it may become necessary to replace the RP at short notice. Agreement of the National Competent Authority should be sought in advance for replacement of the designated RP by an employee with appropriate competence, experience, knowledge and training in GDP or a third party RP.

If the newly designated RP within the timeframe of the COVID-19 crisis does not meet all the qualifications and conditions provided for by the legislation of the Member State concerned, the RP should at least have appropriate competence and experience as well as knowledge of and training in GDP to fulfil all delegated responsibilities.

Prior notification of the supervisory authority is necessary.

In all cases, the RP should have appropriate knowledge about the QMS of the new company.

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

6.6. Is it possible to use new equipment or newly authorised premises for storage and distribution of medicinal products with limited prospective qualification?

Yes, when relocation of medicines is necessary to meet demand within the timeframe of COVID-19 pandemic, new equipment or re-purposed equipment may be used with limited prospective qualification to allow it to be used as soon as possible.

Where prospective validation has been limited for premises and equipment used for the storage and distribution of medicines then this should be compensated by employing sufficient ongoing monitoring such that there is evidence that medicines are stored and transported under the required conditions. The principles of Quality Risk Management as per Chapter 1.5 of the EU GDP guidelines should be employed to determine the extent of ongoing monitoring required and the approach should be approved by the RP.

Special attention should be paid to equipment and premises used for the storage and distribution of products with specific handling instruction or storage conditions.

Agreement of the National Competent Authority should be sought before using any new premises for wholesaling activities.

The full qualification and validation should be completed without delay following this period.

6.7. Can I introduce planned deviations from normal practice (temporary change controls) in the context of the COVID-19 pandemic?

Yes, when documented within the quality system, approved by the RP and assessed on a case by case basis in accordance with a quality risk management process as per

Chapter 1.5 of the EU GDP Guidelines, temporary flexibility can be introduced as follows:

i. Documentation

The timeframe for the performance of routine Standard Operating Procedure (SOP) reviews can be extended during the period of the pandemic.

ii. Audits and internal audits

Where on-site audits of contract acceptors are not possible, the RP can rely on paper-based audits also and take into consideration the results of inspections or audits performed by third parties.

Remote audits should provide confidence that the contracted party is fit-for-purpose and will not negatively affect the wholesale distribution process.

The internal audit (self-inspections) schedule can be adapted, where necessary and under quality risk management, in order to free personnel for tasks deemed critical during the period of the pandemic crisis.

However, each situation should be assessed, documented and authorised on a risk based approach.

iii. Non-conformities and CAPA management

Following a risk assessment approved by the RP to determine the impact of a deviation or non-conformity, the implementation of CAPAs to address a deviation determined to have low risk to product quality or wholesaling activities, can be deferred. Investigations into events classified as 'minor' can also be deferred provided that the deferrals are tracked and resumed once pandemic restrictions are lifted.

The issuing of change management documentation in relation to CAPA implementation can be postponed in order to facilitate a faster and more flexible change management process, however, the approval of the change should be recorded. Remaining change management documentation should be completed retrospectively.

iv. Training

The company's training plan may be adapted with respect to routine retraining of experienced personnel to reflect prioritised needs during the period of the pandemic crisis.

Training of new and recently hired personnel should be conducted and special emphasis should be given to any current atypical working conditions.

The principles of quality risk management should be applied in determining appropriate prioritisation of training needs to ensure competence of the personnel with respect to the duties assigned to them.

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