European Medicines Agency
Pre-Authorisation Evaluation of medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDANCE DOCUMENT ON QUALIFICATION OF BIOMARKERS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	EFPIA	
2	FDA	USA
3	EuropaBio	Belgium
4	Hoffmann-La Roche Ltd	
5	Merck Sharp & Dohme (Europe) Inc.	
6	GE Healthcare Ltd.	UK
7	European Biopharmaceutical Enterprises (EBE)	Belgium
8	Schering-Plough	
9	Gilead Sciences International Ltd	UK
10	Critical Path Institute: Predictive Safety Testing Consortium	USA

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
SPECIFIC COMMENTS ON TEXT		
GUIDANCE document		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
1. General (definitions)	Although the guideline states (see top of page 2) that it is applicable to all sorts of 'innovative methods or drug development tools' (i.e. not just biomarkers), the word 'biomarker' appears almost exclusively throughout the document, including the title. This is confusing and potentially restrictive.	The procedure has been renamed to "Qualification of novel methodologies for drug development" to avoid this confusion.
2. General (definitions)	The definition of the EU term "qualified" is not clear a suggestion would be e.g. EMEA recognition of biomarker for a specific defined purpose in (pre) clinical development or regulatory decision-making.	The term "qualified" is not used any longer but an "opinion" will be given by the CHMP.
3. General (other routes of advice)	Currently companies can request briefing meetings with the Pharmacogenomics Working Party (PGWP) or the Innovation Task Force to discuss biomarkers/new methodology. Will this still be possible?	Yes. Briefing meetings with the PGWP on development of genetic biomarkers can still take place (before the procedure of qualification of biomarkers) and are encouraged in an early stage of development. Briefing meetings are not granted during the biomarker qualification procedure. However, in case of genetic biomarkers the PGWP will be usually involved in the discussion meeting with the company. Briefing meetings do not result in a consolidated CHMP view on the issue. Based on the concept of scientific brainstorming briefing meetings are normally granted once only on a specific issue. Meetings with the Innovation Task Force are still also possible.

[1] Where applicable

4. General (definitions)	The distinction between “Qualification Advice" and "Scientific Advice on future protocols and methods for further method development towards qualification” and the existing “Scientific Advice/Protocol Assistance” procedure is not clear.	The existing Scientific Advice/Protocol Assistance procedure is prospective advice related to a specific product(s), indication(s) or technology within a development program. There is no change this type of advice even when the new qualification of biomarker procedure has been fully implemented. The existing Scientific Advice procedure is always confidential. The terminology has been changed into Qualification Opinion and Qualification Advice (on future protocols and methods for further method development towards qualification**)**. The new Qualification Opinion is an assessment of data which can result in an opinion from the CHMP qualifying the biomarker for a specific purpose. Information on a qualified biomarker will be made public. The content of the public document will be agreed with the sponsor. The Qualification Advice is also assessment of data in addition to recommendations from the CHMP for further development needed to qualify the biomarker. This procedure will always be confidential.
5. General (procedure)	Given the difference in confidentiality and data requirements between the two procedures (“Qualification Advice" and "Scientific Advice on future protocols and methods for further method development towards qualification”), it would seem critical that there is agreement with the Applicant on which procedure is to be followed prior to submission and initiation of the process.	It is not necessary to have an agreement at the start of the procedure on which route is to be followed, this can be decided after assessment. The Applicant can choose to go for either procedure as preferred.
6. General (appeal)	In the event of that the qualification is not accepted what options does the Applicant have to appeal or request that the public consultation is held/not held? Will a negative outcome be made public?	If the biomarker is not accepted for an opinion the procedure will turn into a Qualification Advice which will not be made public. There is no appeal procedure; the Applicants are encouraged to come for follow-up procedures. Clarification requests on the Qualification Advice can be submitted.
7. General (follow-up)	What should the sponsors (or EMEA) do in the event that significant new scientific information relevant to the qualified biomarker becomes available after final adoption of the biomarker Qualification Advice?	A follow-up procedure can be initialised.
8. General (public consultation)	Why is a public consultation needed and what are the reasons for having it at the suggested time point of the procedure (i.e. after the finalisation of the SAWP report)?	The public consultation of the scientific community will ensure that CHMP/SAWP shares information and is open to enlarged scientific scrutiny and discussion. The EMEA will organise workshops as deemed needed and the final

		report will be prepared after discussion and consideration of the comments received. Nothing will be published without the Applicant's consent.
9. General (time lines)	The timeframe for Qualification advice/Scientific Advice on biomarkers development is very long compared with the existing Scientific Advice procedure. Please explain why this is?	The published timelines have been shortened and are a suggestion only. EMEA can always discuss and try to satisfy the wishes of the sponsor regarding timelines (The time lines are given in calendar days.) After the pilot phase we will be able to readjust the time lines if deemed necessary.
10. General (time lines)	Will clock-stops be possible?	Yes, the Applicant can ask for a clock-stop at any time point during the procedure.
11. General (fee)	What will the fee be?	The procedure for "Qualification Opinion" and "Qualification Advice" will have the full scientific Advice fee i.e. 72 800 EURO. Follow-up advice will be 36 400 EURO accordingly. Small and Medium sized Enterprises (SME) will have the usual 90% fee reduction.
12. General (final use)	Please clarify that if a Biomarker has been successfully qualified it is immediately available for usage and that sponsors would not have to wait for the update of any regulatory guidelines.	Yes, this is correct.
14. General (other agencies)	How will "other agencies" be involved in the procedure and at what stage?	It is up to the Applicant to contact other agencies than the EMEA before the start of the procedure (if the Applicant wants to involve more agencies than the EMEA). There is no formal parallel Qualification Advice with any other agency. There is, however, the confidentiality agreement between the FDA/PDMA and the EMEA which makes it possible to have the procedure going on at the same time in more than one agency. If the Applicant wishes to include more than one agency this should be done before the start of the procedure. Consequently there is no formal joint Qualification Advice at the end of the procedure but separate qualifications by the EMEA and the FDA/PDMA. Nevertheless, Applicants are encouraged to apply in parallel to the EMEA and FDA. The agencies will then communicate the assessment

		and meet with the Applicant together. This will maximise the chance for scientific consensus.
15. General Review of procedure	How will the review of the pilot procedure be conducted?	Once experience has been gained with approximately 10 procedures the EMEA will review the current proposal and amend it as required. Comments form the (ca 10) Applicants will be taken into consideration.
16. Page 2	It is unclear whether or not an applicant may choose to use the existing Scientific Advice procedure for advice on biomarker future development and qualification, alone or in combination with other questions related to the development programme on a molecule.	It is definitely possible for an applicant to choose the existing procedure for Scientific Advice/Protocol Assistance to discuss the development of biomarkers related to a specific drug product or indication.
17. Page 2	Please clarify if the same Qualification Team will be involved in all procedures for a single biomarker, or set of biomarkers, related to a single molecule.	Yes, every effort will be undertaken to keep the same team to ensure optimal use of the experience accumulated.
18. Page 2 Operations	What will be the criteria for the selection of the Qualification Team? Will this be a transparent process including a publication of the composition of the Qualification Team and when will such publication occur?	The Qualification Team leader will be a volunteer from either the SAWP or the CHMP. The Qualification Team leader will select team members from his/her network including external experts. In addition to these Qualification Team members experts can be suggested for the Qualification Team from SAWP members, CHMP members, the EMEA secretariat or the Applicant. The Qualification Team members will be announced to the Applicant a week before the start of the procedure.
19. Page 2 Operations	Please indicate if a shorter "Scientific Advice on future protocols and methods for further method development towards qualification" procedure may be possible for a follow-up request.	In principle, the same timelines will be followed for follow-up advices, because it is expected that new data will be submitted. However, these timelines have been shortened and are a suggestion only. EMEA can always discuss and try to satisfy the wishes of the sponsor regarding timelines
20. Page 4 Day -30	Will there be fixed dates for the start of the procedure?	The start dates will be fixed around the SAWP meeting dates but no fixed deadline for submission of Letter of Intent is foreseen for now.
21. Page 4 Day -30	Please clarify timing for submission of the final dossier in relation to Day 0?	It is foreseen that the Applicant should send in more or less final package at the stat of the procedure. If the Applicant wishes to discuss the format/content of the package the EMEA secretariat and the assigned Scientific Administrator will be available for discussions before the start of the procedure.

22. Page 4 Day -30	Will the submission be done both electronically and in paper?	Yes, one paper copy has to be submitted as well as the request in electronic format.
23. Page 4 Day -30	Could you please clarify the period of validation?	Validation as for the existing Scientific Advice/Protocol Assistance procedure is not foreseen (see above).
24. Page 4 Day 0	Five members should be the *minimum*, not the *maximum*, for the Qualification Team.	We appreciate this comment and will change the procedure accordingly.
25. Page 4 Day 0	It is suggested that a statistician is always a member of the Qualification Team.	We appreciate this comment and will normally have a statistician as part of the team.
26. Page 4 Day 0	It appears to be possible that the Qualification Team could include industry experts. Please clarify.	Industry experts would only be considered for the Qualification Team if they did not have any conflict of interest with the procedure.
27. Page 4 Day 0	It is unclear who will participate in the preparatory meeting within 15 days after submission.	The Qualification Team (as many members as possible) and the EMEA scientific administrator will take part.
28. Page 5 Day 90-120	An additional meeting with the Applicant is mentioned. The circumstances under which this would be needed are not clear. Would this trigger a clock stop?	The need for an additional meeting would be reached by continuous discussion with the Applicant. A clock-stop may not be needed but will be possible if the Applicant wishes so.
29. Page 5 Day 90-120	What happens if the Applicant withdraws the request?	If the procedure has started the applicant will be eligible to pay the full fee. No information will be made public. A Qualification-Team report will still be sent to the Applicant.
30. Page 5 Day 130	It is unclear if the draft report of the Qualification Team to CHMP will be shared with the applicant prior to the CHMP meeting.	In line with the current Scientific Advice procedure draft reports will not be shared with the Applicant. However, in the List of questions there will be a scientific background section describing all issues raised in the reports in depth.
31. Page 5 Day 130	Will the Applicant have the opportunity to attend an Oral Explanation at the CHMP?	In line with the current Scientific Advice procedure, there will be no Oral Explanations at the CHMP. All face-to-face discussions will take place between the Qualification Team/SAWP and the Applicant.
32. Page 5 Day 160-220	Clarify timelines further (without lengthening the overall process) e.g. reduce consultation to 6 weeks, allowing 5 working days for removal of confidential information and 5 additional ones for consolidation of the	We appreciate this comment and will amend the procedure accordingly.

	public comments.	
33. Page 5 Day 160-220	Specify the conditions for when a Workshop would be needed and the associated timelines. Clarify if this is an open forum.	A workshop will be organised if comments are received during the public consultation, which potentially have a significant impact on the scientific conclusion. The aim of the workshop will be top engage all experts, academia, industry, regulators
34. Page 6 Day 220	When will the final Qualification Advice be made public?	The final Qualification Advice will be published within 15 working days after the final CHMP opinion.

Template for pre-clinical submission

Line no. + para no.	Comment and Rationale	Outcome
General	There is not a template for translational safety biomarkers.	Sections from both templates could be combined into a single document in the case of translational safety biomarker.
Page 9	It is unclear if the headings in the italics are the sub-sections of the Executive Summary or separate parts of the dossier.	The headings in Italics are separate parts of the dossier. The heading of the executive summary will be changed to avoid confusion.
Page 9	There is separate guidance on the content and format of a VXDS submission (EMEA/CHMP/PGxWP/20227/2004) to the EMEA. A statement could be included if the content and format of a VXDS submission to the EMEA could be useful for the applicant to consider.	Agreed. The proposed format is not binding and alternative formats such as the one used for VXDS could be acceptable.
Page 9	The content of section a) seems also to be included in section c) i " Scientific rational for the proposed biomarker."	The section a) refers to the condition where the biomarker could apply whereas the section c) to the biological, pharmacological or physiological background of the proposed biomarker.
Page 9	For Clinical drug development setting: 1. statement a) "Briefly summarize" is described here whereas "summarize" in statement a) in nonclinical setting.	The documents will be harmonised accordingly
Page 9	The process should also include provision of scientific advice on the initial use of a biomarker in humans based on submission of only preclinical data.	The clinical template does in no way exclude the submission of preclinical data.
Page 9 **Section 1c**	**Background information on the proposed biomarkers**: Section needs clearer information on analytical validation of the testing	Agreed: Reference to the analytical validation and the biological variability will be included in the document.

	methodology, particularly if a common method (with immunological basis) is used across different species. Regarding analytical/technical issues, the emphasis should be more on the limits of quantification (analytical sensitivity) rather than the limits of detection. The acceptance criteria that the applicant used to derive such limits should be emphasized. More importantly, the expected dynamic range of the biomarker measurements in the intended target population should be provided, and the emphasis should be more on whether or not the dynamic range of the analytical/technological platform covers this intended range. Also, the biological (inter-subject) variability of the biomarker measurements should be reported.	
Page 9 **Section 1c**	Any preliminary information on the characteristics of the biomarker signal will assist in the assessment of suitable protocol design.	Agreed. The sponsors are welcomed to present any preliminary information that could assist in optimising the protocol design. :
P9 Section 1.d.i)	The term 'candidate drug *prenomination'* is unclear. Another word is thus proposed.	Agreed: "candidate drug ~~prenomination~~ **identification**"
Page 9 Section 1.d iii)	Clarification regarding the claims on biomarker performance (e.g., sensitivity, specificity) will be helpful; for example, comments/emphasis about internal and external cross-validation methods.	We acknowledge the point made but we will not include additional information on the claims since the document is sought to be a **high level** guidance.
Page 10 Section 2	The draft guidance indicates that the requirements for submitting evidence from primary data are more stringent than for submitting evidence from the published literature to serve the same purpose. For non-clinical experiments the document appears to require that our experiments will be conducted under GLP (-like) conditions, a burden that is not placed on experiments that others conducted and reported in the literature. Primary data from non-GLP experiments should be acceptable for scientific advice review purposes.	This is not stated in the guideline. Obviously in the majority of the cases that the applicants submit primary data, they will be able to submit a more comprehensive package compared to the cases where data come from literature. GLP experiments will not be a requirement for generating biomarker qualification data.
Page 10 Section 2.a i)	Clarification regarding "prespecified statistical analyses" will be helpful. Biomarker studies (e.g., genomics/proteomics experiments) typically require a multitude of statistical methods for interrogating the data and deriving insights on the utility of biomarkers. So a broad	Agreed. The term "pre specified statistical analyses" will be replaced by "statistical plan"

	overview of the statistical analysis strategy will be more appropriate for a biomarker study plan rather than a specific analysis plan that are required in typical clinical trials.	
Page 10 Section 2.a i)	Moreover, some clarification will be helpful regarding additional requirements/considerations when the applicant uses retrospective sample cohorts for deriving the biomarker findings (e.g., analysis of archived samples from old clinical trials, case-control studies, etc.).	We acknowledge the point made but the scope of this guidance is to suggest the formatting and not to address methodological issues.
Page 10 Section 2aiii) & b and Page 12 Section 2aiii)	It is unclear whether the term "raw data" accurately reflects what is required. It is unlikely that "raw data" would be available from published literature.	On a case by case basis raw data might be requested. The document will be updated accordingly.
Page 10 Section 2aiii) & b and Page 12 Section 2aiii)	It will be important to agree with the EMEA on the electronic format of any submitted data sets prior to initiation of the procedure. A suggested rewording is thus proposed: "The ~~raw~~ data **set** should be **provided on request and** submitted electronically in a ~~pre-specified~~ format agreed with the agency **during the review**."	OK, however the term raw data will not change.
Page10 Section 2.b)	The following statement under "Evidence from published literature" is unclear: "Discussion with the EMEA on appropriate methods/approaches is recommended prior to submission." It is unclear how and when and with whom this discussion would take place. As a briefing meeting? With whom? As scientific advice?	The document will be updated. The discussion refers to the validation step. It involves communication with the Scientific Advice secretariat and the appointed product manager. The discussion will be organised as an informal teleconference or a face to face meeting
Page10 Section 2.b)	The sentence "Consider issues such as Search Strategy, Selection of Studies, … " is unclear. Terms such as "Search Strategy" look like specific technical terms which is implied by the fact that they begin with capital letters.	The terms in capital are not specific technical terms. The section will be updated.

Template for clinical submission

Line no. +	Comment and Rationale	Outcome

para no.		
General	The draft proposed application formats separated into non-clinical and clinical BM are restrictive given that non-clinical data could be used to support a clinical BMs and vice versa and does not easily adapt to the mix of clinical and non-clinical data that would be used to support translational BMs. The application formats should allow submission of non-clinical and clinical data to support BM usage in either/both setting(s).	The application format refers to the intended use of the BM in a non-clinical or clinical setting. The proposed format does not exclude the possibility to include non-clinical data in support of a clinical application and vice versa. It will be added that the proposed format is not binding and thus sections from both templates could be combined into a single document in the case of translational safety biomarker.
Pages 9-11	In the sections addressing the impact of the proposed non clinical and clinical biomarker it may be useful for the applicant to include any details of where the biomarker may have an impact on current guidelines / requirements.	Agree. This will be added.
P11	The text for clinical format is very similar to that for preclinical format. The text for clinical format could easily be combined with that for preclinical format (with appropriate subsections where necessary). If it is kept separate there should be a check for consistency between the similar paragraphs describing the preclinical and clinical formats. For example; 'summarise' vs 'briefly summarise' there is no mention of 'raw data from publications' in the clinical format paragraph on 'Evidence from published literature'.	Separate templates for non-clinical vs. clinical applications are considered appropriate, but it is agreed that harmonization should be done where possible.
Page 11 Section 1. b ii)	Recommend defining meaning of "*reference standard*".	Agree. The sentence is changes to: "Describe and justify the proposed reference standard for the intended application of the exploratory biomarker in clinical trials. The reference standard should optimally provide a true value of the variable being assessed by the exploratory biomarker in the relevant clinical setting, and thereby validate the exploratory biomarker and define its diagnostic performance."
Page 11 Section 1. ci)	The "technical aspects" of the proposed biomarker are discussed, and specific analytical performance measurements are mentioned. New IVD tests are regulated under the *In Vitro* Diagnostic Directive (IVDD). It is not clear how the EMEA's role would fit with the existing IVDD. Please clarify the EMEA's role in assessing the analytical performance as part of the scientific advice/qualification procedure.	This template should be used as a format guidance and does not address the actual assessment of data.
Page 12 Section	'EU and non-EU populations' are not defined and are not consistent with the ICH racial definitions (Asian, Black, Caucasian). EU	Agree. The following has been added to section 4: "Potential impact of various intrinsic and extrinsic factors on expected test performance, e.g.

1.d.iv)	populations contain a mix of these races due to immigration so the statement "Expected test performance in populations with proven, probable or possible disease/condition, both in EU and non-EU populations" is inappropriate. Please clarify what is the definition of an EU and non-EU population; if not definable a suggested rewording is thus proposed.	gender, age, ethnicity, smoking habits, clinical practice etc."
Page 12 Section 2 a)	Pharmacogenomic studies are often conducted by pooling data across clinical trials. Do "*protocol*" and "*study report*" in this section refer to the clinical study protocol and clinical study report from the trials from which samples were obtained or does this refer to a protocol and study report specifically for the biomarker study?	Agree. This will be clarified
Page 12 Section 2b	The reference "… Cochrane Collaboration (www.cochrane.org)" is restrictive. A proposed rewording is thus suggested.	Agree. Changed to: "It is recommended to perform a systematic review following a predetermined search protocol and analysis plan (such as the scientifically sound search strategies published by The Cochrane Collaboration (www.cochrane.org)."