EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<14 July 2014>

Submission of comments on Best practice guidance for pilot EMA HTA parallel scientific advice procedures (EMA/109608/2014)

Comments from:

Name of organisation or individual
Joint industry comments EFPIA EuropaBio Vaccines' Europe

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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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)*
	Industry welcomes the EMA consultation on parallel scientific advice (PSA) procedure, understanding that feedback from HTA bodies (HTAB) has been directly solicited by EMA and that these bodies have reviewed and endorsed the proposed framework. Our member companies have made use of the optional EMA procedure since 2010, as they recognise it can facilitate decisions on development plans and align evidence requirements both pre- and post-approval. Based on their concrete experience, individual companies will be best placed to respond to the specific questions put forward by the EMA in the framework of its online public consultation. EFPIA, EuropaBio and Vaccines Europe would like to contribute to the debate by providing their thoughts and input on the current practice of PSA and future development of a sustainable joint process of scientific advice involving regulators and HTAB. Industry notes and welcomes the different activities relating to the developing of scientific advice involving regulators and HTAB at the European level[1]. However in the long run, industry considers that lessons learned from the different existing pilots should be drawn together to	

[1] The EMA pilot and other pilots such as those coordinated by EUnetHTA in the past and now by the SEED consortium.

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	develop a sustainable joint (rather than parallel) process for scientific advice involving regulators and HTAB as equal partners, as well as other stakeholders such as payers, patients and clinicians. This should be available to applicants alongside (and without prejudicing) other scientific advice mechanisms at the European level (regulatory only or multi-HTA only) and national level (regulatory only, HTA only, joint regulatory-HTA). We look forward to engaging in discussions with the EMA and HTAB to continuously improve these processes, and incorporate industry's experience. In this respect, we would welcome that EMA and HTAB develop metrics to measure success of the procedure and plan a stock taking exercise in order to review the best practice guidance and improve the process based on stakeholders' experience within a defined time frame. As part of this exercise, it might be worthwhile considering how to deal with orphan medicinal products due to their specific considerations both from a regulatory and HTA point of view. Vaccines' Europe would also like to draw the attention to a very specific vaccine issue. In the case of vaccines, HTA bodies are not systematically involved in the national processes of issuing advice to ministries of health/policy makers on whether a vaccine should be included or not in the national immunization programmes (for example in the UK it is not NICE but the Joint Committee on	

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	Vaccination and Immunisation (JVCI) that is issuing advice for vaccines). In many countries it will be National Immunization Technical Advisory Groups that will issue these kind of advices. For vaccine manufacturers it would therefore be important to involve when relevant other bodies than HTA bodies in these parallel scientific advice procedures. The possibility for EMA to involve other vaccine relevant bodies was confirmed during a business pipeline meeting of at least one of the Vaccines Europe manufacturers. Vaccines Europe would like to propose that this possibility is acknowledged in the EMA best practice guidance.	
	<u>Industry principles for a sustainable joint process of scientific advice involving regulators and HTAB</u> The coordinated and consistent joint process of scientific advice should be based on shared discussions involving the company representatives, regulatory, HTAB and payer authorities and result in consistent advice documents with the aim of resolving differences of opinion and delivering a pragmatic, scientifically-robust and relevant advice document where feasible. However, since their remits are different, the advice documents might take a different form (see below section on outcome). <u>General principles</u> • Confidentiality: To preserve the competitiveness of	

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	the R&D, confidentiality of advice requests and the related submission documents should be guaranteed by all parties. • Good governance: Adequate governance structure, clear responsibility in HTA authority, coordinated funding and project management capabilities need to be available to ensure that the system can deliver consistent output with high quality within a strict timeline. • Scientific excellence: Sound expertise for the assessment is mandatory to ensure scientific excellence and efficient decision-making. • Concise process: The timeline for the advice process needs to be no longer than 60 days to fit into the drug development process as companies strive to shorten their development cycles. • Joint, reliable outcome: the documented advice needs to represent the consistent advice of participating regulatory and HTA authorities to support company decision-making on development plans. Any divergences need to be clearly outlined in the documented advice. <u>Pre-notification</u> • Sponsors need clear guidance and more transparency around any specific requirements from national HTAB. The national contact points for questions and submissions must be clearly identified. A compilation	

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	of information around the national mandatory consultation processes and any conditions that must be fulfilled and national timelines should be available at a central location. <u>Pre-validation</u> • One harmonized guideline for briefing booklet building on Regulatory documents should be developed jointly between Regulators/HTA in consultation with Industry to avoid extensive re-work of existing documents. The booklet should be clear, concise and focus on the essential elements. This will significantly streamline the sponsor resource requirements during the pre-validation phase as well as the assessor's time required for conducting an assessment. <u>Discussion meeting</u> • The list of issues to be discussed at the meeting should be set by the sponsor. Clarification on issues and other questions by agencies should be available to sponsors in advance of the meeting to ensure a good preparation of arguments and background. It is valuable for sponsors to know which party raised which issue. • The discussion among Regulators, HTAB and sponsors should focus on issues of divergent views to ensure best use of available meeting time. Attendance of	

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	high-level experts during the discussion meeting is required to foster scientific debate and facilitate the development of compatible scientific solutions than can address those issues. • A method for resolving differences in opinion should be developed and the discussion should allow sufficient time and opportunities to resolve differences where possible. <u>Outcome</u> • A CHMP SA letter must be available after a specified timeline, in line with current processes. • A timely and precise joint HTA SA report should be available that is approved by all participating national HTAB. Where differences exist between HTAB, these should be clearly outlined in the joint HTA SA report. This report should be available to the sponsor as a reference document for subsequent HTA discussions. • Minutes of the meeting should clearly outline the outcomes of discussion and include both regulatory and HTA topics. Areas of agreement and difference of opinion between regulators and HTAB should be part of these detailed minutes.	

	<u>Industry views on the best practice guidance for pilot EMA HTA parallel scientific advice procedures</u> EFPIA conducted a survey amongst its members over the summer 2013[2]. The survey highlights a number of areas, which companies consider could be improved in the current EMA PSA procedure. In the comments below, we make some concrete suggestions for improvement to the EMA PSA procedure but as highlighted in our general comments above, we consider that a joint process should be implemented moving forward, owned equally by the EMA and HTAB. Key comments include the need for: • ***More active involvement of HTAB, better alignment between HTAB and more structured feedback from HTAB***: experience from some processes show that certain HTAB act more as observers than active participants to the process. We understand that some of the reasons for this cannot directly be addressed by the EMA guidance, however in the PSA procedure, further coordination steps amongst HTAB could be introduced. o The identification of a project manager at the HTAB, who would be responsible for preparing the discussions upfront, seeking alignment between HTAB before the meetings. o In order to support the goal of equal partnership by HTAB, documentation	

[2] The results of which were presented at the EMA PSA workshop in November 2013 and also included in a publication in Nature regulatory affairs in February 2014

	requirements and timings should be aligned, and a discussion should take place with the company on how to share documents in a timely manner (including the EMA list of questions). o The current procedure foresees detailed minutes and a feedback that fits each HTAB national requirements. Whilst we understand this is constrained by the national remits of each agency, we would welcome efforts within the pilots to work towards a timely and precise joint HTA SA report that is approved by all participating national HTAB. Where differences exist between HTABs, these should be clearly outlined in the joint HTA SA report, which should also deliver a core set of views that are shared by all HTABs. This report should be available to the sponsor as a reference document for subsequent HTA discussions. • ***Better alignment between HTAB and EMA, including consolidated HTAB-EMA feedback***: the current procedure allows highlighting differences where they exist, but opportunities to discuss and find solutions to these differences remain limited. The pilot procedure should foresee more time to address and discuss areas of differences, in particular during the face-to-face meeting involving the company. The outcomes of this discussion should be clearly articulated in detailed joint minutes of the meeting, including areas of agreement and difference of opinion between regulators and HTAB.	

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)*
Line 49-52		We fully agree that "there is a clear need to initiate early dialogue between medicines developers, regulators and HTABs" and look forward to further sharing of experience on the already completed pilots.	
Vaccines Europe specific comment In the section "Products and indication in scope; HTABs" after line 80		Add "As for some medicinal products, like for example vaccines, other national advisory bodies than HTABs will be involved in issuing advice to payers/healthcare-guidance organizations, applicants can chose to approach these national advisory bodies for participation in the parallel scientific advice procedure"	
Line 82		We understand that this draft guidance concerns specifically the EMA pilot process existing since 2010. Therefore, we file comments specifically on this pilot process, which we understand is embedded in the current EMA framework and procedures. However, as outlined in our general comments above, we consider that a joint process should be implemented moving forward, owned equally by the EMA and HTAB.	
Line 83 and 86		Although this guidance aims at all parties, we consider it currently rather provides recommendations to the applicant as the one responsible for connecting all involved parties. A	

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		particular issue may be coordination across the various HTAB involved in each pilot, and a project manager from the HTAB should be identified early on in the process.	
Vaccines Europe specific comment After line 90 in the section 1.2 Principles		Insert the following text: "It is acknowledged that for certain medicinal products, like vaccines, HTA bodies are not systematically involved in the issuing of national advices to payers/healthcare-guidance organizations. In these cases applicants may propose the participation of other relevant national advising bodies (following their agreement/confirmation of interest) to the parallel scientific advice procedure. In that case the same principles as described in this best practice guide may be applied"	
Line 91-104 and 105-116		There should be alignment between the EMA and HTAB on 'products and indication in scope', and both paragraphs could therefore be merged. For the paragraph related to HTAB, in line with what is outlined for the EMA, it should be explicitly stated that HTAB will engage in PSA at any stage in the process (before phase III, during phase III, later in the process, i.e. at all stages of the product life). If this is not possible at this stage because of national remits, this should be considered in the development of any future sustainable process.	
Line 97-99		We agree that the PSA should be open to industry at any stage of the development process, where questions exists that would best be addressed in a collaborative discussion involving	

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		regulators and HTAB; we also agree that PSA may be used to discuss post-authorisation safety and efficacy studies and that this would allow companies to consider incorporating the needs of HTAB in these studies, where this is feasible (in particular as regards to timelines).	
Line 107-08		Rather than being available on demand from EMA, the information collated by HTAs participating in the pilot regarding their scope, prerequisites and activities should be made available on a public website. It should also include information on how HTAB utilise the outcomes of PSA in their national processes.	
Line 111-112		Whilst there is no obligation to participate, where HTAB agree to participate, they should involve those individuals within their national HTAB which play a role in national scientific advice procedures, so as to ensure usefulness of the European outcome in subsequent national procedures.	
Line 113-114		We assume all HTABs have agreed to the briefing template as outlined in the EMA best practice guidance.	
Line 115		Whilst we understand that the advice is not legally binding, it would be useful to get clarity that all participants will ensure that relevant statements that have material influence on further scientific and economic decisions by companies are consistent with the authorities' general direction and policy; effort should be put to ensure that the outcomes of advice	

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		processes are useful to guide companies' developments and can be relied on in future national discussions.	
Line 121		Early engagement prior to formal procedure initiation is logical to ensure full, meaningful participation. This point should be clarified (i.e. how early) and who should be contacted at the EMA and within HTAB.	
Line 124-126		According to the current procedure the preferred meeting date and time appear to be confirmed prior to submission of the Letter of Intent. Is this the intention or is it referring to the preferred session of the Scientific Advice (SAWP Meeting)? Does this pre-notification link to the 'early engagement' advocated for in line 121? The order of events here is not clear.	
Line 135		This information should be publicly and centrally available on a website.	
Line 139-161; 186-189; 260-263		In order to avoid hurdle of dissemination of documents to HTAB, it would be useful to use the same IT technology to share documents and comments that is used by EMA. Where agreed by the company, information could be shared with the EMA and HTAB at the same time and with the same content in order to ensure a more coordinated process.	
Line 140-141		We agree that it is preferable to have one principal point of contact and seek clarification of who this principal point of contact should be. There should be one project manager for	

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		each main participant, i.e. one scientific advice officer, one HTAB project manager, one project manager from the company. It would be useful to clarify that a specific annex or section in the Letter of Intent will be dedicated to this information, and that it will be shared with all participants.	
Line 144-148		We agree with the need for involvement of clinical experts and patient representatives. The process for their identification should be further clarified, especially if several experts come into question. The company should also be able to make proposals in that respect and have the right to bring their own experts. The company should also be advised in advance of the meeting which experts the HTAB and EMA have invited to participate. The EMA refers to its standard policies for conflict of interest, and it would be useful to have an indication on whether HTAB will also rely on the EMA standard policies in that respect.	
Line 149		The process, timeline and expectation of an early draft timetable should be better defined.	
Line 153		Will the EMA also send the calendar meeting requests to the applicant?	
Line 154-156		Would it be possible to give HTAB access to Eudralink?	
Line 157		The roles and responsibilities of all participants should be further clarified, especially in a scenario with one principle	

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		point of contact for all stakeholders.	
Line 165-169		It should be mandated and not optional that the participating HTABs review the draft briefing book and provide comment or confirmation of this. In case only a limited number of HTABs plan to attend the TC, the company should be allowed to cancel the TC and to ask for the receipt of written comments, if any.	
Line 188-189		We would favour a stronger statement regarding the need to share comments made amongst participants.	
Line 190-191		The timelines for the EMA and HTAB to send comments on the draft should be specified in advance and allow the company ample time to make the appropriate changes if needed.	
Line 192-194 and 221-223		There is value in accommodating discussion on unplanned topics that emerge through the natural course of meeting dialogue. These ad hoc questions could perhaps be addressed by the EMA and HTABs with preliminary commentary (and noted as such) in contrast to the formal responses that accompany the pre-specified applicant questions.	
Line 192-194		The final briefing document should be shared with all participants (also including clinical and patient experts, if they took part in the discussion).	
Line 199		The figure could be further refined and made clearer. In particular, it would be helpful if the timeline without pre-	

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		validation TC (option 2) would be included in this diagram. Submission of the LOI is not listed here. If this is the activity that initiates the pre-notification phase then it should be stated and any activities prior to this (i.e. early engagement pre-LOI) should also be specified. One page dedicated to this table would make it easier to read.	
Line 209-210		In order for the applicant to better prepare the face-to-face meeting, HTAB should agree to some key principles, including the need to clarify a list of questions to be discussed during the meeting and the background for these questions. It should also be clarified if/how HTAB comments will be send to EMA.	
Line 213		Suggest to define the deadline for the company to send the PSA meeting presentation as a minimum number of days before the meeting rather than "within 2 weeks of receipt of the list of issues"	
Line 213-228		The timelines for sending the written responses to the list of issues (line 213) and the amended development plan (line 228) do not appear to be consistent.	
Line 232-239		A preparatory TC between the EMA and HTAs is welcome. Beyond identifying divergences, this TC should also clarify where there is alignment between the regulators and the HTAB. Alignment should also be clearly communicated to the applicant prior to the face-to-face discussion. This will allow re-allocating more time during the face-to-face meeting to	

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		address the identified divergences and find ways to address them. The timing of a preparatory TC should also be clarified. It should occur in advance of provision of slides and responses.	
Line 232; 235-236		In the current PSA process, it seems that HTAB have limited opportunities to also coordinate amongst them. More effort should be put on aligning HTA positions prior to meetings and interactions. This role should be taken by the HTA project manager identified at the beginning of the process and should also be communicated to the industry in order to support the project manager with any relevant information and input.	
Line 240-243		We welcome the HTA co-chair function in order to ensure that HTAB are actively engaged in the discussion. All participants should commit to active contributions in PSA and the co-chair should ensure that all HTAB actively contribute to the discussion.	
Line 250-252		Where patient representatives are involved, they should be involved early on in the process and not only at the stage of the face-to-face meeting. Further clarification is needed in terms of who decide on the participation, who contact them, who brief them on the purpose and role of the meeting. Furthermore, in addition to patient representatives, the inclusion of other experts including clinical experts should be considered and agreed with the company.	
Line 253-54		The discussion among regulators, HTAB and sponsors should	

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		focus on issues of divergent views to ensure best use of available meeting time. A method for resolving differences in opinion should be developed and the discussion should allow sufficient time and opportunities to resolve differences where possible.	
Line 258		The minutes should also reflect the EMA views.	
Line 260-263		There should also be a consolidated feedback from HTAB. The feedback from HTAB should go beyond minutes and should take the form of a joint SA report; it should be timely and precise and approved by all participating national HTAB. Where diverges exist between HTAB, these should be clearly outlined in the joint HTA SA report. This joint SA report should be available to the sponsor as a reference document for subsequent HTA discussions. It should therefore be aligned with any requirements listed in national advice protocol for official purposes. The HTAB co-chair identified could be responsible for delivering this consolidated feedback.	
Line 272		It would also be helpful if an example of a timeline without pre-validation TC (option 2) would be included. It would also be helpful to include the early engagement or pre-notification steps and ensure this lines up with the earlier flow chart.	