13 April 2021
EMA/191686/2021
International Affairs

# Overview of comments received on 'Public guidance: Parallel application for EU-M4all (Article 58) opinion and Centralised Marketing Authorisation procedure' (EMA/104275/2021)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | World Health Organisation (WHO) Regulatory Convergence Network and Facilitated Product Introduction Teams |
| 2 | Global Accelerator for Paediatric formulations (GAP-f) |
| 3 | EFPIA (European Federation of Pharmaceutical Industries and Associations) |
| 4 | Wellcome Trust |
| 5 | Centre for Innovation in Regulatory Science (CIRS) |
| 6 | ClinChoice |
| 7 | NextraResearch S.r.l. |

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# 1. General comments – overview

| Stakeholder no. *(See cover page)* | General comment (if any) | Outcome (if applicable) |
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| 1 | The proposal to have parallel EUM4-All and marketing authorisation applications is very well received and strongly supported. The efficiency gained in parallel submissions and reviews will hopefully encourage more applicants to use the EUM4-All procedure. | Thank you for the support. Your interest in this important topic is appreciated. |
| 1 | Additional highlights on the advantages of having the possibility of two separate dossiers with allowed differences could be added (e.g. different packaging, different line of manufacturing, different product information for the different markets, differences in benefit-risk considerations etc.) versus a standard marketing authorization application supported by data in various settings (including clinical data from LMICs) with involvement of NRA from LMICs (as done in the case of Ebola vaccines). | Thank you for this consideration, it is a very good point. We have noted it, but we prefer not to include examples in this specific case at this point in time. This may be addressed when more experience has been gained. |
| 2 | The guidance states "This initiative offers opportunities for work-saving and reduced duplication of efforts since elements of the CHMP scientific advice and assessment for the centralized procedure and EU-M4all are the same." If that is the case, and there are efficiencies, could some partial fee reduction be considered as two full filing fees for both dossiers maybe very prohibitive for many applicants? | As included in the guidance, applicants can request a total or partial fee waiver from EMA's Executive Director, who will evaluate and decide on this request. |
| 2 | Please consider adding further clarifying language around how centralized authorization and therefore marketing rights can be obtained for a EUM4all application would be beneficial. Considering the intent of the original procedure was for medicines that were not to be marketed in the EU (and that was a requirement to meet the eligibility of an Article 58 application), it is unclear how this can have changed now for a parallel process. | There is no change as previously it was possible for a MAH to also obtain a scientific opinion under EU-M4all (Article 58). Both procedures (EU-M4all and EU-MAA) remain with the same exact obligations/requirements as if they were run separately. |

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| | | After the adoption of the CHMP scientific opinion for an EU-M4all medicine, there is no European Commission decision, and no marketing rights in Europe.<br><br>The marketing authorisation decision is under the remit of the NRAs in the target countries (reliance principle). |
| 2 | How is eligibility assessed for an EUM4all dossier if now there is no restriction on marketing in EU? What are the eligibility criteria? | Medicines/vaccines eligible to EU-M4all are intended to prevent or treat public health priority diseases. Eligibility is agreed with WHO. In the case of the centralised procedure, eligibility is unchanged and assessed by the Committee for Medicinal Products for Human Use (CHMP). The medicines in this parallel procedure should be suitable for both EU and non-EU populations.<br>For more information, see: questions 2.1, 2.2 and 2.3: Pre-authorisation guidance \| European Medicines Agency (europa.eu) and question 2-6: PRE- and POST- "ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu) |
| 2 | In both the Public Guidance text and the Visual Guide, there are references to two eCTD dossiers that may be similar but not exactly the same with significant amount of overlap in the submissions. How exactly are the dossiers different in the case of parallel processes? Do all post-approval documents need to be duplicated as well (safety reports, annual reports, etc.)? | Both technical dossiers of the medicine shall be identical. Some differences may exist, such as different formulations, pharmaceutical forms, storage conditions or routes of administration, in relation to the conditions of use in EU versus target countries.<br><br>Since different post-approval procedures may apply to either procedure, different post-approval documents may have to be submitted. For instance, the frequency of PSUR submissions should be in accordance with what is stated in |

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| | | the scientific opinion under the EU-M4all procedure, which can be different for the EU-MAA. The format of the PSUR shall follow the structure described in the Commission implementing Regulation (EU) No 520/2012. In addition, the EU-M4all opinion Holder needs to address the national requirements of the countries where a marketing authorisation has been granted, including estimated exposure, adverse events, risk minimisation measures, etc. Therefore, a single PSUR covering both procedures shall not be acceptable. |
| 2 | Can the product to be reviewed for both EU-MAA and EU-M4All be identical in all respects (Active Pharmaceutical Ingredient, formulation, indication, instructions for use)? | Indeed, it can be identical.<br>We have updated the text accordingly:<br>'The technical dossier of the intended medicines shall be identical. Differences such as different formulations, pharmaceutical forms, storage conditions or routes of administration should be discussed with the Agency before the submission to determine whether they are compatible with a parallel assessment.' |
| 2 | How is this duplicated effort and cost likely to increase use of the EU-M4All pathway compared to the SRA to WHO pre-qualification/CRP pathway? | This initiative is an additional pathway intended to facilitate rapid access to innovative medicines with special focus in LMIC population. It is an improvement of the existing procedure.<br>Applying for the parallel EU-M4all + EUMAA does not prevent to apply for WHO pre-qualification/CRP procedures, in fact the CRP SRA remains a way to speed up and increase access to medicines/vaccines by patients. |
| 3 | EU-M4all is a welcomed approach to accelerate global access to important medicines and this guideline is very useful. However, further clarifications and alignment regarding terminology used in the | Thank you for the support and comments. We will strive to reduce any discrepancy in terminology. |

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| | draft guideline as compared to other EMA communications such as the M4all promotional leaflet as well as the EMA webpage "Medicines for use outside the European Union" and the EMA Q&A on Article 58 procedures is necessary.<br><br>**Scope of the EU-M4all procedure**<br><br>The scope of the EU-M4all procedure regarding supported countries and type of eligible medicines requires clarification. Art 58 stipulates that the Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. However, the legal provision does not limit this cooperation with WHO to LMIC or to only "essential" medicines. As such, the procedure should not be ruling out a collaboration with other countries in the context of reliance or a collaborative registration procedure. Furthermore, the scope may not be strictly limited to "essential" medicines but could include other important health products. The EMA Q&A on Article 58 procedures does not provide these limitations.<br><br>**EU-M4all opinion vs CHMP opinion/EC Decision**<br><br>The overall benefit for the applicant of using this parallel procedure is unclear.<br>Parallel procedures make the process very complicated and burdensome from an administrative perspective, specifically for accelerated procedures. The advantage of the EU-M4all parallel application versus obtaining a normal CHMP opinion/EC Decision and utilising it for the submission in countries relying on EU assessments or approvals is unclear. A single procedure that allows EU approval together with the possibility to feed into Ex-EU NRA local approval procedures would be preferred.<br><br>**Local uptake and impact of EU-M4all opinions is crucial** | This is noted. The text has been checked to avoid any unwanted restriction.<br>The guidance should not limit, even if EU-M4all procedure is mainly focused on low- and middle-income countries (LMICs).<br><br>This comment is noted. The scientific opinion for EU-M4all takes into consideration the target population and the local conditions of use, which can be different from the EU population and EU conditions of use. However, assessing both at the same time decreases the duplicative assessment of the common parts.<br><br>This is fully supported and implemented in practice. |

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| | We would recommend the WHO to closely engage with regulators or experts from the countries where the medicines are intended to be used, to ensure that CHMP opinions are well accepted and the timeline of national assessment is faster than with other SRA approvals.<br>The involvement of local NRAs and the opportunity for capability building should be included in the procedure. A description of the involvement of local NRAs should be included.<br><br>**Life-cycle management**<br><br>Life-cycle management of the EU-M4all opinion and the CHMP opinion should be pragmatic to conserve resources from EMA and applicants. A simple cross-reference to the EU license should be allowed in case parallel changes are pursued.<br>If applicants do not develop the medicines for all different markets strictly parallel, there is no need to keep the EU-M4all license updated. Further discussion about the efficient management of the life-cycle post-opinion is required. | WHO also fully supports this initiative and the collaboration between WHO, EMA and national regulators/experts is a necessity.<br>A sentence regarding Experts/Observers has been included. Information regarding experts/observers involvement can also be found in section 27 of the Q&A [PRE- and POST-"ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (ec.europa.eu)]. The information contained in this document applies to the parallel submission.<br><br>Although we could agree, this is unfortunately not possible for reasons of possible impact of legal challenge of a combined outcome.<br>See also comments below. |
| 4 | We are supportive of the proposal to run the evaluation of centralised and EU- M4all applications in parallel. The aim to reduce work and avoid duplication is needed and we hope that it leads to wider use of the EU-M4all pathway to enable faster access to vital medicines for those living in LMICs.<br><br>A critical part of the process is that WHO nominated experts and observers from target country authorities take part in the evaluation. We would encourage greater inclusion of target country authorities, and we would not wish to see this move to parallel assessment being to the detriment of this inclusion.<br><br>It is also vital that the process is clear to the applicants to encourage use of this pathway. The details in the "general criteria for a parallel assessment" are helpful particularly allowing for differences in formulation, storage conditions and route of | Thank you for the support and comments.<br><br>A sentence regarding the roles/responsibilities of Experts/observers has been included in the guidance. See above response.<br><br>Both technical dossier of the intended medicines shall be identical. However, some differences may exist, such as different formulations, pharmaceutical forms, storage conditions or routes of administration. These differences |

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| | administration. This will allow developers to consider the different needs of LMIC health care systems.<br><br>It is also useful to highlight the differences between the two dossiers needed and signpost to more information.<br><br>It would be helpful to know more about what happens when timetables differ and how this affects or could impact the parallel assessment process. | should be discussed with the Agency before the submission to determine whether they are compatible with a parallel assessment. This will be assessed in a case by case basis and will be matter of assessment.<br><br>Guidance updated accordingly. |
| 5 | It would be useful to clarify the exact differences between the old and the new process – it may be helpful to demonstrate this graphically, as well as to show what are the common touch points as part of the parallel process, and what remains separate.<br><br>It may also be helpful to provide further rationale on the parts of the process that will remain separate e.g. validation | Thank you for this suggestion. We will add a visual representation of the procedure as an annex in a second phase (not to delay publication). |
| 6 | Do we need to consider & furnish country specific requirement intended for marketing of the medicinal products while submitting dossier for EU-M4all parallel review? | The EU-M4all Holder needs to address the national requirements in the countries where a marketing authorisation is intended. EMA does not hold this information (we would suggest to refer to WHO). |
| 7 | Concerning the post-opinion phase, from line 70, it could be useful to add an impact analysis for the benefit risk of these products in the annex to module 1, related to the analysis of clinical and preclinical data, possibly then planning update times for the PSURs in relation to the results of the impact analysis document | The same requirements for pharmacovigilance systems and risk management plans (RMPs) apply to applications under EU-M4all and centralised procedure. This is explained in question 31 "Is a pharmacovigilance system and risk management plan needed?" on the PRE- and POST-"ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu) |

## 2. Specific comments on text

| Line no. | Stakeholder no.<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br><br>*(To be completed by the Agency)* |
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| 14-15 | 3 | Comment: "This work is done in cooperation with the World Health Organization, and with regulators and experts from the LMICs where the medicines are intended to be used."<br><br>The Procedure should not be limited to LMIC as this restriction is limiting its scope beyond what is written in the legal provision of art 58.<br><br>It is proposed to clarify in the current guideline how regulators and experts from the Ex-EU NRAs are chosen for cooperation, under which confidentiality agreements, as well as at what stage of the procedure and with what remit they are included in the review process.<br><br>Proposed change (if any): Article 58 of Regulation (EC) No 726/2004 provides that the European Medicines Agency (EMA) may give a scientific opinion for medicines intended to be used outside the European Union~~, primarily for low-and middle-income countries (LMICs)~~. This work is done in cooperation with the World Health Organization, and with regulators and experts from the ~~LMICs~~ **third countries** where the medicines are intended to be used.<br><br>Please add more details on the collaboration framework with third countries. | Text modified.<br>-The procedure is mainly focused on low- and middle-income countries (LMICs), hence this reference is maintained.<br>-Agree with second change (reference to third countries).<br>-A sentence has been included regarding the roles/responsibilities of Experts/observers. See response above.<br>Information regarding experts/observers involvement can be found in section 27 of the Q&A [PRE- and POST- "ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu)] and applies to the parallel submissions. |

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| 14 | 7 | Comment:<br>The Parallel application for EU-M4all could be extended to the medicines for veterinary use<br><br>Proposed change (if any):<br>medicines for human use and for veterinary use | Article 58 of Regulation (EC) No 726/2004 refers to human medicines. This point is outside the scope of this guidance. We will inform our colleagues of this suggestion. |
| 21 | 5 | Comment: Could a reference be added to support this statement?<br><br>Proposed change (if any): | Guidance generally don't include such references.<br>We refer you to the publication:<br>Cavaller Bellaubi M, Harvey Allchurch M, Lagalice C, Saint-Raymond A (2020): The European Medicines Agency facilitates access to medicines in low- and middle-income countries, Expert Review of Clinical Pharmacology, DOI: 10.1080/17512433.2020.1724782. |
| 22-25 | 3 | Comment:<br>This guideline will be applicable for some time, hence please delete wording that may become obsolete.<br><br>Proposed change:<br>Since the introduction of the procedure in 2004, ~~11~~ **a number of medicine**s have received a positive EU-M4all opinion. ~~Five~~ **Some** of them also have **received** ~~(or have had)~~ a centralised European marketing authorisation (MA) **obtained before or after the EU M4all opinion**. ~~Four of these 23 medicines obtained the centralised authorisation before the EU-M4all opinion, one after the EU-M4all opinion.~~ | Accepted. |
| 26-28 | 3 | Comment:<br>We assume that the EU-M4all procedure continues to be applicable to dossiers which are not submitted in parallel with a Centralised Marketing Authorisation. There are many good reasons why applicants might not be able to submit applications at the same time when | Accepted. Use of 'third countries' rather than foreign markets for consistency. |

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| | | considering the specific local healthcare system contexts.<br><br>Proposed change:<br>**In addition to the EU-M4all review of dossiers exclusively intended for foreign markets**, the EMA is now offering the possibility to run the evaluation of centralised and EU-M4all applications in parallel, to obtain an EU-M4all Scientific Opinion and a Centralised Marketing Authorisation about the same time. | |
| 29-30 | 3 | Comment:<br>Please clarify how the efficiency and reduced duplication of efforts beyond same overall procedure and Scientific Advice is to be gained. E.g. the EU-M4all leaflet mentions the assignment of the same CHMP/PRAC rapporteurs.<br><br>Proposed change:<br>This initiative offers opportunities for work-saving and reduced duplication of efforts since elements of the CHMP scientific advice and assessment for the centralised procedure and EU-M4all are the same, **and the CHMP/PRAC rapporteurs are the same for both parallel procedures**. | The benefit of having the same CHMP/PRAC rapporteurs for the procedure is stated in line 56.<br>The new approach is just beginning. When actual benefits are analysed more specific elements can be added. |
| 32 | 4 | Comment: Overall, this is a simple and straightforward section, however a pictorial timeline depicting key milestones may help applicants fully comprehend the process.<br><br>Proposed change (if any): Add timeline with key milestones to this section | Comment acknowledged.<br>A visual annex wil be added in a second phase not to delay publication.<br>In the meantime, thee timelines can be found on the EMA public webpage. |

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| 33-35 and footnote 1 | 3 | Comment: "…To meet the criteria for a parallel EU-marketing authorisation application (MAA) and EU-M4all assessment, the active substance(s) of both applications must be identical and the intended indication(s) must be comparable…"<br><br>"…Indications may differ slightly to reflect the context of use…"<br><br>Proposed change (if any): It would be helpful if the footnote could provide more clarity, i.e. what "differ slightly" includes. For example, whether an applicant could file parallel applications seeking a treatment indication in the EU but a prevention indication for markets outside of the EU. An example might be pre-exposure prophylaxis (PrEP) in HIV-1 infection vs. treatment of HIV-1 infection. If comparability is likely to be disease area specific, then disease area specific guidance is also welcome. | Thanks for the suggestion.<br>The text and footnote have been updated.<br>There will be an element of assessment on a case by case basis. |
| 33-38 | 3 | Comment:<br>The eligibility scope should be further clarified.<br>There is no restriction regarding the type of medicine that can be reviewed under the EU-M4all scheme. Please clarify that the medicines can also be identical.<br><br>Proposed change: Concerned medicines **can be identical or** may have different formulation, pharmaceutical forms, storage conditions or routes of administration. This means that the intended medicines must be chemically/biologically and clinically identical but can be physically distinct. | Accepted.<br>Paragraph has been updated. |
| 35 | 1 | Comment:<br>"EMA expects that both procedures are submitted by the same applicant". Would different applicants be | Not accepted.<br><br>The applicant/sponsor should be the same. |

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| | | accepted (e.g. two companies with signed agreements)?<br>The text could be made clearer<br><br>Proposed change (if any):<br>Both procedures should be submitted by the same applicant. | |
| 39-40 | 3 | Comment:<br>The timeline to request for the parallel process prior to submission is quite long.<br><br>Proposed change (if any):<br>As for any other initial MAA, eligibility for both procedures should be requested to EMA at the earliest 18 months before submissions and, at the latest 3 months before the MAA/EU-M4all are filed with the EMA. | Not accepted.<br><br>This is a standard timeline for EU centralised and EU-M4all applications.<br>The EMA recommends providing the eligibility request at the earliest 18 months and, at the latest, 7 months before the applications are filed with the European Medicines Agency. |
| 39 | 5 | Comment: Would it be of value to encourage stakeholders to request eligibility at the same time to ensure efficient planning?<br><br>Proposed change (if any): …eligibility for both procedures should be ideally requested at the same time to EMA | Accepted. |
| 41-50 | 3 | Comment: "…At time of filing, two separate eCTD submissions are required and cross-referencing to the other application is not allowed…" This means de facto the submission of 2 full dossiers, even if the dossiers for centralised procedure and EU-M4All are exactly the same. We see no benefit for the applicant as this requirement will only increase the regulatory burden. | One eCTD has to be submitted per application. The cover letter should explain whether the content is the same or highlights differences between the two to streamline the assessment. Following validation and if the parallel assessment meets the required criteria, both applications should follow the same timetable. The applications will start |

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| | | Further, it would also be helpful to clearly identify the differences between the centralised procedure dossier requirements and the EUM4All dossier requirements. **The document should clarify if two draft assessment reports will be produced (if two separate submissions are required)**; whether the same questions will be sent for each application and whether responses will be required for each application.<br><br>Clarity is also needed if the dossier should simultaneously be submitted to the concerned Ex-EU countries. Will there be direct collaboration with the EU-M4All evaluators and the NRAs regarding the application? In general, more information on interaction between EMA and NRA's on this process should be provided.<br><br>Proposed change (if any): To maximise the efficiency benefits of this parallel procedure and reduce duplication, **cross-referencing should be allowed**. The sections of the dossier where cross-referencing would be possible should be identified.<br>Only one set of questions and responses should be required for the parallel process. | with the same timetable, however during the assessment the procedural timetables may end up differing.<br>A single rapporteur assessment report (AR) and a joint List of Questions are envisaged during the evaluation timeframe. However, at the time of opinion two CHMP ARs and Opinions will be created, one for each procedure.<br><br>Former EU Member States are considered as third countries and the same considerations apply.<br>Information regarding experts/observers involvement can be found in section 27 of the Q&A [PRE- and POST- "ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu)]. The information contained in this document also applies to the parallel submission. See response above.<br><br>Not accepted.<br>Cross-referencing is not possible. See response above. |
| 41 | 5 | Comment: It may be helpful to clarify the rationale for this, as parallel validation may further increase efficiency.<br><br>Proposed change (if any): | One eCTD per application has to be submitted. Each application is subject to a full validation as they are stand-alone applications. The cover letter should explain whether the content is the same or highlights differences between the two to streamline the assessment |

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| 48-49 | 5 | Comment: This seems contradictory to line 37 where it is stated that the "medicines must be chemically/biologically and clinically identical"<br><br>Proposed change (if any): | Accepted.<br><br>Lines 36-38 have been updated. |
| 53-55 | 3 | Comment:<br>It would be helpful if the final guidance could provide more detail as to what circumstances may lead to different timetables being followed. This will enable applicants to identify potential strategic risks early and thus help them decide whether to use the parallel procedure or file independent applications.<br><br>Proposed change:<br>Following validation and should the parallel assessment meet the required criteria, both applications should follow the same timetable and be assessed in parallel. It is to be noted that the applications will start with the same timetable, however during the assessment the procedural timetables may differ (e.g. delays in submission of responses; **oral hearings related to differences in the dossier, procedure outcomes and subsequent steps, change of timetable of one application from Accelerated to Standard timelines**). | Accepted. |
| 57 | 3 | Comment: Before the EU-M4all opinion is issued, there should be an opportunity for the WHO/third countries to be consulted on the draft opinion before finalisation. This seems to be good business practice for a good collaboration between the parties, specifically if they have not been involved earlier. | Accepted.<br>Paragraph regarding the involvement of WHO experts/NRA observers is included. See also response above.<br>Section 27 of the Q&A [PRE- and POST- "ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu)] also applies to the parallel submission. |

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| | | Proposed change: add a paragraph to clarify this procedural step. | |
| 60-62 | 3 | "…In the pre- and post-opinion phases, EU-M4all can be subject to Good Manufacturing Practices (GMP) Good Laboratory Practices (GLP), Good Clinical Practices (GCP) and pharmacovigilance inspections as for a centralised product…"<br>Proposed change (if any): The document should confirm that if there is such an inspection, it will be valid for both applications | The understanding is correct. However, this will need to be checked on a case by case basis. |
| 68 | 1 | Comment: It would be good to highlight the potential for work-sharing for the management of post-opinion/post-approval variations.<br><br>Proposed change (if any): It would be good to highlight the potential for work-sharing for the management of post-opinion/post-approval variations. | Comment acknowledged. |
| 68 | 3 | Comment: Art 58 does not require the MAH to keep the opinion up-to-date. It is our understanding that this is a voluntary requirement in case the post-approval life-cycle management of WHO/third countries is facilitated continuously via this mechanism. We believe that a commitment from WHO and participating countries, the EMA and the MAH is required to implement such procedure.<br><br>Proposed change: **If the EMA, WHO, third countries and MAH have agreed that the M4All procedure should also be used to facilitate the life-cycle management of the product after the initial opinion, the MAH commits to keep** ~~In the post-~~ | Not accepted.<br><br>By analogy to the centralised procedure, the scientific opinion holder shall keep the scientific opinion up-to-date and submit any corresponding change to the EMA.<br><br>Please refer to question 42 (What information do I need to submit after the opinion?) of the Q&A [PRE- and POST-"ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu)]. |

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| | | ~~opinion phase~~ the EU-M4all scientific opinion ~~needs to be kept~~ up to date. | |
| 68-72 | 3 | "…In the post-opinion phase the EU-M4all scientific opinion needs to be kept up to date. The opinion holder should inform EMA of any changes concerning their medicine (post-authorisation guidance) by submitting relevant variations, periodic safety update reports (PSURs) and other post-opinion applications as for a centralised product. The opinion holder must also fulfil the pharmacovigilance requirements agreed with EMA…"<br>It is not clear how and to what extent any post-authorisation submission will be evaluated in parallel (if at all), as some requirements will be specific to the EU-M4All procedure. It is also unclear if in this case cross-referencing to identical documents is possible. This section of the guideline needs to provide more detail. For example, for parallel submissions one PSUR can cover both medicines and can be cross-referenced.<br><br>It is unclear if changes requested by the Ex-EU NRA post EU-M4All opinion should also be submitted to EMA for review. Further discussions how to handle the different post-approval scenarios are necessary.<br><br>Proposed change (if any): In the post-opinion phase the EU-M4all scientific opinion needs to be kept up to date. The opinion holder should inform EMA of any changes concerning their medicine (post-authorisation guidance) by submitting relevant variations, periodic safety update reports (PSURs) and other post-opinion applications **only for the** ~~as for a~~ centralised product. **The variations will be referenced automatically to the EU M4All license without the need of duplicated post-approval submissions, unless the** | Any amendment to the opinion needs to be assessed by the EMA in collaboration with WHO, though variation applications.<br><br>Please refer to question 42 (What information do I need to submit after the opinion?) of the Q&A [PRE- and POST-"ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu)].<br><br>The PSUR should be submitted in accordance with the frequency stated in the scientific opinion under the EU-M4all procedure, which can be different from the EU-MAA. The format of the PSUR shall follow the structure described in the Commission implementing Regulation (EU) No 520/2012. Nevertheless, the EU-M4all Holder needs to address the national requirements of the countries where a marketing authorisation has been granted, including estimated exposure, adverse events, risk minimisation measures, etc. Therefore, a single PSUR covering both procedures shall not be acceptable.<br><br>The considerations that apply to third countries apply to the former EU Member State.<br>"The United Kingdom (UK) formally left the European Union (EU) on 31 January 2020 and became a third country. During a transition period from 1 February to 31 December 2020, |

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| | | **applicant requests specifically not to. In cases where the submission only concerns the EU-M4all dossier, a separate review will take place**. The opinion holder must also fulfil the pharmacovigilance requirements agreed with EMA. **One PSUR covering both procedures is acceptable.** | EU pharmaceutical law continued to apply to the UK. From 1 January 2021, EU pharmaceutical law applies to the UK in respect of Northern Ireland only". In the centralised MAA procedure only the final outcome documents will be forwarded to the UK, so that they can fulfil their responsibilities for the Northern Ireland territory. This does not apply to the EU-M4all procedure. |
| 68-72 | 6 | Comment: Please also clarify with in the same paragraph about post-opinion regulatory obligation like "Whether applicant also need to inform about any country specific HA (Health Authority) query and response, any obligation or mandate posed by concern country where the medicinal product is intended to market to EMA within the prescribed time frame.<br><br>Proposed change (if any):<br><br>In the post-opinion phase the EU-M4all scientific opinion needs to be kept up to date. The opinion holder should inform EMA of any changes concerning their medicine (post-authorisation guidance) by submitting relevant variations, periodic safety update reports (PSURs) and other post-opinion applications as for a centralised product, country specific HA (Health Authority) mandate or obligation and any query with proposed response submitted to the | Not accepted.<br>Applicants are recommended to liaise with local authorities where the medicinal product is authorised to ensure compliance with the national legislation.<br><br>Post-authorisation activities related to the EU-M4all scientific opinion are without prejudice to the scientific opinion holder's obligations; Opinion holders shall ensure compliance with the legislations of the countries where the medicinal product is authorised.<br><br>Please refer to question 43 (What are the pharmacovigilance requirements in relation with the Article 58 Scientific Opinion?) on the Q&A [PRE- and POST- "ARTICLE 58" SCIENTIFIC OPINIONS PROCEDURAL ADVICE FOR USERS (europa.eu)]. |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | concerned health authority of respective country. The opinion holder must also fulfil the pharmacovigilance requirements agreed with EMA. | |
| 73-76 | 3 | The fee should be proportionate to the work provided. If reduced workload and duplication of efforts is expected as mentioned in the communication due to common parts and one assessment, it should be appropriate for the applicant to pay one full fee and one reduced fee and not 2 full fees. It is also not clear which criteria are used to identify exceptional cases for fee waivers. Some examples might be helpful. | Comment acknowledged.<br>The guidance specifies that applicants can request to EMA's Executive Director a total or partial fee waiver who will evaluate and decide on the request.<br>Please see: Fees payable to the European Medicines Agency \| European Medicines Agency (europa.eu) and 0028 SOP - Processing of requests for fee reduction falling under paragraph 1 of Article 9 of Council Regulation (EC) No 297/95 (europa.eu) |