HAI HEALTH ACTION INTERNATIONAL

A. General comments on the draft reflection paper

Question **General comments on the reflection paper**

	General comments	Is this a major concern/comment Yes;No
1	The paper mentions 'high-risk AI uses for medicines regulation' but does not give a definition of what the EMA classifies as such high-risk uses. We recommend inclusion of classification criteria on high-risk AI uses for medicines regulation.	Yes
2	The paper is unclear regarding the role of the EMA and its ability to monitor and guide the use of AI in pharmaceutical R&D and related activities. We recommend the EMA asserts its authority as a regulator and provide details on how oversight and accountability mechanisms will be set in place and implemented.	Yes
3	This draft reflection is vague on the next steps to be taken by EMA and other stakeholders that will ensure safeguards on AI in medicine R&D are in place. In line with comment 2 (above), we recommend the EMA develops a roadmap of actions to be taken which enable it to execute its responsibility and safeguard and ensure independent regulatory assessment. This should include the acquisition of sufficient technical expertise on AI and machine learning which will limit EMA's dependence on corporate know-how and capacity, which is evident in the realm of medical devices, for example.	Yes
4	It is unclear what concrete next steps the EMA will take to guide the use of AI in pharmaceutical R&D. Will it develop a guideline or policy? We recommend the EMA provide clarity on the next steps they will take to guide the use of AI in pharmaceutical R&D.	Yes
5	It is unclear whether applicants will be required to specify whether they used AI in any stage of their R&D processes on submission of a market authorisation request. Furthermore, a detailed specification of the information/documentation that must be provided by manufacturers should be developed.	Yes

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B. Specific comments on the draft reflection paper by section

Section 1: Introduction

Question **Section 1: Introduction**

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	56-60	The internal aim of the reflection paper is phrased vaguely. It is not clear what is meant by 'reflect on scientific principles'. What are scientific principles for regulatory decision making in this context?	If the internal aim is clearer, it will help to understand whether the paper meets its aim.	Add what is meant by scientific principles and why is it needed/what is gained by reflecting on them.	Yes
2	56-60	The external aim of the reflection paper is lacking: how will this paper be used by the EMA?	Defining the external aim helps to give clarity on the purpose of the document, and enables the reader to read the rest of the text in that light.		Yes
3	56-57	This sentence does not specify use of AI by who is included in the scope. Use of AI by manufacturers is obvious, but also by e.g., EMA itself in its regulatory decision making?	This change will help to specify the papers' aim.	Add 'by…'at the end of the sentence and include actors.	No
4	61-63	From this sentence, it is not clear whether this is what the reflection paper will do, or is just something that is important	Being as clear as possible on what is within and outside of the scope of the reflection paper.	This reflection paper will identify aspects of AI/ML that would fall within the remit of EMA or the National Competent Authorities of the Member States. This is crucial as the level of scrutiny into data during assessment will depend on this remit.	Yes
5	75-78	Also differences in fundamental rights protection between the human and veterinary domain exist.	The sum up includes some fundamental rights but not all.	Add: 'and fundamental rights protection in general'	No

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Section 2.1 General considerations

Question **Section 2.1 General considerations**

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	85	Instead of just 'used', 'developed and used' for more comprehensive meaning.	As the development process of AI and decisions during this phase are crucial for the eventual functionality and risks of an AI system.	'developed and used'	No
2	85	Instead of just 'support', 'support or improve', for more comprehensive meaning.	Ultimately we would like AI to also improve the way we do these things, and this should be reflected.	'support or improve'	No
3	95-96	Stronger use of language is needed.	'May depend' is too weak, as the context of use and degree of influence will influence the risk of the technology.	Change 'may depend' to 'depends'	Yes
	96	Instead of just 'degree of influence' also level of autonomy with which the technology operates.	Level of autonomy with which a system operates is an important determinant for risk as it provides fewer safeguards and malfunctioning may go unnoticed.	Add 'and level of autonomy with which a system operates'	Yes
	100-103	In this case: Shouldn't regulatory interaction be obliged instead of advised? It is important to also outline at which stage of AI application this interaction should happen. Now it seems like a very informal/ad hoc process.	Outlining clear responsibilities and processes, provides direction and clarity.	Include obligation for interaction when AI influences benefit-risk ratio. Also describe that interaction should happen before AI implementation/use.	Yes
	105-108	But what is the role of the EMA? Will there be mechanisms through which the EMA will check whether applicants are indeed compliant	Clearly explaining the EMAs oversight mechanisms will help to also understand the role of the EMA in this.	Include the role/responsibility of the EMA.	Yes

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		with scientific guidelines & standards when they deploy AI/ML?			
	85-113	In this section, before talking about the specific uses, it's important to outline a framework to define high-risk uses, with concrete indicators. In addition, the concept of risk needs to be unpacked as it should be made explicit what type of risks the EMA believes are relevant to their practice. E.g., risks to patient safety, risks to scientific rigour, but also risks for access to treatment?	Defining high-risk AI for regulatory decision making will help to delineate the types/uses of systems that need scrutiny.	Include definition high risk AI (uses) and define the types of risks of interest to the EMA.	Yes

2.2. AI in the lifecycle of medicinal products

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	114	Do you have any data on what types of AI are currently used in pharmaceutical R&D? As well as in which percentage of regulatory approval requests these different AI systems have been used?	It's important to know for the reader how small/big the practice currently is, and whether it's something for the future, or that's already playing out today.	Statistics on type of AI used in R&D and % of applications that used the different AI systems.	Yes

2.2.3. Clinical trials

2.2.3.1. Good clinical practice (GCP)

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No

1	139-142	Really important indeed! 'Clinical trial purposes' on line 139 could be further defined.	Defining clinical trial purposes can help improve clarity.	Include: "Clinical trial purposes are defined as…"	No
2	137-142	This would be a suitable place to mention the importance of transparency of clinical trials results. While it's a broader issue than just AI, it can be reiterated here that all clinical trials should be published in appropriate registries, as per the EU Clinical Trial Regulation. In addition, for transparency purposes it would be of value to include reporting requirements on the type and purpose of AI used in trial registries for clinical trials which use AI/ML.	Transparency provisions under the EU Clinical Trial Regulation are currently poorly abided. To increase accountability and reduce duplication of effort, its essential that AI-assisted clinical trial results are correctly registered.	Include reporting obligations under the EU Clinical Trial Regulation and reflect on the addition of new reporting requirements for AI-assisted clinical trials.	Yes

2.2.3.2. Use of medical devices and in vitro diagnostics in clinical trials

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	157	Does 'CE marked devices' refer to any CE marked devices, or CE marked medical devices specifically.	Improved clarity	Rephrase to: CE marked medical devices	No
2	157-159	This line states that extra requirements may be needed, will EMA take on a role in developing these requirements? For example, develop a guideline?	Important to provide clarity on the role of the EMA. If the EMA is not responsible, then who is?	At the end of the sentence include: "For this reason, EMA will…"	Yes

2.2.3.3. Data analysis and inference

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No

1	186-187	Who should have the responsibility to manage this repository? And, who should have access? Why is it important that they are included in this repository?	Increased clarity/understanding of the functioning of the repository	Include more details of management and purpose of and access to the repository	Yes

2.2.4. Precision medicine[4]

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	189-192	Will the EMA develop guidelines to prevent bias in case of individualising treatments?	Individualising treatments with AI carries a huge risk of bias.	Include the ambition to develop a guideline to counter bias in AI assisted individualised treatments.	Yes
2	196	'Is a matter for medicines regulation'. It's unclear what is meant with this. Does it mean that this is an issue over which the EMA has responsibility? Or does it mean it should adhere to EU regulation on medicinal products?	Rephrasing will increase clarity.	Rephrase 'is a matter for medicines regulation' to include specifics.	No
	197-198	Define beforehand how the EMA will classify high-risk uses, so you can compare AI devices according to your pre-specified criteria of high-risk use.	It's absolutely essential to define high risk use in the paper in order to know what systems classify as high risk and what systems do not.	Include: "high-risk uses are defined as …"	Yes

2.3. Regulatory interactions

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	234-236	Good, very important to include this impact assessment! Will the	It's important to give clarity on what an impact	Include details on how the impact and risk	Yes

		EMA develop a detailed guideline on how the regulatory impact and risk analysis should be carried out? (Including the dimensions of impact and risk that should be assessed). Should the results of the impact & risk assessment be submitted to EMA? Will EMA keep oversight?	& risk assessment should entail and what are the processes to follow to ensure uniformity as well as regulatory clarity. Applicants need to know what the criteria are based on which a system would be considered high impact or high risk.	analysis should be carried out, what types of impact and risk should be measured and what type of information should be provided to EMA. Also specify the role of the EMA in oversight/governance.	
2	238	'recommend': to ensure patient safety and access to treatment it's important to make interaction with regulators an obligation.	AI use with high impact on regulatory decision making should be carefully governed.	Change 'always recommend' to 'obliged'	Yes
3	245	'high-impact cases': it should be clearly defined when EMA classifies a use of AI as 'high impact'.	It cannot be left to the applicant to decide what counts as a high-impact case, as every applicant will have their own perception.	Include: 'high-impact cases are defined as: …'	Yes
4	250-252	Other essential questions are about the data that is used. Where does the data come from, how is it collected, what is its quality, implications of the system's use on fundamental rights, patient safety, and on (equal) access to treatment, and what are risks of biases, as well as mitigation strategies?	It's important to include additional information in the documentation so patients' rights are protected	Include after 'clinical applicability': "Origination, characterisation and quality of the data, implications of the system's use on fundamental rights, patient safety, and on (equal) access to treatment, and risks of biases, as well as mitigation strategies."	Yes

2.4. Technical aspects

2.4.1. Data acquisition and augmentation

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	263-267	Good! These requirements should also be added to the documentation requirements as specified in line 205-252.	Ensuring alignment of the paper throughout sections.	Include requirements lines 263-267 into lines 250-252.	Yes

2.4.6. Model deployment

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	354	'risk management plan'. Should this plan also be submitted to the EMA?	It will improve clarity on governance processes.	Specify whether the risk management plan should be submitted to the EMA	Yes

2.6. Data protection

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	370-371	Is this realistic? Shouldn't the EMA make more specific guidelines to govern data protection in case of AI in medicine R&D	Data protection authorities are overburdened. We cannot risk weaknesses in oversight.	Include role/responsibility of the EMA.	No

2.8. Ethical aspects and trustworthy AI

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	415	'systematic impact analysis': what should this impact analysis entail, how should it be carried out? Should result be submitted to the EMA?	Provide clarity on role & responsibility of the EMA	Include details on the contents, execution and assessment processes of the systematic impact analysis.	Yes

3. Conclusion

	Line number(s) of relevant text	Comment	Rationale for change	Propose change (text to be introduced)	Is this a major concern/ comment Yes;No
1	420-434	This section misses a clear conclusion on what will change as a result of this reflection paper for the use and governance of AI systems in medicine R&D by the EMA. It also misses an outline on next steps that will be taken to monitor and guide the use of AI in medicine R&D.	The reader needs much more practical information on what this reflection paper has changes/laid bare, as well as the way forward that the EMA will take.	Include: “this paper has resulted in…”, “next steps that the EMA will take are…”	Yes.

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