2 November 2023

European Commission, Directorate-General for Health and Food Safety

Reference: CELEX number: 52023PC0193
Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006
COM/2023/193 final

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the above-referenced **Regulation**. ISPE has the following high-level comments for consideration.

- **Collaborative mechanism to advise on regulatory discretion proposals** The Agency should consider a collaborative mechanism to advise on regulatory discretion proposals in advance of potential, substantial disruptive events. This collaborative mechanism could minimize product unavailability for patients. For example, products that require a Risk Management Plan and Shortage Mitigation Plan (regulatory plans) would present a meaningful impact to patients if unavailable. For these products the applicant holder could, as appropriate, proactively share their regulatory plans, which could include regulatory discretions, with the Agency for comments and suggestions.
- **Application of Risk-Based Approaches for Drug Shortage Prevention and Mitigation Plan** Ensuring availability of medically necessary drug products for patients in all end-markets is of paramount importance and ISPE believes that steps to address risks or offset supply disruptions with significant impact to patients should be rigorous. Applying similar levels of rigor and formality for less significant supply disruptions could dilute limited resources and reduce focus on ensuring a continuous supply of medically necessary products for the most vulnerable patient populations. Many of the following recommendations are intended to provide appropriate risk-based flexibility for the mitigation or prevention of drug shortages in alignment with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH Harmonised Guideline -Quality Risk Management Q9(R1) to ensure a risk-balanced, resource-effective approach for both industry and the Agency.
- **Harmonization Opportunities** Terminology for aligned expectations (e.g., Critical Medicinal Products, Required Reporting Timeframes) should be standardized across the EU and ideally with other regulatory agencies
- **System Interoperability & Transparency** Proprietary Information shared by MAH with Agency should remain confidential and secure.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. The 21,000+ members of ISPE lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

Specific comments on the articles are attached.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

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ISPE President and CEO
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cc: Scott Billman, ISPE Chair

Response to a request for comments EUC 52023PC0193

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

General Comments
ISPE welcomes the supply chain provisions that are included in the regulation. Supply chain provisions should be maintained in the regulation to allow an EU-wide approach.
Regarding *International regulatory cooperation,* ISPE acknowledges and supports the need for harmonization between regulatory authorities in many activities regarding medicinal products not only in marketing authorisation and inspection but also in **drug shortage prevention.** Harmonization between Member States is requested to optimize resources for both MAH and regulators, as well as ensure complete and robust shortage mitigation plan construction.
The Proposal should consider a collaborative mechanism to advise on regulatory discretion proposals in advance of potential, substantial disruptive events. This collaborative mechanism could minimize product unavailability for patients. For example, for products that require a Risk Management Plan and Shortage Mitigation Plan (regulatory plans) would present meaningful impact to patients if unavailable, the applicant holder could, as appropriate, proactively share their regulatory plans with the Agency for comments and suggestions.
The regulatory sandbox is an innovative concept and a valuable tool to “future-proof” regulation and is viewed very favorably. However, it is unclear how to apply the regulatory sandbox concept to CMC innovations/pathways. Comments to specific text are provided below.
There should be coordinated and designated communication between the MAH to the respective Competent Authorities, and requests for additional information from MAH, to ensure accurate, timely, and up-to-date information. When the Union requires further detail from MAH relevant to a shortage situation requiring Union level coordination, there should be designated points of contact (POCs) at the Member State level with which the MAH directly communicates. This will ensure the efficient utilization of resources from both Industry, as well as Regulators, and limit the potential for inaccurate, misleading, or duplicative efforts.
ISPE recommends that the scope of a critical medicinal products list is coordinated at the EMA level, to avoid complexities or discrepancies between EMA and each Member State, and between member states. For a global company that markets products across the European Union, the development and management of risk assessments, shortage prevention plans, and shortage mitigation plans become a significant investment and challenging to meet both local, European level, and global expectations.
Implementation of the Shortage Prevention Management Plans for all products could be very challenging for companies with large portfolios or complex supply chains. Additionally, manufacturers may need time to incorporate requirements for information sharing in their quality agreements with suppliers and CMOs. Consequently, Competent Authorities should consider the inclusion of an implementation period of at least 1 year from the publication of the final regulation prior to requesting Risk Assessments of the Impact of Suspension, Cessation, Withdrawal, Shortage Prevention Plans, or Mitigation Plans.

Specific Comments on the Text: ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Article 2	(15) 'critical shortage in the Member State' means a shortage of a medicinal product, for which there is no appropriate alternative medicinal product available on the market in that Member State, and that shortage cannot be resolved.	(15) 'critical shortage in the Member State' means a shortage of a**n essential** medicinal product, for which there is no appropriate alternative medicinal product available on the market in that Member State, and that shortage cannot be resolved.	We appreciate the Agency's efforts to focus and prioritize shortage efforts on a specific subset of products that are significant to patients, where insufficient supply results in serious harm or risk of serious harm to patients. The current proposed definition could apply to any product where there is no appropriate alternative, such as a cosmetic product without an alternative, which is not medically significant. Consider clarifying that a critical shortage is a shortage of an "essential" medicinal product, for which there is no appropriate alternative MP available. Comment: ISPE suggests not introducing new terminology to classify medically significant products. Currently, there are several terms to classify these products, e.g., Essential medicines, Major Therapeutic Interest products, etc. We anticipate potential divergences between EMA critical medicines and critical shortages and essential medicines and shortages in Member States. Refer to the guidance issued by EMA-HMA EMA/632473/2018 and EMA/674304/2018. To achieve harmonisation and transparency across Member States as well as other countries outside of Europe, we suggest the adoption of an existing term, such as 'Essential Medicines'. If this is not possible, we request clarification to differentiate a critical medicinal product from an essential medicine.
Article 113.4	"The Agency shall not recommend to set up a regulatory sandbox for a medicinal product that is already advanced in its development programme."	ISPE recommends this statement be revised or removed;	The Agency should be able to maintain discretion regarding when it is appropriate to set up a regulatory sandbox. CMC innovations may be introduced pre- or post-approval and it is potentially desirable that a regulatory sandbox could usefully be applied to these innovations. These innovations may be considered advanced in development.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Article 113.5	"the plan [for a regulatory sandbox] should include a proposed timeline for the duration of the sandbox."	The proposal should consider carefully how the text relating to timelines could apply to regulatory sandboxes created for new CMC innovations.	Where the sandbox relevant to a CMC innovation includes derogations to regulation (as described in article 114.3, the sandbox may need to remain in effect for the lifecycle of the product. Additionally, considering article 114.2 indicates the validity of the authorization shall not exceed the duration of the regulatory sandbox, and Article 113.7 indicates decisions establishing a regulatory sandbox are limited in time. One possible way to address these requirements is to set the expiry for the sandbox at the end of the drug product lifecycle, however, the drug product lifecycle is not a predictable date in time. For that reason, it is proposed that for CMC-based regulatory sandboxes, the expiry is assumed to be for the product lifecycle
Article 114.4	"The summary of product characteristics and the package leaflet shall indicate that the medicinal product has been developed as part of a regulatory sandbox."	ISPE proposes removing Article 114.4	Although an alternate pathway has been followed, there is still the expectation that the product that is approved is safe and efficacious. If the product is safe and efficacious, there shouldn't be a need to note what pathway was used.
Article116	*Marketing authorisation holder notifications*	MAH is not always responsible for shortages; all stakeholders have to be considered in the alert system.	Comment: The root cause of a shortage may occur outside of the MAH operations; all stakeholders have to be considered as part of the alert system. Within a supply chain, there are many stakeholders aside from solely the MAH. There are upstream stakeholders (e.g., API suppliers, other suppliers) as well as downstream stakeholders (e.g., Wholesaler, distributors, Hospital, Pharmacy, etc.). However, there is a need for one specified stakeholder to act as the lead and coordinate. It would be beneficial to have a single system owner. Potentially, the final distributor may be in the best position to act as lead. There should be consolidation between incoming information from all stakeholders in all EU countries.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Article 116	*Marketing authorisation holder notifications*	The Agency should consider a collaborative mechanism to voluntarily advise on regulatory discretion proposals in advance of potential, substantial disruptive events. This collaborative mechanism could minimize product unavailability for patients. For example, for products that require a Risk Management Plan and Shortage Mitigation Plan (regulatory plans) would present meaningful impact to patients if unavailable, the applicant holder could, as appropriate, proactively share their regulatory plans with the Agency for comments and suggestions.	ISPE suggests creating an opportunity for the MAH to submit proposals that could mitigate or minimize critical drug shortages, to the Agency for feedback and approval as "approved regulatory discretions". Health Authority discretion could enable the continuity of supply through measures and mitigations outside of the approved drug product applications, for situations wherein regulators determine (a) the patient benefit or necessity outweighs the potential risks associated with exercising the discretion, and (b) the proposed temporary solution is timely enough to mitigate or prevent a shortage. Examples of HA discretion include: allowing additional product testing prior to release, extending the expiry of selected product batches on the market, temporarily allowing distribution of products with outdated or modified labeling and packaging, supplementing product distribution with accessories such as filter needles or other administration components to remove particulate matter, etc. Precedent in other major markets: The United States Federal Food Drug & Cosmetic Act (FD&C Act), Section 506D requires FDA to determine whether an enforcement action (e.g., Issuance of a Warning Letter to MAH for non-compliance) could cause or exacerbate a shortage and requires FDA to evaluate the risks associated with the impact of such a shortage. In September 2017, Hurricane Maria devastated Puerto Rico, creating a shortage in the United States of a significant number of critical medical products manufactured on the island, including human drugs and components. To mitigate the public health impact of the shortages, the FDA worked with drug manufacturers to approve new facilities and temporarily import products from other countries. The FDA also used data provided by drug manufacturers to extend expiry dates and issued guidance to provide alternate treatment and conservation strategies.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Article 116(1), point (a)	(a) its decision to permanently cease the marketing of a medicinal product in that Member State no less than twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;	Proposed change: (a) its decision to permanently cease the marketing of a medicinal product in that Member State ~~no less than~~ **at least** twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder **or, if this is not possible and where duly justified, as soon as they become aware of such decision to permanently cease the marketing of a medicinal product, to allow the Member State to monitor any potential or actual shortage in accordance with Article 118(1).**	Comment: we recommend that a decision to permanently cease the marketing of a medicinal product in that Member State should be notified at least twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder. Consideration should be made by the MAH to notify earlier than twelve months based on the therapeutic indication, product lifecycle, and estimated time needed to establish a new supplier or find alternate solutions, to ensure uninterrupted therapy for patients **Below we provide an example of different product modalities and their approximate lead time to set up a new supplier.** A decision to permanently cease the marketing of a medicinal product may be due to circumstances outside of the MAH's control (e.g., API supplier decides to discontinue business) and may be unexpected. Therefore, where duly justified, we recommend providing flexibility for MAHs to notify as soon as they become aware of the decision to permanently cease the marketing of a medicinal product.
Article 116(1), point b	(b) its request to permanently withdraw the marketing authorisation for that medicinal product authorised in that Member State no less than twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder	Proposed change: (b) its request to permanently withdraw the marketing authorisation for that medicinal product authorised in that Member State **~~no less than~~ at least ~~twelve months~~** before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder**, or, if this is not possible and where duly justified, as soon as they become aware of such decision to permanently withdraw the marketing of a medicinal product, to allow the Member State to monitor any potential or actual shortage in accordance with Article 118(1).**	Comment: Consideration should be made by the MAH to notify earlier than twelve months based on the therapeutic indication and provide ample time to enable MA transfer to companies who are willing to keep the product on the market, to ensure uninterrupted therapy for patients. Additionally, MAH should consider the schedule needed to remove all the products in the supply chain before the withdrawal of the MA, which could take more than one year in some cases. A decision to permanently withdraw the marketing authorization of a medicinal product may be due to circumstances outside of the MAH's control and may be unexpected. Therefore, where duly justified, we recommend providing flexibility for MAHs to notify as soon as they become aware of the decision to permanently withdraw the marketing authorization.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Article 116(1), point c	(c) its decision to temporarily suspend the marketing of a medicinal product in that Member State no less than six months before the start of the temporary suspension of supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;	Proposed change: (c) its decision to temporarily suspend the marketing of a medicinal product in that Member no less than six months before the start of the temporary suspension of supply of that medicinal product into the market of a given Member State by the marketing authorisation holder, **or, if this is not possible and where duly justified, as soon as they become aware of such decision to temporarily suspend the marketing of a medicinal product, to allow the Member State to monitor any potential or actual shortage in accordance with Article 118(1).**	Comment: The MAH's ability to reliably predict 6 months in advance that a temporary suspension may occur is limited. This information is difficult to attain and forecast, and the timeframe should be commensurate with the risk and the amount of time the disruption is expected to last (i.e., different for 2 weeks than 2 months). The regulation should provide some flexibility in case of an unexpected disaster, where the alert should be given as early as possible after the event. In addition, we recommend the agency define temporary suspension as opposed to a permanent suspension to ensure stakeholders' awareness and alignment with the agency's expectations.
Article 116 (d)	(d) a temporary disruption in the supply of a medicinal product in a given Member State, of an expected duration of in excess of two weeks or, based on the demand forecast of the marketing authorisation holder no less than six months before the start of such temporary disruption of supply or, if this is not possible and where duly justified, as soon as they become aware of such temporary disruption, to allow the Member State to monitor any potential or actual shortage in accordance with Article 118(1).	(d) a temporary disruption in the supply of a medicinal product in a given Member State, **of an expected duration of in excess of two weeks or**, based on the demand forecast of the marketing authorisation holder**,** no less than six months before the start of such temporary disruption of supply or, if this is not possible and where duly justified, as soon as they become aware of such temporary disruption, to allow the Member State to monitor any potential or actual shortage in accordance with Article 118(1).	Comment: The typical inventory coverage for products is approximately 100 days. However, each product may have different inventory coverage based on lead time and demand forecasts, which is best understood by the MAH for each of their products. Depending on the product and inventory coverage in the supply chain, a temporary disruption greater than 2 weeks may not impact patients. Therefore, ISPE recommends removing a specific timeframe correlating to the reporting.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Article 117(1)	*"The marketing authorisation holder as defined in Article 116(1) shall have in place and keep up to date a shortage prevention plan, for any medicinal product placed on the market. "*	Proposed change: The marketing authorisation holder as defined in Article 116(1) shall have in place and keep up to date a shortage prevention plan, for ~~any~~ **a 'critical** medicinal product' placed on the market. [Please use Regulation Definition for "Critical"]	Comment: Focus shortage prevention plan requirements on a well-defined set of prioritized products. Applying prevention plan requirements to all products dilutes valuable resources, and could put some manufacturers out of business, further straining supply. Patient impact should be considered when determining the level of rigor in documenting prevention plans to optimize the use of limited resources for drug shortage prevention measures. Developing prevention plans for all medicines without a risk-based approach would strain resources for both industry and regulators and lack focus. MAHs may consider developing, maintaining, and implementing shortage prevention plans for products outside of those deemed as 'critical medicinal products', as appropriate, to provide the reliability of supply.
Article 119(3)	*To prepare a risk assessment of impact of suspension, cessation or withdrawal referred to in Article 118(2), the marketing authorisation holder as defined in Article 116(1) shall include the minimum set of information set out in Part II of Annex IV and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).*	Proposed change: To prepare a risk assessment of impact of suspension, cessation or withdrawal **for critical medicinal products** referred to in Article 118(2), the marketing authorisation holder as defined in Article 116(1) shall include the minimum set of information set out in Part II of Annex IV and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).[Please use Regulation Definition for "Critical"]	Comment: Apply a risk-based approach to optimize resources for both MAH and regulator; focus on the requirement to prepare a risk assessment for impact of suspension, cessation, or withdrawal for critical medicinal products **only**.
Article 120 (1)	*Obligations on other actors* Wholesale distributors and other persons or legal entities that are authorised or entitled to supply medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] to the public may report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority in that Member State.	1) Wholesale distributors and other persons or legal entities that are authorised or entitled to supply medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] to the public ~~may~~ **should** report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority in that Member State.	Comment: Within a supply chain, there are many stakeholders aside from solely the MAH. There are upstream stakeholders (e.g., API suppliers, other suppliers) as well as downstream stakeholders (e.g., wholesalers, Distributors, Hospitals, Pharmacies, etc.). Upstream and downstream stakeholders have knowledge and visibility of their stockpiling within their supply chain. We suggest when product volumes or availability begin to deplete or are disrupted, downstream stakeholders such as distributors should alert the respective NCA regarding the impact of delay or temporary of the product.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Article 121 b)	**(b)** publish information on actual shortages of medicinal products, in cases in which that competent authority has assessed the shortage, on a publicly available website;	**(b)** publish **status** information on actual shortages of medicinal products, **and the expected timing to resume normal operations through to the wholesaler inventories**, in cases in which that competent authority has assessed the shortage, on a publicly available website;	Comment: We suggest having a system that includes the status (not volumes) for a potential shortage, actual shortage, and expected timing to resume normal operations. This information should be complemented with wholesalers' information to provide an accurate reflection of product availability. When the MAH notifies the NCA of resuming normal operations and product availability, this does not necessarily mean that the entire supply chain has immediately recovered (i.e., wholesalers, distributors, pharmacy). Providing a status for when customers can begin to order product can help prevent misinterpretation. As this can be a cost and resource-intensive task, a system owner in the competent authority should be defined.
Article 180		**Reg 180 add: 14**. The Commission shall ensure the continuation of applicability of the Sectoral Annexes on Pharmaceutical Good Manufacturing Practices (GMPs) in Agreements on Mutual Recognition between the Union and 3rd countries, as established.	In the event that this legislation replaces Dir 2001/83/EC, ISPE recommends the proposed change to Art. 180 of the Regulation to ensure that MRAs are kept operational because the MRA EU/US has the Dir 2001/83/EC named as a basis for the similarity assessment.

General Comments on the Annex IV

To avoid loss of information, ISPE recommends that MAH information e.g. relating to potential or actual drug shortages is submitted to a platform in Member States and that this platform is interoperable across all agencies. In addition, we suggest that such platforms (databases) are implemented with robust cybersecurity measures to ensure security of the confidential information. Information must be submitted with potential shortage in each Member State; The system should be flexible to accept Central Authorised and National Marketing Authorisation or Decentralised Authorised products.

Lastly, ISPE suggests including a clause for any revision or on periodicity after a major event. This could be linked with the Risk Review step which is part of quality risk management.

Specific Comments on Annex IV

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Annex IV AVAILABILITY Part I	(1) Product details: (j) Alternative, pharmaceutical form, strength, route of administration or pack size, not affected by the suspension, cessation or withdrawal; (2) Details of action (suspension, cessation or withdrawal): (d) Reason for action and information on alternative medicinal product(s), where relevant;	Proposed change: (1) Product details: (j) Alternative**,** pharmaceutical form, strength, route of administration or pack size, not affected by the suspension, cessation, or withdrawal, **when known (e.g., for generics);** (2) Details of action (suspension, cessation or withdrawal): (d) Reason for action and information on alternative medicinal product(s) **the MAH places on the market,** where relevant;	Comment: **1(j) and 2(d):** Identification of suitable alternative therapy is outside the scope of the MAH, as this decision resides with Health Care Providers using their best clinical judgment. The MAH's ability to determine the potential impact on the consumption or demand for other competitors' medicinal products is limited and may provide incomplete conclusions. Actions taken based on incomplete conclusions can consume unnecessary resources that could be allocated to focus on minimizing or mitigating significant disruptions. • Treatment approach is not solely based on a diagnosis, there are other critical factors such as patient history, other disease/conditions, concurrent therapies, etc. • Product is not selected based on the approved indication(s) alone. Products may be prescribed outside of their approved indication, which is outside of the MAHs control. • Generic manufacturers may be able to identify therapeutic equivalents, thus we recommended providing this information when known by the MAH.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Annex IV AVAILABILITY Part II Risk assessment of impact of suspension, cessation or withdrawal	(1) Risk assessment of impact of suspension, cessation or withdrawal, including: (a) Potential alternative medicinal products; (d) Manufacturing capacity globally per manufacturing site; (h) Potential impact on the consumption of or demand for other medicinal products. (2) Any risk-mitigating measures taken by the marketing authorisation holder to address the shortage	Proposed change: (1) Risk assessment of **the** impact of suspension, cessation or withdrawal, including: (a) Potential alternative medicinal products **which MAH places on the market;** ~~**(d) Manufacturing capacity globally per manufacturing site;**~~ ~~**(h) Potential impact on the consumption of or demand for other medicinal products.**~~ (2) Any risk-mitigating measures taken by the marketing authorisation holder to address the shortage**, as applicable** *[If letter d and h remain, confidentiality should be assured]*	Comment**:** **Add to 1(a):** Identification of suitable alternative therapy is outside the scope of the MAH, as this decision resides with Health Care Providers using their best clinical judgment. **1(d):** ISPE proposes removing letter d. From an Industry perspective, providing the manufacturing capacity globally per manufacturing site is unrelated to a MAH's decision to temporarily suspend, permanently cease, or withdraw a product. If part 1(d) is to remain, we request that a high level of confidentiality and assurance be made between the MAH and the Agency to ensure proprietary information provided remains confidential. Additionally, the forecast and supply volumes provided by the MAH are only representative of what the MAH has within its control and can be different due to the limited visibility of what wholesalers or distributors have. **(2)** There may not be a shortage to address. To optimize resources for both MAH and regulator, focus on risk-mitigating measures when there is a risk for a significant supply disruption of a critical medicinal product during a temporary marketing suspension, e.g., for a quality event or extended timescale to approve a post-approval change management to update facilities. The MAH can only manage what is within its control, and for its products. Once the MAH releases the product, other actors become involved in the supply chain (wholesalers and distributors) **Remove 1(h):** The MAH's ability to determine the potential impact on the consumption or demand for other competitors' medicinal products is limited and may provide incomplete conclusions. Actions taken based on incomplete conclusions can consume unnecessary resources that could be allocated to focus on minimizing or mitigating significant disruptions.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
			• Treatment approach is not solely based on a diagnosis, the are other critical factors such as patient history, other disease/conditions, concurrent therapies, etc. • Product is not selected based on the approved indication(s) alone. Products may be prescribed outside of their approved indication, which is outside of the MAH's control.
Annex IV AVAILABILITY Part IV The Shortage Mitigation Plan	1. Shortage mitigation plan, detailing the risk assessment of impact of shortage, including, where available: (a) Potential alternative medicinal products; (d) Manufacturing capacity globally per manufacturing site; (h) Potential impact on the consumption of or demand for other medicinal products; (i) Any risk-mitigating measures taken or planned by the marketing authorisation holder to address the shortage.	1. Shortage mitigation plan, detailing the risk assessment of impact of shortage, including, where available: (a) Potential alternative medicinal products **which MAH places on the market;** ~~(d) Manufacturing capacity globally per manufacturing site;~~ ~~(h) Potential impact on the consumption of or demand for other medicinal products;~~ (i) Any risk-mitigating measures taken or planned by the marketing authorisation holder to address **a potential** shortage**, as applicable.**	**Add to 1(a)** Identification of a suitable alternative therapy is outside the scope of the MAH, as this decision resides with Health Care Providers using their best clinical judgment The MAH's ability to determine the potential impact on the consumption or demand for other competitors' medicinal products is limited and may provide incomplete conclusions. Actions taken based on incomplete conclusions can consume unnecessary resources that could be allocated to focus on minimizing or mitigating significant disruptions. • Treatment approach is not solely based on a diagnosis, the are other critical factors such as patient history, other disease/conditions, concurrent therapies, etc. • Product is not selected based on the approved indication(s) alone. Products may be prescribed outside of their approved indication, which is outside of the MAH's control. **Remove 1(d):** ISPE proposes removing sub-section (d). From the Industry perspective, providing the manufacturing capacity globally per manufacturing site is unrelated to a MAH's decision to temporarily suspend, permanently cease, or withdraw a product. **Remove 1(h):** ISPE proposes removing sub-section (h). From the Industry perspective, the MAH's ability to determine the potential impact on the consumption or demand for other competitors' medicinal products is limited and may provide incomplete conclusions. Actions taken based on incomplete conclusions can consume unnecessary resources that could be allocated to focus on minimizing or mitigating significant disruptions.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Annex IV AVAILABILITY Part IV The Shortage Mitigation Plan **(Cont)**			• Treatment approach is not solely based on a diagnosis, the are other critical factors such as patient history, other disease/conditions, concurrent therapies, etc. • Product is not selected based on the approved indication(s) alone. Products may be prescribed outside of their approved indication, which is outside of the MAH's control. **1(i):** Recommendation for clarity because these plans are created well in advance of any specific event.
Annex IV AVAILABILITY Part V The shortage prevention plan	(2) Shortage prevention measures and supply chain risk assessment: (a) Alternative marketed medicinal products; (b) Supply chain map, with risk identification and analysis with particular attention to supply chain vulnerabilities;	**(2):** Shortage prevention measures and supply chain risk assessment **for Critical Medicinal Product** (a) ~~Alternative marketed medicinal products;~~ **Other available pharmaceutical formulations of MAH's marketed medicinal product** (b) ~~**Supply chain map,**~~ **Identify supply chain entity (name, site registered, registered activities). Document the outcome of the risk identification and analysis as a summary.** ~~with risk identification and analysis with particular attention to supply chain vulnerabilities~~	**(2):** Shortage prevention measures and supply chain risk assessment should focus on identifying and evaluating risks to significant disruptions in the supply of the critical medicinal product. **(a):** Identification of suitable alternative therapy is outside the scope of the MAH, as this decision resides with Health Care Providers using their best clinical judgment. •Treatment approach is not solely based on a diagnosis, the are other critical factors such as patient history, other disease/conditions, concurrent therapies, etc. •Product is not selected based on the approved indication(s) alone. Products may be prescribed outside of their approved indication, which is outside of the MAH's control. **(b):** Supply chain maps contain commercially confidential information. MAH should list the supply chain entity as given In MAH's dossier (e.g., name, site registered, registered activities). The outcome of the risk identification and analysis should be documented as a summary.

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