EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2021

Submission of comments on 'Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications' (EMA/CHMP/BWP/QWP/IWG/694114/2019)

Comments from:

Name of organisation or individual
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	ISPE thanks EMA for the opportunity to comment on the draft document "Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications." We believe this is a very important document and is, to our knowledge, the first time that a regulatory agency has put into a guidance document the potential science- and risk-based approaches that can be used to accelerate availability of important medicines to patients. ISPE commends EMA for their willingness to publish a toolbox of flexibilities that may be possible for early access programs. We strongly believe that transparency provided by this guideline will lower the perceived barriers for companies looking to accelerate their development and approval of innovative medicines for patients, especially for smaller companies with less regulatory experience. ISPE considers the document to contain an excellent description of the toolbox of flexibilities that may be possible for early access programs. In particular, we appreciate the clarity provided by the potential flexibilities in use of scientific tools such as *in-silico* models, process validation activities, stability data in the initial filing, and the GMP flexibilities when supported by clear justifications and quality risk management. We further appreciate the clear description of how to engage the Agency in early dialogue. ISPE does, however, recommend that the scope of the document is clarified and broadened. Some suggestions and rationale are given below. ISPE's greatest concern of the document is its appearance of a very narrow scope. The document gives the appearance of being specific to PRIME marketing authorisation applications; the title and Introduction (background) section are specific to PRIME. Yet	

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	many of the science- and risk-based approaches that are included in document are applicable to ALL products, and most of the flexibilities discussed may be applicable on case-by-case basis for non-PRIME medicines for unmet medical needs or of major public health interest. While lines 135-137 of the document briefly addresses applicability of the toolbox to non-PRIME early access products, that point can easily be lost in the language of the rest of the document which specifies PRIME. Since all, or nearly all, of the tools discussed are equally applicable to PRIME and early access products on a case-by-case basis when justified, ISPE recommends that the scope of the guideline is broadened and not apparently restricted to only PRIME products. The broadening of the scope would provide consistency with EMA's commitment described in lines 619-623. Such revision would also provide consistency with the Agency's experience with Conditional Marketing Authorisations of COVID drugs and vaccines, which ISPE understands may have included some of these flexibilities although outside of the PRIME program. ISPE's first recommendation is to change the title, introduction, and scope of the guideline to be reflective of "early access products" rather than "PRIME marketing authorisation applications." Alternatively, the Agency could broaden their access to the PRIME process, especially at the early, proof of principle stage to be inclusive of all early access products. The enhanced dialogue available from the PRIME pathway would benefit sponsors who may have great uncertainties regarding how to balance and optimise the required clinical and safety studies with the necessary quality studies to achieve a good regulatory submission and accelerate availability of these important medicines for patients. ISPE's second recommendation is that the guideline be clarified which tools and sections of the document provide are applicable for all products and which sections	

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	contain regulatory flexibilities and thus may be reserved for early access products. Some of the General scientific tools in Section 4.2 (e.g., Prior Knowledge, Risk Assessment, Continuous Process Verification) are not specific to PRIME or early access products; they are simply science- and risk-based approaches consistent with the enhanced development approach described in ICH Q8(R2), ICH Q10, ICH Q11 and ICH Q12. Similarly, the regulatory tool of Post-approval Change Management Protocol (PACMP) discussed in Section 5.4 is not specific to PRIME products. Lack of clarity about what tools are available for all products vs. limited to PRIME could lead to general misunderstanding about the applicability of the tools. We recommend that the concept of enhanced development tools vs. tools for flexibility be included in the document and clarified for each tool discussed. Thirdly, ISPE recommends that in the Section 5, Regulatory tools section, consideration be given to liaising with other agencies that a sponsor may be approaching to try to align flexibilities being considered for the EU with those of other agencies. Finally, while out of scope for this specific guideline, ISPE suggests that any future revision of EU GMP Annex 15 consider inclusion of some of the clarifications relating to process validation given in this toolbox document. As a worldwide not-for-profit association dedicated to connecting pharmaceutical knowledge to enhance industry efforts to develop, manufacture and reliably deliver quality medicines to patients, ISPE has been actively involved in advancing scientific and regulatory approaches for accelerated development and approvals, such as for PRIME scheme products. Our volunteer members have published several articles on this topic which we will gladly share with EMA, upon request. ISPE encourages EMA to	

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	continue dialogue with industry on this topic, either directly with organizations such as ISPE, or through follow-up workshops similar to the regulator-industry workshop held November 2018, in which the US FDA participated. ISPE does not have line by line edits for the document.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.