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Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG)

## MSSG Toolkit on recommendations on tackling shortages of medicinal products

Guidance document for use by the MSSG to facilitate identification of recommendations on critical shortages of medicinal products

Step	Date
Consultation with Medicine Shortages SPOC WP, CMDh, QRD, IWG	31.08.2023
Endorsement by MSSG	6.10.2023

# 1. Introduction

Regulation (EU) 2022/123<sup>1</sup> (the Regulation) established the Executive Steering Group on Shortages and Safety of Medicinal Products (the 'Medicine Shortages Steering Group – MSSG') to ensure a robust response to major events or public health emergencies, including through provision of advice and recommendations on the necessary actions to safeguard the quality, safety and efficacy of medicinal products as well as to safeguard the supply of medicinal products and to ensure a high level of human health protection.

The Regulation provides a framework to be deployed by the Agency in preparation for and during public health emergencies and during major events, as defined in the Regulation, to enhance the Union's capacity to react quickly, efficiently, and in a coordinated manner to such emergencies.

The role of the MSSG is to ensure a robust response to major events/public health emergencies, and to coordinate urgent actions within the Union in relation to the supply of medicinal products. The MSSG also has a role in monitoring critical shortages<sup>2</sup> that could lead to a major event or public health emergency.

According to the Regulation, the MSSG shall provide recommendations to the Commission and Member States on any appropriate action that it believes needs to be taken at Union level on the medicinal products concerned in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004. The MSSG, on its own initiative or at the request of the Commission or a Member State, may also provide recommendations on measures that the European Commission (EC), Member States, marketing authorisation holders and other entities, including representatives of healthcare professionals and of patients, could take to prevent or mitigate actual or potential shortages of medicinal products or to ensure preparedness for dealing with actual or potential shortages of medicinal products.

The MSSG is supported by a working party comprised of single points of contact related to shortages from national competent authorities for medicinal products, the so-called Medicine Shortages SPOC Working Party (SPOC WP).

The SPOC WP is responsible for monitoring and reporting events that could affect the supply of medicines in the European Union. The SPOC WP may escalate availability events to the MSSG that are likely to lead to a major event or a public-health emergency.

This document is built on the experience gained by the European Medicines Regulatory Network during the COVID-19 pandemic, the experience acquired by dealing with critical shortages escalated by the SPOC WP since the MSSG was set up, and guidelines issued by the European Commission during the pandemic<sup>3</sup>. It enlists the main types of actions that MSSG should on a case-by-case basis consider recommending in order to tackle critical shortages that have been escalated to this forum. It includes both frequently-applied measures for tackling medicine shortages, as well potential measures that may only be appropriate in exceptional critical-shortage situations (i.e. would not need to be considered or applied for majority of cases that are managed at national or SPOC WP level). It is not, however, exhaustive and MSSG may also identify other recommendations that may be appropriate for the particular shortage situation.

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<sup>1</sup> [Regulation \(EU\) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices](#)

<sup>2</sup> Critical shortage means a critical shortage in the Member State for which coordinated Union level action is considered necessary to resolve that shortage.

<sup>3</sup> [Communication from the Commission. Guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak](#)

This is a living document that will be updated when needed, e.g. if additional types of recommendations on tackling critical shortages are identified.

## 2. Types of recommendations

Recommendations will be assessed by the MSSG on a case-by-case basis, considering their proportionality, and tailored individually according to the medical need and criticality of the shortage of concern. The MSSG will decide whether regular activities conducted by the SPOC WP remain adequate to manage the shortage or if exceptional flexibilities might be applicable. The MSSG will decide when recommendations are no longer required.

Among others, the MSSG can provide the following recommendations to prevent or mitigate actual or potential critical shortages of medicinal products:

### 2.1. *Monitoring of available stocks, supply and demand*

- Monitoring of medicinal products' demand forecast is essential for correct adjustments in their manufacturing and distribution to avoid or at least mitigate the impact of shortages.
- The MSSG may recommend monitoring forecasts of supply and demand for medicinal products for human use in the EU/EEA and monitoring of available stocks in the whole supply chain.

### 2.2. *European cooperation*

- Monitoring of events and the supply situation by the SPOC WP. Creation of specific subgroups which could be composed of multidisciplinary experts to monitor relevant events more closely.
- Liaison with the Commission to establish measures that could be undertaken at EC level to mitigate the impact of shortages (see also steps for increasing supply in section 2.3).
- Liaison with the European Directorate for the Quality of Medicines & HealthCare (EDQM) to establish measures in the context of European Pharmacopoeia monographs and certificates of suitability to support mitigation of shortages (see also steps for use of pharmaceutical preparations in section 2.3).

### 2.3. *Increase supply and fair distribution of medicinal products*

- **Interactions with marketing authorisation holders (MAHs) and manufacturers**– Interactions with companies at national level and by EMA to agree possible mitigating measures to address the current shortages, among others:
  - Increase in manufacturing capacity (increase of manufacturing shifts) of medicinal/s product/s involved or their alternatives;
  - Reorganisation of manufacturing capacity (use of alternative manufacturing lines or facilities, for some medicines manufacture of large volumes to increase the number of patients reached);
  - Establishment of minimum safety stocks;
  - Redistribution of available stock among member states to address urgent needs.

- **Identification of alternative treatments<sup>4</sup> in third countries that could be imported for use in the EU** – collection of information on possible alternatives outside EU and their possible availability can enable additional supplies of required products. Consideration of importation of medicinal products from trusted countries<sup>5</sup> should receive priority treatment. See also steps for allowing use of unauthorised medicines in section 2.4.
- **Gap analysis** – Ad-hoc assessment to provide supporting information for individual national decisions on importation of unauthorised product (see also section 2.4. ).
- **EU purchases** – Use of mechanisms in place to facilitate central negotiation and central or joint purchase of medicines for EU/EEA Member States.
- **Use of pharmaceutical preparations (e.g. magistral or officinal) where appropriate** - These preparations may be used to replace unavailable medicines. The EDQM is drafting a **methodological guide** for selecting medicines at risk of shortage during public health emergencies that can be prepared as standardised stock preparations, and a **European Shortages Formulary** consisting of texts (monographs) for the temporary preparation and quality control of unlicensed medicines in case licensed medicinal products are unavailable and whose active substances are not affected by a shortage that should be taken into account.
- **Use of veterinary medicines where appropriate** – Use of equivalent medicines (the same active substance and suitable strength and pharmaceutical form) authorised for veterinary use should be considered to address critical shortages of medicinal products for human use in exceptional circumstances. See also considerations on regulatory flexibilities in section 2.4.
- **Controlled distribution** - Optimisation of sales in dispensing pharmacies and healthcare institutions to ration existing stocks and ensuring that patients with highest need get treatment. Restriction of number of units dispensed.
- **Advice on alternative clinical protocols or dose-sparing measures to ensure continuity of care** – National positions, possibly supported by an EU-level scientific input, or a common EU position, with advice on use of therapeutic alternatives, as appropriate.
- **Lifting of export restrictions at national level and other recommendations to ensure a fair distribution of medicines to patients regardless of where they live.**

#### **2.4. Implementation of regulatory flexibilities**

In order to prevent or mitigate critical shortages<sup>6</sup> of medicinal products the MSSG may recommend application of the below-listed flexibilities by the respective competent authorities. The competent authorities can decide whether to apply the recommendations on a case-by-case basis considering the context, the justification provided and the specific MSSG recommendation.

When nationally authorised products are concerned, CMDh should be informed to enable promotion of harmonised implementation of regulatory flexibilities.

While most of the measures can be used to address any medicine shortages including those that have not been escalated to MSSG (e.g. labelling exemptions or allowing importation of non-authorised medicines), **some measures**, marked below as “**Exceptional:**” (e.g. use of Exceptional Change

<sup>4</sup> This may include products with same active substance(s) or therapeutic alternatives containing other substance(s)

<sup>5</sup> Countries with comparable stringent regulatory standards and mature regulatory systems. See e.g. definition of trusted authorities in the [Compilation of Union Procedures on Inspections and Exchange of Information](#)

<sup>6</sup> Critical shortage means a critical shortage in the Member State for which coordinated Union level action is considered necessary to resolve that shortage.

Management Process or batch-specific deferral for release testing in the EU), **are reserved for exceptional situations** and should only be applied based on a recommendation from MSSG (i.e. their application cannot be proposed by the manufacturers and marketing authorisation holders, but rather initiated only by regulatory authorities), and only in cases where other measures are not sufficient. The 'Exceptional' measures are expected to be applied, as warranted, in case of a public health emergency, a major event and in a limited number of other cases of critical shortages of a given medicine that have been discussed by the MSSG and for which other Union-level co-ordinated actions (or mitigation measures) have not resulted in the shortage being resolved, and after careful consideration, on a case-by-case basis, of all options and of the severity of the situation in order to protect the health of patients. Such MSSG recommendation may cover a particular critical shortage situation, a defined number of medicinal products, or a category of medicinal products with shortages related to a particular major event or public health emergency (e.g. shortages of various ICU medicines during a pandemic).

While most of the regulatory flexibilities are agreed and applied at national level, the MSSG may agree on a coordinated approach at EU level for their acceptance by MSs in certain situations. The MSSG may also consider the need for an EU-wide scientific position to support application of the flexibilities and request such input from respective scientific bodies.

The impact of any deviations from the terms of the marketing authorisation on the quality, safety and/or efficacy will be carefully evaluated, and distribution of batches might be allowed provided that the risk-benefit balance remains positive (benefits outweigh the risks).

- **Flexibilities facilitating prompt implementation of changes to alternative (sources of) raw materials, manufacturing site(s), manufacturing equipment, packaging, batch size, and other changes to enable increased production and support sparing use of the product:**
  - Use of Post-Approval Lifecycle Management Protocols (PACMP) to facilitate rapid implementation of changes as soon as the pre-agreed, required supportive data are available;
  - Facilitated variations including accelerated timetables for required variations for introduction of new suppliers, sites, equipment etc. or for changes to the medicinal product itself that may help to mitigate shortages (e.g. introduction of optimised packaging sizes that help reducing waste, or larger primary and/or secondary packaging that alleviates a bottleneck in production capacity). When in exceptional circumstances for a centrally authorised medicine accelerated timelines for adoption of the commission decision on the required variations might be needed, they should be proposed to the Commission, who will decide on a case-by-case basis considering the context and the justification provided for the specific urgency of the request.
  - Enhanced cooperation among national competent authorities on prompt review and approval of urgent variations for nationally authorised products, in particular through the use of formal and informal work-sharing procedures or other types of reliance on an assessment conducted by another authority.
  - Reliance on outcomes of inspections conducted by other authorities and, when appropriately justified and agreed by the supervisory authorities, distant assessment<sup>7</sup> for

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<sup>7</sup> Distant assessment is not expected to accelerate compliance verification but may enable in some cases where otherwise it may not be possible.

an accelerated GMP compliance status confirmation for new manufacturing sites or an extended scope at existing sites.

- Application of scientific tools which can offer flexibility in terms of the timepoint for full completion of certain quality data packages by analogy to the Toolbox guidance for PRIME and marketing authorisation applications targeting an unmet medical need.<sup>8</sup> For example, deferring provision of some process validation data supporting required changes to post-approval, defining shelf-life based on stability models and/or supportive knowledge.
- **Exceptional:** when the respective change is not subject to prior regulatory approval, use of exceptional flexibilities under GMP and GDP concerning limited prospective qualification and postponement of certain testing in the third country or the EEA. See further details on the application of such exceptional flexibility in Annex II.
- **Exceptional:** allowing application of Exceptional Change Management Process (ECMP) that enables implementation of certain changes for which it has been established that they will prevent or mitigate a critical shortage, and which otherwise would be subject to prior regulatory approval, based on a simple notification, with a formal variation to be submitted afterwards within defined timelines. See further details on the application of such exceptional flexibilities in Annex II. Changes proposed under ECMP should be carefully considered depending on the particular circumstances and may include, for example, introduction of new manufacturing sites or suppliers (with related required minor adjustments), scaling up of production in existing sites, or change to alternative packaging materials. Prior discussion with the regulator before notification and application of ECMP is essential.
- **Flexibilities to support agile product redistribution between markets**
  - Full or partial exemption from certain labelling and packaging requirements for authorised products to be agreed by respective national competent authorities (NCAs)<sup>9</sup>. These may include *inter alia* local language exemptions, reduced information on the packaging, alternative ways of providing certain labelling information and other exemptions.

**Exceptional:** the MSSG may recommend developing a specific, harmonised EU-wide approach to labelling flexibilities in certain situations, based on voluntary agreements among competent authorities, who retain the ultimate decision making on their application<sup>10</sup>.
  - Allowing importation of non-authorised products – EU pharmaceutical legislation contains certain provisions that allow Member States to authorise, in accordance with their national legislation, the supply of medicines without a marketing authorisation. In particular, use of exceptions foreseen in Articles 5(1), 5(2) and 126a of Directive 2001/83/EC should be considered, where relevant. See also identification of alternative treatments in third countries described in section 2.3. National authorities retain ultimate decision making on application of these exemptions.
  - Release by the Qualified Person (QP) of a product with deviations from the requirements set in the EU marketing authorisation that do not have any substantial impact on safety or

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<sup>8</sup> See [Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need](#)

<sup>9</sup> Certain labelling exemptions for centrally authorised products are agreed by the QRD group, see [Recommendations for the implementation of the exemptions to the labelling and package leaflet obligations in the centralised procedure](#)

<sup>10</sup> e.g. as put in place during COVID-19 pandemic through a [Memorandum of Understanding](#) and QRD guidance for [vaccines](#) and [therapeutics](#)

efficacy of the product (e.g. due to a minor quality defect or for a product that originally has been produced for other markets with differences in the authorisation dossier), subject to agreement by the Rapporteurs/ Lead MS, Supervisory Authority (SA) for the EU batch release site and respective local NCAs for the impacted MSs.

- **Exceptional:** Batch-specific waiver of deferral of certain requirements for the release of a medicine on EU market (e.g. for repetition of batch testing in the EU), following careful consideration of possible implications for the quality of the medicine concerned and the urgency and extent of public health needs.
- **Shelf-life extension**
  - Potential shelf-life extension for individual batches already released, subject to decisions by local NCAs and the supervisory authority for the EU batch release site. Upon a request from MSSG in the context of critical shortages (from EU perspective), the EMA may in certain cases facilitate an assessment of available data to support national decision making.

## 2.5. Communication and engagement

- **News announcements and public health communications** – These can be issued to provide information to the public on critical shortage situations and on measures taken at EU level to address shortages of medicines in the EU, promoting the rational use of such medicines and providing reassurance to the public.
- **Lines to take** – LTTs provide messages that are not intended for publication but to support the network when addressing media queries on critical shortages.
- **Shortages catalogue** – The European Medicines Agency (EMA) publishes information on medicine shortages that affect or are likely to affect more than one European Union (EU) country, where it has assessed the shortage and provided recommendations to patients and healthcare professionals.
- **Direct healthcare professional communications** – Direct communication to HCPs on medicinal products affected by the shortage to inform them of the need to take certain actions or adapt their practices in relation to the medicine affected by the shortage.
- **Liaison with stakeholders** – Early and continuous engagement with European industry, healthcare professionals, patients and Learned Societies to get their perspectives on critical shortages, their impact and possible mitigation.

## 2.6. International cooperation

- Exchange of information with **international regulators** including request for information on authorised manufacturers to explore the possibilities to increase supply to Europe on a temporary basis without creating a shortage situation in other jurisdictions.

# 3. Adoption of recommendations by the MSSG

At the request of the MSSG, the SPOC WP shall support the development of the set of recommendations to prevent or mitigate actual or potential shortages of medicinal products.

The MSSG may consult the EMA Scientific Committees, their working parties, other expert groups including the Emergency Task Force (ETF) and/or the CMDx.

The procedure for the adoption of recommendations by the MSSG is described in article 4 of the Rules of Procedure.

## **4. Publication of recommendations**

Article 14 of the Regulation lays down the communication regarding the MSSG.

Recommendations will be documented in the minutes of the MSSG.

## **5. Reporting to EMA on recommendations from measures taken at Union level**

According to article 11.4 of the Regulation, Member States shall take into account any recommendations and guidelines issued by the MSSG or the EC in response to a public health emergency or major event, inform the MSSG of any measures taken and report on the results of those actions.

These recommendations and guidelines shall be shared with the SPOC WP and impacted scientific committees and working parties at EMA, as appropriate, to be considered at national level.

Member States, through the SPOCs, shall inform the MSSG Secretariat promptly of any measures taken and report on the results of those measures, including information on the prevention of potential or resolution of actual medicine shortages. For this purpose, the SPOC WP will use a dedicated template (Annex I).

Where an alternative course of action has been taken at a national level, the Member State(s) where such alternative course of action occurred shall promptly share, through the SPOC, the reason(s) with the MSSG via the MSSG Secretariat at EMA using the dedicated template (Annex I).

The MSSG Secretariat shall collect the information including alternative actions taken at national level and will share it with the MSSG, either at the following MSSG meeting or in writing, depending on the urgency.

**Annex I – TEMPLATE FOR MEMBER STATES TO REPORT ON MEASURES TAKEN, RESULT OF ACTIONS, ALTERNATIVE COURSE OF ACTION**

**Member State:**

Measure taken	Date	Result including resolution of the actual or potential shortage

Alternative course of action	Date	Reason for the adoption of alternative actions

## **Annex II - Internal guidance on application of certain exceptional regulatory flexibilities**

### ***Exceptional Change Management Process***

An exceptional change management process (ECMP) can be made available to MAHs only in exceptional cases. The ECMP permits the swift implementation of changes to suppliers and/or manufacturing/control sites (with related required minor adjustments), scaling up of production in existing sites or change to alternative packaging materials necessary to reduce the risks of shortages. The ECMP is subject to certain conditions intended to ensure the quality of the medicinal product, while deferring the full assessment of the variation. Under the ECMP, MAHs are 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 are 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. Related minor adjustments), scaling up of production in existing sites or change to alternative packaging materials may also be included. The ECMP is only available in case of a recommendation from MSSG and based on instructions provided by the relevant competent authorities (EMA for centralised marketing authorisations). ECMP is not applicable in cases when all required related changes can be introduced through type IA variation(s).

### **Scope**

The ECMP can be made available for the following changes:

- Changes in the manufacturing and/or control sites that are necessary to prevent/mitigate critical shortages of supplies in the EU and related required minor adjustments.
- Changes in suppliers of starting materials, reagents, intermediates or active substances where that is necessary to prevent/mitigate critical shortages of supplies in the EU and related required minor adjustments.
- Scaling up of production in existing sites if it is necessary to prevent/mitigate critical shortages of supplies in the EU.
- Change to alternative packaging materials if it is necessary to prevent/mitigate critical shortages of supplies in the EU.
- Other changes necessary to prevent/mitigate shortages of supplies in the EU, following a careful considerations on case by case basis of the risks involved and the urgency and extent of public health needs to avoid or mitigate the shortages concerned.

Changes proposed under ECMP should be carefully considered depending on the particular circumstances. The need for an EU wide scientific position, based on input from respective scientific bodies, to support application of ECMP may be considered.

### **Procedure**

1. It is foreseen that MSSG would only recommend use of ECMP in cases where it is expected that its use for certain product(s) will prevent or mitigate a critical shortage that could not be mitigated by the means of other measures. Following MSSG recommendation, the respective competent authority/-ies (in case of centrally authorised medicine – EMA) should inform the respective

MAH(s) that use of ECMP may be considered and organise a discussion with the MAH(s) to discuss suitability and possible scope of ECMP in the particular situation.

2. If the use of ECMP is deemed appropriate, concerned MAHs that wish to rely on the ECMP should be instructed that they 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:
  - a) Specify the intention to use the ECMP for the specific medicinal product.
  - b) State the medicinal product concerned.
  - c) Provide a summary description of the changes that will be implemented. Such notification should be submitted for each change (e.g. supplier and/or manufacturing/control site) that is implemented under the ECMP.
  - d) 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 must 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 (it is acknowledged that the GMP certificate for the site may not specifically cover the medicinal product at stake). If the latter conditions are not met, a variation in accordance with Commission Regulation (EC) No 1234/2008 should be submitted.
  - e) 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.
  - f) Commit to submit the corresponding variation application to the competent authorities no later than within 6 months following the implementation of the change.
3. The relevant competent authority will assess the notification and specifically whether the application falls within the agreed scope (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 should be informed whether the relevant competent authority has agreed to the application of the ECMP. The MAH should also be informed, prior or upon submission of the notification, that 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.
4. The MAH should be instructed that, within 48 hours after the change is implemented by the MAH, a notification is to be 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.
5. The MAH should be instructed that within 6 months after the implementation of the respective changes, a corresponding variation covering the implemented changes must be 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.

**Important remarks:** THE MAHs should be reminded that other changes falling outside the scope of ECMP should be notified as a variation and that absence of the submission of the relevant variation constitutes a breach of the obligations of the MAHs. It should be highlighted that 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).

#### ***Limited prospective qualification (under GMP)***

When new lines or re-purposed facilities are to be used to ensure continuous availability of medicines (e.g. through use of ECMP), it is possible in exceptional cases, based on a recommendation from MSSG, to accept introduction of premises and/or equipment into use following limited prospective qualification. In such cases the respective MAHs should be informed by respective competent authority (for centrally authorised medicines – by EMA) in coordination with the Supervisory Authorities that for relocation or extension of production of concerned 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 possible.
- 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.

The SA may decide to conduct an inspection according to a risk-based approach at a later stage to verify the correct implementation.

#### ***Concurrent validation of a manufacturing process (under GMP)***

When new lines or re-purposed facilities are to be used to ensure continuous availability of medicines (e.g. through use of ECMP), it is possible in exceptional cases, based on a recommendation from MSSG, to accept performance of concurrent validation of a manufacturing process. In such cases the respective MAHs should be informed by respective competent authority (for centrally authorised medicines – by EMA) in coordination with the Supervisory Authorities that it is acceptable to conduct process validation concurrently rather than prospectively for the medicinal product concerned, provided that:

- The use of a concurrent validation approach according to the provisions given in Annex 15<sup>11</sup> should be documented within the pharmaceutical quality system (PQS) and approved by authorised personnel including the QP. It should also be supported by application of quality risk management

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<sup>11</sup> [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10\\_annex15.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10_annex15.pdf)

principles using an appropriate approach such as described in ICH Q9<sup>12</sup> within Part III of the GMP Guide<sup>13</sup>.

- 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, any changes to the manufacturing process itself or the quality requirements must be approved in advance through the existing variation process under Commission Regulation (EC) No 1234/2008.

The SA may decide to conduct an inspection according to a risk-based approach at a later stage to verify the correct implementation.

#### ***Postponing or waiving the testing in the third country for imported medicines***

For imported medicines it is possible in exceptional cases, based on a recommendation from MSSG, to accept temporary postponing or waiving the testing in the third country. In such cases the respective MAHs should be informed by respective authority that 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, subject to following conditions:

- 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.

#### ***Postponing certain testing in the EEA for imported medicines***

For imported medicines it is possible in exceptional cases, based on a recommendation from MSSG, to accept to temporary deviate from the requirement for importation testing in the EEA, prior to QP certification. In such cases the respective MAHs should be informed by respective competent authority where there is imminent shortage, the QP may give consideration to certification of specified batch(es) of concerned medicines based on testing performed in a third country where it has been ascertained that:

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<sup>12</sup> 6 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.

<sup>13</sup> [https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use\\_en-3.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf)

- The product is in short supply in the EEA market(s) and the application of this measures for the particular product has been agreed by the respective competent authority based on a recommendation from MSSG.
- Shortage in supply must be stated/confirmed by the relevant competent authority in the market concerned;
- 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;
- 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;
- Review of the testing history in the third county laboratory shows results consistent with the EU test results;
- Identity testing of all the active substance(s) for each batch as described in the marketing authorisation, has been carried out in the EEA;
- For biological products, specialist analyses, notably vaccine inactivation tests, continue to be performed in the EEA before batch certification;
- 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.

### ***Limited prospective qualification (under GDP)***

It is possible in exceptional cases, based on a recommendation from MSSG, to accept use new or re-purposed equipment or newly authorised premises for storage and distribution of medicinal products with limited prospective qualification, to allow it to be used as soon as possible when relocation of medicines is necessary to meet demand within short timeframe. In such cases the respective MAHs or distributors should be informed by respective competent<sup>14</sup> and/or supervisory authority that the equipment may be used with limited prospective qualification, provided that:

- Where prospective qualification 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 Responsible Person (RP).

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<sup>14</sup> for centrally authorised medicines – by EMA

- 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 SA may decide to conduct an inspection according to a risk-based approach at a later stage to verify the correct implementation.

The full qualification should be completed without delay.