21 June 2012
EMA/314313/2012
Committee of Human Medicinal Products (CHMP)/ Committee of Veterinary Medicinal Products (CVMP)

Overview of comments received on Draft Guideline on Active Substance Master File procedure (CHMP/QWP/227/02 Rev 3 - EMEA/CVMP/134/02 Rev 3)

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

Stakeholder no.	Name of organisation or individual
1	AESGP
2	EGA
3	Synthon BV
4	APIC
5	EFPIA

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1. Introduction general comments

Five stakeholders have commented to this guideline as a response of the public consultation (EGA, AESGP, Synthon BV, APIC and EFPIA). All stakeholders were located in the European Union.

Few comments were related to the revised core text of the guideline. Only these comments have been considered by the QWP. The remaining comments have been considered by the joint CMD/QWP/EMA ASMF drafting group.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	-	
2	The EGA welcomes the draft EMA guideline on ASMF Procedure. In particular, the following aspects are considered improvements: Introduction of numerous clarifications and additional details Clarification of the scope (exclusion of biological) Creation of a detailed list of administrative details accompanying the submission letter Creation of a withdrawal letter	Response to comment not applicable.
2	Regarding the ASMF numbering system, the EGA would like to highlight three important aspects: The detailed guidance on the procedure to obtain a number should be available in its final form at the moment the present guideline enters into force; A unique numbering system will only be viable if the possibility for several versions of the same ASMF to coexist is safeguarded as this is a practical consequence of having several users of the same ASMF at different stages of the registration procedure; The new numbering system and allocation of an EU AMSF number to a new ASMF should not delay the submission process.	A separate document is being prepared regarding the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.
2	The draft EMA guideline touches upon several procedural aspects, however, the possibility of worksharing by regulatory is not addressed in details. We believe worksharing could provide relief both for industry and regulatory authorities and that a dedicated section highlighting this approach should therefore be introduced. Ideally, the section should cross-refer to a separate guideline addressing the detailed procedural aspects of ASMF assessment worksharing. This guidance should be available in its final form at the moment the present guideline enters into force. Worksharing of an ASMF (unique number) should not delay the assessment of MAA referring to the same (unique number) ASMF. It is important to note that the timing at which the EU ASMF number will be issued	Separate documents are being prepared regarding a proposed assessment worksharing system and the EU numbering system for ASMFs to be used by competent authorities. The comments made will be taken into account when developing the above systems

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	(before or after submission) as well as the process elected for worksharing could have an impact on the handling and assessment of multiple parallel applications and exert an undesirable effect on competition between applicants.	
2	Although the primary users of the guideline are the MAH/applicants, ASMF holders have an essential role to play in this process, particularly in the compilation of information and timely interaction with NCA/EMA and MAH/Applicant. The guideline should therefore also reflect that it is intended to help ASMF holders in the compilation of their ASMFs.	This comment is already reflected in the scope of this guideline (line 59-61).
2	Veterinary: VMF holders should be able to present new VMFs in CTD-format to have one standard template for all master files.	The guideline already foresees that it is possible for veterinary ASMFs to be submitted in CTD-format.
2	Herbal: considerations for herbal medicines should be introduced	Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.
3	Via this comments document Synthon would like to express its view on the proposed revision of the draft "Guideline on Active Substance Master File Procedure". Synthon strongly supports the long term objective of improvement of the ASMF procedure across the Regulatory Network and the underlying goal to have a unique version of an ASMF for one active substance valid for the entire EU/EEA. Sharing assessment reports of ASMFs between the various National Competent Authorities, the EMA including all CHMP and CVMP Members and their experts, and the Certification of Substances Division of the EDQM is a crucial point in this aspect	Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system. The initiatives to improve the ASMF procedures are being developed by the CMD, partly in response to the described scenario where the same ASMF is licensed out in multiple procedures in multiple Member States, resulting in duplication of the ASMF assessment, multiple requests for

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	and is fully endorsed by Synthon. Synthon is a pharmaceutical company with a licensing out strategy for generic drug products in Europe. API's are both manufactured in-house and purchased externally. Pharmaceutical companies with a licensing out strategy are often engaged in multiple, parallel registration procedures for a multitude of customers. Furthermore, one drug substance can be used in multiple drug product formulations (injectables, tablets, capsules, etc.). For this reason the revised ASMF procedural requirements and new administrative aspects, like handling of ASMF versions, are in particular not suitable for pharmaceutical companies with a licensing out strategy or for ASMF holders not directly affiliated with the MAA. Synthon would like to assist where possible in reaching the long term objective to have a unique version of an ASMF for one active substance valid for the entire EU/EEA. To reach that goal some suggestions for corrections of the proposed guideline are provided on the following pages. Key words are facilitating harmonization of ASMF versions and prevention of duplication of information and duplication of review by the authorities. Please find more detailed comments below.	information, responses and divergent updates of the ASMF,
3	*Administrative Details Annex* The main change to this guideline is the new annex "Administrative Details Annex" which involves duplication of information and the associated complication of ASMF version management in the EU. The purpose of the "Administrative Details Annex" is to be able to share the information among authorities. The Active Substance Manufacturing Sites are declared in the following documentation: ASMF Section S.2.1 Letter of Access to the ASMF	The comment is not endorsed. The Submission Letter and Administrative Details Form (Annex 3) was designed to collate in one document all the necessary information to enable NCAs/EMA to easily identify where the same ASMF is being used in multiple procedures and member states. This and the proposed worksharing system will aim to reduce duplication of assessment and requests for information by NCAs/EMA, leading to harmonisation of the ASMF and consequently reducing regulatory burden on the ASMF holder and the

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	Application form to the MAA MA dossier Quality Overall Summary In the revision of the guideline it is additionally required to repeat this information in the "Administrative Details Annex" to the submission letter and therewith with every response to authority questions or with every variation. Considering the number of MAAs handled by pharmaceutical companies with a licensing out strategy this is an administrative burden, while the added benefit of sharing information is questionable. Furthermore, this is requested irrespective of the content of the deficiency questions or the purpose of the variation. For instance the information should also be provided when the content of the information in the "Administrative Details Annex" remains unchanged and no ASMF sections need to be updated. The repetition of information is also applicable for: ASMF holder information ASMF holder's active substance specifications Both are located in defined sections of the ASMF (S2.1 and S4.1 respectively) and can be found in numerous other places. Including this information from the ASMF in the Quality Overall Summary and additionally in the "Administrative Details Annex" for new submissions and with every response creates another bureaucratic hurdle which does not result in added value to clarity and consistency of the provided documentation that should be associated with the Pharmaceutical Activities. Synthon proposes to reduce the information in the "Administrative Details Annex" and share this among authorities with the Quality Overall Summary	MAH, It should also be noted that similar information was requested in the previous version of the Annex 3.

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	attached. Therefore please find some suggestions for rephrasing the text of the guideline in the table: Specific comments on text.	
3	*Template Submission Letter* This template contains a box in which the Name of the Medicinal Product, the Procedure Numbers and the intended Submission date of the MAA should be stated. This information regarding the name of the medicinal product and the respective procedure number is already available in the Letter(s) of Access that is/are issued specifically for this purpose and which is/are submitted to all authorities involved in assessing the ASMF. Duplication of information might lead to mistakes and inconsistencies in the provided documentation and should therefore be avoided as much as possible. The intended submission date and the EU/ASMF reference number are often not known at the time the ASMF is submitted, which creates complexity or repetition of sending submission letters. Synthon would like to propose to include the Letter of Access with the first submission of the ASMF. This is preferred over creating another document with similar information.	Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document. However, it is intended that the Letter of Access is provided only with the initial submission of the ASMF and will be valid for subsequent updates, until revoked by the Withdrawal of Access Letter (Annex 4). The Submission Letter and Administrative Details Form (Annex 3) will be provided with the initial submission, plus response to deficiency questions, updated, etc. Therefore, this should include information on the associated MA/MAV.
3	*Comments related to ASMF versions* Especially for pharmaceutical companies that submit multiple MAA's per country at different time points, maintaining one unique version of the ASMF per drug substance for the entire EU, are often hindered by several aspects related to the revised ASMF guidance. The difficulties with respect to ASMF versions are explained below. Usually multiple submissions with the same ASMF are taking place during a period of time, combining MRPs, DCPs and national submissions. As these are reviewed by multiple authorities they result in different sets of requirements from each MRP, DCP and	Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system The initiatives to improve the ASMF procedures are being developed by the CMD, partly in response to the scenario where the same ASMF is licensed out in multiple procedures in multiple Member States, resulting in duplication of the ASMF assessment, multiple requests for information, responses and divergent updates of the ASMF,

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	national submission with different timelines. This leads to diverging ASMFs in the EU, each with a different implementation date of the requested changes. This is unavoidably the result of having various decentralized reviews over a longer period of time of the submitted ASMF. In Europe there are examples of API's for which there are 14 different versions in 27 countries.	These initiatives will aim to reduce duplication of assessment and requests for information by NCAs/EMA, consequently leading to leading to harmonisation of the ASMF across Europe.
3	The Applicant Part that is submitted as part of the ASMF to the authorities needs to be aligned with the Applicant Part in the MAA. When there is one MAA this can be easily achieved, but if there are multiple MAAs it is not an easy if not impossible to align the Applicant Parts for all MAAs. An example is the update of an ASMF to add a test specifically for an injectable drug product. The MAA with only the tablets dossier will be requested to update the dossier via costly variations while the added information has no relevance to the product (tablets) that has been approved.	Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system.
3	Harmonization of the ASMF to one version number throughout the EU would also be favourable for an ASMF holder linked to multiple MAA's per country. However, because the large number of registrations connected to one ASMF and the variety of drug products that can be referring to one ASMF the costs in labour and variation costs for both the ASMF holder and the MAAs would be extremely high while no added value is created. For this reason pharmaceutical companies with a licensing out strategy cannot harmonize their ASMFs. While the guideline encourages in wording to keep the ASMF up-to-date both the variation guideline and the requested documentation in this ASMF guideline leads to the opposite.	Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system. The initiatives to improve the ASMF procedures are being developed by the CMD, partly in response to the scenario where the same ASMF is licensed out in multiple procedures in multiple Member States, resulting in duplication of the ASMF assessment, multiple requests for information, responses and divergent updates of the ASMF, These initiatives will aim to reduce duplication of assessment and requests for information by NCAs/EMA, consequently leading to leading to harmonisation of the

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		ASMF across Europe.
3	Though ASMF holders already aim to having one unique version of the ASMF per active substance for the entire EU, at the moment this is only possible via the EDQM certification procedure (CEP). This approach is only scarcely applicable as there are several obstacles for using the certification procedure. Firstly, a CEP request can only be applied for if a monograph is present for the active substance. Secondly, timelines to obtain a CEP are currently around 18 months. For these reasons the majority of the first submissions are performed using the ASMF procedure. In Synthon's view, a centralized review (and approval) of the ASMF could be implemented in line with the current EDQM certification procedure with a defined renewal of the approved ASMF. This would also facilitate dossier maintenance while the EDQM certification procedure reduces the number of variations considerably, which is a major obstacle for pharmaceutical companies with a licensing out strategy. Such centralized approach would also reduce the number of assessments by the National Competent Authorities. Further reduction of the current hurdles for dossier maintenance could be achieved by shortening variation timelines, facilitating regulatory requirements with variations (tightening specs, adding a test, showing Ph. Eur. compliance) and the costs associated with the ASMF (and subsequently Medicinal Product Dossier) maintenance.	Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. The recommendation has been noted for further discussion.
3	*Applicant Part* As mentioned above keeping the Applicant Part in the MAA harmonized with the Open Part of the ASMF is the most challenging aspect of ASMF maintenance for a pharmaceutical company with a licensing out strategy and also for ASMF holders not affiliated with a	Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.

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	pharmaceutical company. Most changes to the ASMF affect the Applicant Part, while the changes affecting the Restricted Part are limited. The ASMF procedure would greatly benefit from the simplification that only the Restricted Part is submitted to the authorities, preferably with centralized review, while the Applicant Part is only present in and reviewed as part of the MAA.	
4	We are well aware of the fact that the proposed revision of this guideline aims to support the recommendations and proposals made by the CMDh ad hoc group on ASMF assessments. We generally welcome the aspects that have been incorporated in the current draft to accommodate the proposals from the CMDh group, such as the revision of annex 3 and the introduction of the withdrawal procedure for Letters of Access. However, we would also like to take the opportunity to make some suggestions for improvement as during the past years experience has been gained in the industry with the 2006 draft version of the guideline.	Response to comment not applicable.
4	At present, the ASMF procedure is only applicable to active substances. We would highly welcome an extension of the scope to include intermediates (as e.g. in the US, Canada, Australia,…). Nowadays, there is a tendency to buy starting materials and intermediates and the NCA's request very detailed information such as manufacturing process, critical in-process controls, etc... for these substances. This information is considered confidential by the producers, which may be even competitors. The same concept as for APIs, i.e. Applicants Part and Restricted Part, can be applied ensuring that the API-manufacturer has sufficient information to assess potential impurities.	Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.

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4	Throughout this draft guideline emphasis is laid on the fact that there should be one unique version of the ASMF, recognizable and identical within all member states. In our opinion this means that this number should be assigned at a central point in Europe, preferably before submission of the ASMF. The situation as it is today - all member states assigning their own number (if any) - is an undesirable situation, since it leads to additional paperwork for both NCAs and Industry.	A separate document is being prepared regarding the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.
5	EFPIA has no major concerns with the revised guideline on Active Substance Master File Procedure. We have identified a number of sections of the guideline which are unclear, and would benefit from rewording to improve clarity.	Response to comment not applicable.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
15-28	1	The goal of the revision, i.e. ASMF worksharing of the evaluation should be more precisely explained in the note or, alternatively, reference should be made to another document explaining this initiative.	Accepted: The note has been revised.
17-18	4	The goal to have a unique version of an ASMF for one active substance valid for the whole EU/EEA makes sense for both parties, health authorities as well as industry. It should however be recognized that at present different versions of ASMFs may exist in the EU. For the older national procedures question/answer rounds may have led to different information in different member states. Therefore there must be a realistic time frame given from EMA in which the harmonization of all ASMF versions has to be fulfilled, e.g. something like five years seems to be acceptable.	Partially accepted: Separate documents are being prepared regarding proposed numbering and assessment worksharing system for ASMFs to be used by competent authorities. The comments made will be taken into account when developing the above documents.
17-18	4	It is unclear how the version numbering is foreseen. The guideline should be more explicit. Does every change to one or more of the chapters of the ASMF lead to a change in the version number? In our opinion applicants part and restricted part should have independent version numbers, e.g. if the restricted part is revised (e.g. in answer to a deficiency letter), this should not trigger a revision of the applicants part to prevent unnecessary variations.	Partially accepted: A separate document is being prepared re the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
61-82	2	Comment: The principles applicable to the ASMF procedure should apply for drug substances intended for use in medicinal products for human use and for veterinary use as well as for herbal drug substances and preparations. Relevant guidelines quoted in the draft Guideline on ASMF Procedure should be referenced at the end of the document or in Chapter 3. Legal basis Proposed change: Please clarify the scope and update Chapter 3.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.
84-87	2	Comment: Legal basis for herbal substances / preparations from lines 61-81 should be added in text from lines 84-87 if applicable. Proposed change: Please update section accordingly.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
89-122	2	Comment: Information for content of herbal drugs and preparations should be added to Chapter 4.1. Content of the Active Substance Master File. Additionally, subsections describing content of ASMF with respect to use of drug substance in drug product are proposed for clarity of the guideline:	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		General requirement (applies to all - drug substances for human use, drug substances for veterinary use, herbal drug substances / preparations) Content of ASMF for drug substances used in veterinary drug products (specific requirements) Content of ASMF for herbal drug substances / preparations for use in herbal drug products (specific requirements)	
113-117	2	Comment: The paragraph does not reflect the need for competent authorities and the ASMF holder to discuss the right balance between: Disclosure of more information (confidential or commercially sensitive information) in the applicant's part and, Necessary quality information to allow the MAH/Applicant to fulfil its legal obligations. Proposed change: Please amend as follows: "In such cases, the National Competent authorities/EMA in agreement with ASMF holders may ask for an amendment to the AP.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
117	4	This sentence may result in authorities requiring including confidential information in the AP. In practice, the questions (since "related to the AP") itself may already reveal confidential information to the applicant.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
121-122	4	As stated before, in our opinion this means that this number should be assigned at a central point in Europe,	Partially accepted: A separate document is being prepared re

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		preferably before submission of the ASMF.	the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.
121-122	2	Comment: The draft guideline reads *'Each version of the full ASMF should have a unique number in accordance with the appropriate guidance'*. This is then echoed in the various annexes where EU or National ASMF numbers are to be allocated by the NCA/EMA. As referred to in the General comments, this guidance on ASMF numbering needs to be available at the time of adoption of the final guideline on ASMF procedure. Proposed change: None	Accepted: The reference to appropriate guidance has been deleted. Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document.
122	4	What does "appropriate guidance" refer to?	Accepted: The reference to appropriate guidance has been deleted. Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document.
121-122	3	Comment: The eCTD allows for updates per section, this is tracked and documented. Also the ASMF has clear	Accepted: The reference to appropriate guidance has

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		granulation and could benefit from the same system of updating one section over the entire ASMF. Updating the entire ASMF for tightening of one specification seems needlessly laborious. Proposed change: Preferably each version of the full ASMF should have a unique number in accordance with the appropriate guidance. For ASMFs submitted via eCTD subsections can be updated separately.	been deleted. Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document.
122	1	An example of the numbering system (as the one existing in Rev 2 of this guideline) and/or reference to the "appropriate guidance" number would be helpful. To which guidance is it referred here?	Accepted: The reference to appropriate guidance has been deleted. Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document.
122-123	2	Comment: It is recommended that a reference or chapter on the submission format of ASMF be added. The EGA believes the eCTD should be the preferred and recommended format	Not accepted: Not applicable This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
122	5	Comment: "Each version of the full ASMF should have a unique	Accepted: The reference to appropriate guidance has

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		number in accordance with the appropriate guidance" It is unclear to which "appropriate guidance" is referred to here. It would be helpful to include a reference to the relevant guidelines to avoid ambiguity.	been deleted. Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document.
130-137	1	Comment: The text would be more appropriate in the chapter "scope". Proposed change: Move the text of lines 130 – 137 to the chapter "scope".	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
130-137	5	Comment: The text may be more appropriate in the chapter on Scope. Proposed change: Consider placing the text of lines 130 – 137 in the chapter on Scope.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
139 - 146	4	The requirement *„In cases where the CEP contains too little information (e.g. stability) the National Competent Authority/EMA may decide that additional information should be provided in the dossier*" could be a "door opener" for inadequate requests for documents and data beyond the CEP. The requests for additional information should be limited to information not covered by the CEP procedure. Proposal : requirement *„In cases where the CEP* lacks certain	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		information *(e.g. retest period or particle size distribution) the National Competent Authority/EMA may decide that additional information should be provided in the MAA"*	
141	2	Comment: It is important to specifically address the situation of a same drug substance is concerned. Additionally, it is important to note that a single drug substance manufacturer may have a CEP for a drug substance and an ASMF for the same substance which is manufactured according to alternative synthesis scheme. Proposed change: "an ASMF as well as to a CEP for a single active substance from the same drug substance manufacturer of a particular MAA/MAV."	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
144	1	Even when filing a CEP, supportive documentation e.g. batch analysis is requested. These data being most of the time taken from the ASMF, how can we make this fact coincide with the requirement not to refer to both an ASMF and a CEP?	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
147-155	2	Comment: From the guideline(s) it is not clear when the drug substance manufacturer should submit to applicant and national authorities' complete revision of the ASMF. The EGA recommends that in general, when additional questions from authorities are answered, the concerned	Not accepted: Not applicable. The submission format (e.g. eCTD, NeeS, etc) will determine whether a complete revision of the AP/RP, or whether updated CTD sections, should be provided.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		sections of the ASMF be revised.	
148	1	Comment: Shouldn't this read "a copy of the latest version of the AP (and if applicable response to a deficiency letter ....)"? Proposed change: "a copy of the latest version of the AP (and if applicable response to a deficiency letter from a NCA/EMA)"	Accepted: The comment is endorsed and the text is revised.
148	2	Comment: The latest version of the AP might not be consolidated and the text should reflect that it might be complemented by responses to deficiency letters. Proposed change: Please amend as follows: (*including a ~~or~~ response to a deficiency letter from an NCA/EMA, if relevant*)	Accepted: The comment is endorsed and the text is revised.
148	3	Comment: In line with the update per section the following rephrasing is proposed Proposed change: a copy of the latest ~~version~~ updated sections of the AP (or response to a deficiency letter from a NCA/EMA).	Not accepted: Not applicable. The submission format (e.g. eCTD, NeeS, etc) will determine whether a complete revision of the AP/RP, or whether updated CTD sections, should be provided.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
148	5	Comment: In regards to line 148: "- a copy of the latest version of the AP (*or response to a deficiency letter from a NCA/EMA*)". Would the deficiency letters pertaining to the Restricted Part be shared with the Applicant? Proposed change: "- a copy of the latest version of the AP (or response to a deficiency letter from a NCA/EMA that pertains only to the Applicant's Part)"	Accepted: The comment is endorsed and the text is revised.
149	4	Proposal : Line 149 should probably read: a copy of the QOS or details and critical summary on the latest version of the AP.	Accepted: The comment is endorsed and the text has been revised.
149	4	Please add "*critical summary*" to the Glossary.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.
149 and 343	5	Comment: Line 120-121 seem to indicate that the QOS should be used for CTD formats, while detailed and critical summaries are used for veterinary NtA. It is not clear if this is the case when "QOS/details and critical summary" are referenced in lines 149 and 343.	Accepted: The comments line 149 and 343 is endorsed and the text has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Line 149: - a copy of the QOS in CTD format and/or details and critical summary in NtA format on the latest version of the AP Line 343: QOS in CTD format and/or detail and critical summary in NtA format	
150	2	Comment: To be fully accurate, a copy of the LoA is sent to the MAH/Applicant. Proposed change: Please amend text to read: "- a copy of the Letter of Access […]"	Accepted: The comment is endorsed and the text has been revised.
150-155	4	"… where this letter has not been submitted earlier" This, coupled with the fact that the LoA does not contain the ASMF holder's version number, implies that a new LoA is not required each time a new version of the ASMF is submitted. However, this should be clarified.	Partially accepted: Separate guidance on completing and submitting the Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document
151-152	3	Comment: Addition of Administrative details should be optional when no changes have been made to the previously submitted Administrative details. Proposed change: In addition, ~~it is an essential requirement that~~ the ASMF holder should submit to all National Competent Authorities/EMA involved in the MAA/MAV procedure: the ASMF accompanied by a Submission Letter, ~~and~~ Administrative Details (if changed) or a Letter of Access	Not accepted: This comment is not endorsed. The Submission Letter and Administration Details (Annex 3) is a single document to be provided for every MAA/MAV using the ASMF. This allows the NCA/EMA to establish, maintain and confirm the regulatory history of the ASMF.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(first submission only), see Annex 3. This also applies to the ASMF holder's responses to deficiency letters from a NCA/EMA.	
153	2	Amend as follows: -a copy of the latest version of the ASMF *(same as provided to the Applicant/MA Holder)* accompanied etc…. This also applies to the ASMF holder's responses to deficiency letters from NCA/EMA, *which should also be provided.*	Partially accepted: The comment is partly endorsed and the text amended.
156-157	2	Comment: Echoing our general comment on worksharing and its application to the assessment of ASMFs, we believe that the possibility for ASMFs for single drug substance of single manufacturer to be submitted to each national authority only once would help streamline the ASMF assessment and provide relief in the procedure management for both regulators and industry. The handling of ASMF variations should also be considered in relevant guidelines in connection with this worksharing approach.	Partially accepted: Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system.
156-160	2	Comment: Revision 3 of the guideline now specifies the period in which an ASMF can be submitted by the ASMF-holder in line with an MAA submission. It is agreed that this should be at approximately the same time as the MAA submission as stated, and the timeline *"not more than one month before"* is considered acceptable. However, the statement *"not after the MAA submission"* is	Not accepted: The comment is not endorsed. The ASMF should be submitted no later than the MA/MAV application submission, otherwise the MA/MAV application will be deemed invalid.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		considered unreasonable and unenforceable. It is not clear what the consequences would be in the case the submission of the ASMF by the ASMF holder was delayed slightly in relation to the date of MAA submission. We suggest that this wording is either removed, or changed to a more manageable time limit. If it is not possible to remove this wording, a proposal is given below. Proposed change: "The ASMF holder should submit the ASMF to the National Competent Authority/EMA either for each MAA and each MAV or only once according to national requirements. The submission of the relevant documentation by the ASMF holder to the National Competent Authority/EMA must be synchronised to arrive at approximately the same time as the MAA or the MAV i.e. not more than one month before or ~~and not~~ after the MAA submission."	
157 - 158	4	Current practice is that no NCA requires submission of the ASMF for each MAA and/or each MAV. Allowing this seems to be in contradiction with the aim of the CMDh group. Proposed change: The ASMF holder should submit the ASMF to the NCA/EMA only once.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.
159-160	4	This sentence is not clear: normally the ASMF is only submitted once and further MAA use a new Letter of Access to the same ASMF. Synchronization as proposed in the guideline may be applicable for MAAs, but nor for MAVs	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(e.g. Type 1A Variations). The intended submission date by the MAH is not always known to the ASMF holder (allowances are made for this scenario in Annex 3) , therefore the 1 month time frame is too restrictive Proposal : The submission of the ASMF (first submission) and/or Letter of Access by the ASMF holder to the NCA/EMA must be synchronized to arrive at approximately the same time as the MAA e.g. 2 month time frame.	at this point in time. It has been noted for any future full revision.
159-160	4	Comment: In lines 159-160 the phrase "… not more than one month before and not after the MAA Submission" may be too restrictive and/or needs to be clarified. In cases of multiple MAs referencing the same ASMF, is it expected that the ASMF holder stagger their submissions based on the expected MAA submissions? What if the submission date is unknown to the ASMF holder (allowances are made for this scenario in Annex 3)? Finally, does the one month time period also apply to variations? Proposed change: Clarify the one month time frame and the expectations around submitting the ASMF.	Not accepted: The comment is not endorsed. ASMFs and their updates are regularly being submitted without an associated MA/MAV application, contrary to the note for guidance. The stated time frame aims to reduce this practice. Regular communication between the ASMF holder and MAH is encouraged and should facilitate meeting this timing.
161-163	2	Comment: Lines should be omitted as this is redundant with section 145-155.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision

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163	4	Current practice is that for every letter of Access the original is sent to the NCA/EMA, and the copy to the MAH for inclusion in the dossier. Proposal: Delete "or by the ASMF holder for the product concerned"	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
164-169	2	Comment: Lines 164-169 might be contradictory to text in lines 156-157. (if national authority requires submission of ASMF for each MAA) In addition, this section does not take into consideration the notion of multiple versions of a unique ASMF deriving from the multiple procedures and stages. Proposed change: Please amend as follows: "Where the same active substance is used in a number of applications for different products in one or more Member States, the ASMF holder should submit ~~identical~~ documentation to every national Competent Authority/EMA with a clear reference to the unique number and the version number. ASMF holders should endeavour to limit to a minimum the number of co-existing versions."	Not accepted: Lines 156-157 are regarding the frequency of submission of the ASMF to NCA's: for each MAA/MAH or only once, according to national requirements (which is outside the scope of this guideline). Lines 164-169 are regarding the submission of the same information to all NCA's/EMA (one unique ASMF version, which will be valid for the whole EU/EEA). There are to be no co-existing / multiple versions of one ASMF.
164-166	4	"The ASMF holder should submit identical documentation to every NCA/EMA." The difficulty here is maintaining identical documentation. In a multi-customer / multi-authority environment, a new or existing customer may submit a new	Not accepted: The Submission Letter and Administrative Details Form (Annex 3) will enable NCAs/EMA to easily identify where the same

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		MAA at any time so the ASMF needs to be up-to-date and current. Timing is a major issue in this respect. The same version of the ASMF can be subject to multiple procedures and thus assessments at the same time. This leads to the situation that one procedure may be finalized, thus leading to the request that the ASMF will be updated to include additionally provided information, whereas the ASMF can not be changed as a result of ongoing other procedures or can be subject to conflicting requirements. In addition, consideration should be given to the impact of new applications on already-approved applications, e.g. when more stringent specifications are required for a higher dose product. If the ASMF has to be updated in line with the more stringent specifications, these specifications are then applicable to all previously approved applications (leading to unnecessary variations). See also comments on line 208	ASMF is being used in multiple procedures and member states. This and the proposed worksharing system will aim to reduce duplication of assessment and requests for information by NCAs/EMA, consequently leading to leading to harmonisation of the ASMF across Europe
166-167	4	This needs further clarification to prevent the inclusion of superfluous information in the ASMF. Proposal Please add: "It is therefore important to notice that MA specific information should not be part of the ASMF, but of the MAA/MAV."	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.
175-176	1	Proposed change: "(CTD format section 3.2.S.4.1 and 3.2.S.4.2 or veterinary NtA format part 2.C.1)"	Not accepted: Not applicable. This comment does not relate to the aim of

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
176	5	Comment: Recommend deleting "old human" Proposed change: "... 3.2.S.4.2 or veterinary NtA format .... "	Not accepted: The comment is not endorsed.
177-178	4	Comment: see above Proposed change: The AP in the MA dossier should be the most recent update and it should be identical …	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.
183-195	4	"In the case of a single supplier … the specification for the active substance provided by the applicant/MA holder in the MA dossier should in principle be identical to that of the ASMF holder or the CEP holder." This seems to contradict line 190 where it says that "technical tests in the specification that are relevant for the medicinal product, but are normally not part of the specification in the ASMF (e.g. particle size) should be part of the specification of the applicant/MA holder." This importance of this latter point should be emphasised as ASMF holders are often forced by NCA to put product-specific specifications into the ASMF. Having these parameters in the MA dossier works when	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.

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		using a CEP so it should also work when using an ASMF. The paragraph also overlooks the reality, which is that most ASMFs are referenced by more than one MAH. Proposal: Where the ASMF procedure or CEP procedure is used, the common specification for the active substance provided by the MAH in the MAA should in principle be identical to that of the ASMF holder or the CEP holder. Technical tests in the specification for the API that are relevant for the production of the Medicinal Product are part of the MA.	
185 - 187	4	It seems that the Applicant/MA holder could adapt the API specification (e.g. change "*unnecessarily tight specification limits*"). This may affect the ASMF holder and any quality commitments he has in place. Proposal : If the Applicant/MA holder adapts the specification he should inform the relevant ASMF holder accordingly.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.
192-195	3	Comment: Impurities and solvents are route specific. It is proposed to rephrase the text to specify a test to a specific supplier. Proposed change: In cases where there is more than one supplier, the Applicant/MA holder should have one single compiled specification that ~~is identical~~ contains specifications for ~~each~~ both supplier~~s~~. It is acceptable to lay down in the specification more than one acceptance	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision

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		criterion and/or analytical method for a single parameter with the statement 'if tested' or designated to a specific supplier (e.g. in case of residual solvents).	
200 - 202	4	It seems that the ASMF holder should inform the Applicant/MA holder and the National Competent Authority/EMA regardless of the category of the change. Proposal : It is recommended to distinguish between (potentially) quality-relevant and other (e.g. editorial) changes in order to avoid mandatory information of all customers by the ASMF holder about merely editorial changes.	Not accepted: The comment is not endorsed. If the ASMF holder makes changes to the AP or RP of the ASMF, then the AP and/or RP have been updated. The ASMF holder has undertaken, in their LoA, to inform the MAH and NCA/EMA of any changes to the ASMF.
200 - 215	4	The section on changes and updates to the ASMF in the current guideline is extremely vague and allows for different interpretations as is evident by the publication in January 2012 of "*Obligations regarding updates of Active Substance Master Files*" by the Danish Medicines Agency in which it is recommended that changes to an ASMF be covered by a single Type II variation. The *Guideline on the Classification of Variations* makes reference to ASMFs (e.g. B.I.a.2.e) therefore the procedures contained therein are clearly applicable to ASMFs yet some NCA, like the Danish Medicines Agency, do not recommend to follow these procedures because they "often experience difficulties concerning updates of ASMFs." However, the impact of this on the API industry must be taken into consideration. Making even the smallest process change is extremely difficult, if not impossible, for an ASMF holder in a multi-	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision.

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		customer situation. For example, a minor process change might be an annual reportable Type IA notification for a manufacturer that does not use an ASMF whereas it would be Type IB for an ASMF holder because any process change invariably involves a change to the Restricted Part of the ASMF and one of the conditions of the Type IA is that it does not involve the Restricted Part. Type IB variations can easily take over 2 years to get all the necessary approvals. So the same change may be 'do and tell' for one manufacturer but take over 2 years for another. This is assuming that the MA holders agree to submit the necessary variations in the first place. Often changes are blocked because not all MA holders will agree. If, as in Denmark, all changes to an ASMF are to be Type II, it becomes even less likely / more prolonged. The proposed text in the draft guidance does nothing to alleviate this problem. To avoid confusion, the *Guideline on the ASMF Procedure* should address in more detail how changes to ASMFs should be handled. In particular, how to handle Type IA variations under the annual reporting procedure. It is acknowledged that the variations regulation does not allow for the ASMF holder themselves to submit an annual report but it is imperative that the ASMF holder benefits from this "do and tell" procedure. Direct contact between the authorities and the ASMF holder is essential in order for the ASMF holder to fulfil his responsibilities in accordance with the commitment made in the LoA. We propose that the ASMF holder informs both the MA holder and the authorities of a Type IA change	

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		at the time of implementation. The MA holder would then include the variation in his annual report at his discretion.	
203-204	4	This calls for a distinction in the numbering of the Restricted part and the Applicants Part (e.g. addition of "AP" and "RP") to prevent unnecessary work. See also comment on lines17-18.	Partially accepted: A separate document is being prepared re the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.
205-207, 208	2	In general, restricted part information changes cannot be disclosed to the applicant and are included in an updated RP submitted directly to the competent authority with a notification to the applicant to be submitted as a variation. Therefore, we suggest change to the sentence "To inform the applicant and the competent authority of any significant change in the ASMF" Proposed change: "to inform the Marketing Authorisation holder/Applicant of any significant change which affects the quality of the Active substance ~~Marketing Authorisation holder/Applicant~~ and Competent Authority/EMEA of any change in the Active Substance Master File"	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
205-207	4	See also comment on lines 159-160: there should not be a time limit for MAVs.	Not accepted: Not applicable. This comment does not relate to the aim of

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			this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
205-207	5	Comment: Does the one month time period in line 159 apply here as well? If so, similar comments/concern as those listed under Lines 159-160 are valid for these lines as well. Proposed change: Clarify the wording so all expectations are clear to the MA and ASMF holder.	This comment has been previously addressed (see above)
206	1	We think clarification would be useful as to the type of variation to be filed. We believe a Type IA variation would be appropriate.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
208-211	2	We are concerned that it is not explained clearly what the process is in the case an update has been made to an ASMF (as part of another MAA), but the MAH is not in a position to update the dossier for their MAA in line with this change due to eg pending MRP procedures. Further explanation of this process is requested in this section, along with clarification of how it is expected the ASMF holder will provide data to the MAH and involved NCAs/EMA (before/after implementation of the change), and when the MAH will then be expected to update their dossier by variation to fulfil their legal obligations.	Partially accepted: Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Please expand this section to include above mentioned procedural aspects.	
208-215	2	General comment: Implementation of ASMF changes due to on-going registration procedures of various drug products manufactured by various drug product manufacturers in various countries may take several years. Improved reporting system of ASMF changes would speed up the process, reduce regulatory burden and administrative work of both national authorities and industry. Later date of change implementation generally means higher drug substance production costs for that period and restricts API development.	Not accepted: Response to comment not applicable
208	4	"cannot be changed for a certain period of time because of other procedural provisions". This is practically impossible in multiple customer situations where more procedures may run at the same time with different timings.	Partially accepted: Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system. The initiatives to improve the ASMF procedures are being developed by the CMD, partly in response to the scenario where the same ASMF is licensed out in

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			multiple procedures in multiple Member States, resulting in duplication of the ASMF assessment, multiple requests for information, responses and divergent updates of the ASMF, These initiatives will aim to reduce duplication of assessment and requests for information by NCAs/EMA, consequently leading to leading to harmonisation of the ASMF across Europe.
209	1	Is it the ASMF holder's responsibility to gather the information about applications / renewals ongoing at his clients, and then propose an acceptable implementation date to all ones?	Partially accepted: Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system. The initiatives to improve the ASMF procedures are being developed by the CMD, partly in response to the scenario where the same ASMF is licensed out in multiple procedures in multiple Member States, resulting in duplication of the ASMF assessment, multiple requests for information, responses and divergent updates of the ASMF, These initiatives will aim to reduce duplication of assessment and requests for information by NCAs/EMA, consequently

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			leading to leading to harmonisation of the ASMF across Europe.
211	2	The paragraph below has been removed in draft rev 3 whereas it is included in the guideline in force as well as in draft 2. It concerns the MA Holders declaration and clarifies what is stated in lines 212 ff. "At the occasion of the 5-yearly renewal of a medicinal product, MA holders are required to declare that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress, and that the product conforms with current CHMP/CVMP quality guidelines. They will also declare that no changes have been made to the product particulars other than those approved by the Competent Authority/EMA." Proposed change: Please reintroduce the paragraph above or remove lines 212-215.	Accepted: The comment is endorsed and the text amended. The proposed text has been amended to reflect the fact that MAs undergo a single renewal at 5 years.
211	4	Specifying an implementation date is impossible in a multi-customer situation.	Partially accepted: Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment to be used by competent authorities. The comments made will be taken into account when developing the worksharing system. The initiatives to improve the ASMF procedures are being developed by the CMD, partly in response to the scenario

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			where the same ASMF is licensed out in multiple procedures in multiple Member States, resulting in duplication of the ASMF assessment, multiple requests for information, responses and divergent updates of the ASMF, These initiatives will aim to reduce duplication of assessment and requests for information by NCAs/EMA, consequently leading to leading to harmonisation of the ASMF across Europe.
212	4	It is not clear what the "above declaration" pertains to. This paragraph probably originates from the former version of this guideline, from which the explanatory paragraph has been deleted	Accepted: The comment is endorsed and the text amended. The proposed text has been amended to reflect the fact that MAs undergo a single renewal at 5 years.
219 Annex 1	2	The footnotes 3 and 4 do not seem to adequately capture the current situation. There is no ready experience highlighting the need for Section 3.2.S.2.4 control of critical steps and intermediates to be part of the Applicant's part. It is therefore suggested to adopt the following approach: Applicant's part: (3); with 3) as far as the information is relevant to the Applicant/MAH. Restricted part: X Proposed change: Please amend accordingly.	Not accepted: Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
219		In our opinion chapter 3.2.S.2 should only be submitted in	Not accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		the restricted Part of the DMF. This also applies for 3.2.S.2.4	Not applicable. This comment does not relate to the aim of this revision and will hence not be adopted at this point in time. It has been noted for any future full revision
247-250 Annex 2	2	ASMF reference numbers are not allocated by all European countries and are not available during first ASMF submission.	Partially accepted: A separate document is being prepared regarding the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.
250	4	It is the aim of the CMDh group to have one ASMF number to be used all through Europe.	Not accepted: Response to comment not applicable.
252 Annex 2 Template LoA	2	The inclusion to a reference to the active substance name in the Letter of Access is an improvement. Proposed change: None	Not accepted: No response applicable.
255 Annex 2: Template LoF	2	Annex 2 requires the inclusion of the manufacturing site of the API covered by the ASMF. However in Annex 3, when details are required on the concerned manufacturing sites, a foot note clarifies expectations i.e. *"All companies involved in the manufacture of the active substance,*	Accepted: The text has been deleted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		including quality control / in process testing sites, intermediate manufacturers, milling and sterilisation sites should be listed in separate boxes. Brokers or supplier details are not acceptable and should not be provided". Proposed change: The various meaning of manufacturing should preferably be clarified.	
262	2	Comment: 'Template Letter of Access', [Planned date of submission]: inclusion of planned date of submission of MAA or MAV should be only mandatory for new submissions/variations (inclusion of new supplier). In case of e.g. editorial changes this may not be feasible; Proposed change: A respective footnote 'only mandatory for new submissions/variations (inclusion of new supplier)' is proposed for [Planned date of submission]	Partially accepted: Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document. However, it is intended that the Letter of Access is provided only with the initial submission of the ASMF and will be valid for subsequent updates, until revoked by the Withdrawal of Access Letter (Annex 4).
262	4	Template Letter of Access', [Planned date of submission]: inclusion of planned date of submission of MAA or MAV should be only mandatory for new submissions and variations to include a new API supplier). In case of other changes this is not feasible; Proposal: Include a footnote 'only mandatory for new submissions and variations to include a new API supplier '	Partially accepted: Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document. However, it is intended that the Letter of Access is provided only with the initial submission of the ASMF and will be valid for

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			subsequent updates, until revoked by the Withdrawal of Access Letter (Annex 4).
269 Annex 2	2	Comment: According to Directive 2001/83/EC (p.83), active substance manufacturer should inform the applicant in case of changes in manufacturing process and specifications and not for any change.	Not accepted: This comment is not endorsed. Other changes to the information on active substance can be quality critical, e.g. stability data supporting a re-test period, and maybe required as part of other legislation e.g. variation regulations. Also, the statement is retained from the previous version of the LoA.
271-275 Annex 2 Template LoA	2	Comment: The draft guideline introduces the possibility for NCA/EMA to exchange ASMF Assessment Reports among themselves, regardless of the NCA/EMA being formally involved in the concerned procedures. This is welcome however the core text of the draft guideline does not specifically refer to this approach nor to the possibility of worksharing (See general comments). Proposed change: Please introduce in the core text of the draft guideline a specific reference to this approach and to the possibility of worksharing.	Accepted: The comment is endorsed and the text has been corrected.
274	4	Please revise this paragraph in order to prevent that the assessment reports will be shared by NCA's not participating in any MAA. Proposal:	Not accepted: The comment is not endorsed.

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		Insert "where the MAA is submitted" after the word Healthcare.	
281-372 Annex 3 Template Submission Letter and Administrative Details for documents relating to an ASMF	2	The Submission Letter and Administrative Details are detailed and are an improvement. Administrative Details strongly resemble MAA/MAV Application forms. Proposed change: Please envisage to make the Administrative Details form template available in stand-alone word format.	Accepted: The comment is endorsed. Word versions of Annexes 2, 3 & 4 will be made available on the EMA website.
281	4	Any currently used country-specific administrative form (if applicable) should be replaced by this template, a respective explanatory note would be appreciated.	Partially accepted: The Annex 3 Submission Letter and Administrative Details Form has been developed by the CMD Working Group on ASMF procedures and its inclusion in the note for guidance should discourage country specific administrative forms redundant; an explanatory note is not required.
Annex 3	2	Comment: With regard to Annex 3: 'Template Submission Letter and Administrative Details for documents relating to an Active Substance Master File' we have the following comment: any currently used country-specific administrative form (if applicable) should be replaced by this template, a respective explanatory note would be appreciated.	Partially accepted: The Annex 3 Submission Letter and Administrative Details Form has been developed by the CMD Working Group on ASMF procedures and its inclusion in the note for guidance should discourage country specific administrative forms redundant; an explanatory note is not required.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change:	
299-300, 334 Annex 3	2	Comment: ASMF reference numbers are not allocated by all European countries and are not available during first ASMF submission. Should EMA be added in box line 334?	Partially accepted: A separate document is being prepared regarding the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.
304	4	"Dear Sirs" should read: "Dear Madam, Sir"	Accepted: The comment is endorsed and the text changed
306-308	2	Comment: An ASMF may be referred to in subsequent / multiple submissions of drug products. In this case there is no additional Letter of Submission but only Letter of Access. Therefore, the list of drug products is relevant only for the 1st drug product submission and is not applicable for a Letter of Submission. Please note that this information is included in the letter of access. We recommend deleting this table/ information. In addition, Clarification needed that this form should be submitted only upon the 1st submission of the ASMF. In subsequent submission only LOA is sent. Proposed change:	Partially accepted: Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document. However, it is intended that the Letter of Access is provided only with the initial submission of the ASMF and will be valid for subsequent updates, until revoked by the Withdrawal of Access Letter (Annex 4). The Submission Letter and Administrative Details Form (Annex 3) will be provided with the initial submission, plus response to deficiency questions, updated, etc.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Delete the table of products list Clarification needed that this form should be submitted only upon the 1st submission of the ASMF. In subsequent submission only LOA is sent.	Therefore, this should include information on the associated MA/MAV
308-319	3	Comment: If a Letter of Access in enclosed with the submission letter the information requested in these lines are superfluous. It is proposed to start with line 334 Proposed change: ~~Medicinal product~~ ~~Allocated procedure number (H or V and as applicable)~~ ~~(Intended) Submission date of the marketing authorization application or variation (if known)~~	Partially accepted: Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document. However, it is intended that the Letter of Access is provided only with the initial submission of the ASMF and will be valid for subsequent updates, until revoked by the Withdrawal of Access Letter (Annex 4). The Submission Letter and Administrative Details Form (Annex 3) will be provided with the initial submission, plus response to deficiency questions, updated, etc.
308-319		It is unclear why this information needs to be submitted. Normally, the information required is already incorporated in the accompanying Letter of Access. In the case of changes, the required information needs to be provided in the table under lines 371-372. See also comments on 159-160: normally the ASMF is only submitted once and further MAA use a new Letter of Access to the same ASMF.	Partially accepted: Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document. However, it is intended that the Letter of Access is provided only with the initial submission of the ASMF and will be valid for subsequent updates, until revoked by the Withdrawal of Access Letter (Annex 4).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The Submission Letter and Administrative Details Form (Annex 3) will be provided with the initial submission, plus response to deficiency questions, updated, etc.
308	5	Comment: Clarification requested on how to address an unknown submission date. Proposed change: Omit any reference to a date.	Not accepted: The comment is not endorsed. Regular communication between the ASMF holder and the MAH is strongly encouraged.
311 & 399	1	Proposed change: Please replace "EMEA" by "EMA".	Not accepted: The comment is not endorsed
329-332	3	Comment: It is proposed to revise the text so the submission of all the requested information is only mandatory when the actual information in the Administrative details is new or has been altered in a variation or in response to a deficiency. Proposed change: This Submission Letter should be used for an Active Substance Master File to be assessed in conjunction with a new marketing authorisation application or variation for medicinal product for Human/Veterinary use (if changed), using either a National or Mutual Recognition or Decentralised or Centralised Procedure.	Partially accepted: Separate guidance on completing Annexes 2, 3, & 4 are being prepared and these comments made will be taken into account when drafting the above document. However, it is intended that the Letter of Access is provided only with the initial submission of the ASMF and will be valid for subsequent updates, until revoked by the Withdrawal of Access Letter (Annex 4). The Submission Letter and Administrative Details Form (Annex 3) will be provided with the initial submission, plus response to deficiency questions, updated, etc.
334	1	Would that be worth mentioning that the box "national only" should be ticked in any case of multiple dispatch to several countries, within national procedures (e.g.	Accepted: The comment is endorsed and a footnote added

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		submission of a variation, by national application, to register a new API manufacturer in all concerned countries)?	
334-335	3	Comment: It is proposed to allow updates of subsections instead of the proposed overall version number for the AP and the RP. Proposed change: Applicants part: ~~Version~~ S1 [version number]/date (dd-mm-yyyy) S2 [version number]/date (dd-mm-yyyy) S3 [version number]/date (dd-mm-yyyy) S4 [version number]/date (dd-mm-yyyy) S5 [version number]/date (dd-mm-yyyy) S6 [version number]/date (dd-mm-yyyy) S7 [version number]/date (dd-mm-yyyy) Restricted part: ~~Version~~ S2.1 [version number]/date (dd-mm-yyyy) S2.2 [version number]/date (dd-mm-yyyy) S2.3 [version number]/date (dd-mm-yyyy) S2.4 [version number]/date (dd-mm-yyyy) S2.5 [version number]/date (dd-mm-yyyy) S2.6 [version number]/date (dd-mm-yyyy)	Accepted: The comment is endorsed but no change is made to the text. However, separate guidance on completing and submitting the Annexes 2, 3, & 4 are being prepared and these comments will be taken into account when drafting the above document
336-337	3	Comment: The information mentioned here is duplicated throughout the dossier and submission documentation. It is proposed to remove these lines and request either a Letter of Access or the Quality Overall Summary annexed to the	Not accepted: The comment is not endorsed

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		submission letter. Proposed change: ~~ASMF holder~~ ~~Active Substance Manufacturer~~ ~~Manufacturing site(s)~~	
339 & 343	1	Comment: If an ASMF is replaced by a CEP this will be a variation submitted by the MA holder. It is not clear why the ASMF holder should submit a submission letter in the context of the replacement of an ASMF by a CEP. Proposed change: Deletion of "Replacement of ASMF by a Ph. Eur. CEP", "Copy of Ph. Eur. CEP including annexes (in case of ASMF closing and replacement by a CEP)"	Partially accepted: The statement has been moved to the Withdrawal of Access letter (Annex 4). This will not replace the MAH responsibility to submit appropriate MAV applications.
339 Annex 3	2	Comment: Category "Replacement of ASMF by CEP" should be omitted from the template. Annex 3 is submission letter for ASMF and not for CEP. Authorised CEP is not submitted to national authorities but only to Applicants.	Partially accepted: The statement has been moved to the Withdrawal of Access letter (Annex 4). This will not replace the MAH responsibility to submit appropriate MAV applications.
339 and 343	5	If an ASMF is replaced by a CEP this will be a variation submitted by the MA holder. It is not clear why the ASMF holder should submit a submission letter in the context of the replacement of an ASMF by a CEP.	Partially accepted: The statement has been moved to the Withdrawal of Access letter (Annex 4). This will not replace the MAH responsibility to submit appropriate MAV applications.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Deletion of "Replacement of ASMF by a Ph. Eur. CEP", "Copy of Ph. Eur. CEP including annexes (in case of ASMF closing and replacement by a CEP)"	
341	4	Asterisk 13 states that eCTD is mandatory for applications in the Centralised Procedure for Human medicinal products. Since this is a guideline on ASMFs, it needs to be clarified that this is not required for ASMFs supporting these applications.	Not accepted: In the Centralised Procedure for Human medicinal products the format requirements applicable to marketing authorisations applications also apply to ASMFs.
341	4	In case of an eCTD submission the history of sequences is shown via view options for the eCTD file. Therefore a separate sequence tracking table is not considered to be necessary. Proposal : Please delete the Submission format option "History of the sequences …"	Not accepted: The comment is not endorsed
341	4	The restriction to veterinary medicinal products for CTD is incorrect. Proposal: Please delete asterix 14 in submission format option "CTD".	Not accepted: The comment is not endorsed
341	4	Please add "(V) NeeS" to the list of abbreviations.	Accepted.
343-344	3	Comment: With the submitted documents there is also mention of an ASMF section: 3.2.S.4.1. Specifications. When this section has been updated it is part of a submission, response or variation and is enclosed in the updated eCTD sequence. Duplication of documentation	Accepted: The comment is endorsed and a footnote to state that this is not needed for eCTD or NeeS submission has been added.

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		should be avoided if possible, therefore it is proposed to remove the sentence. Proposed change: ~~A copy of the proposed ASMF holder's active substance specification (3.2.S.4.1 or part 2.C.1.1, as appropriate)~~	
343-344	3	Comment: Deficiency letters contain a lot of information most of which is not relevant to the ASMF holder or the reviewer. It is therefore proposed to remove this request. Proposed change: ~~A copy of the Deficiency letter sent by Competent Authority / EMA (only for submission of response documents)~~	Accepted: The comment is endorsed. The text has been amended to clarify the deficiency letter relevant to the ASMF.
343-Footnote 17	1	It is quite odd to refer to a former version of this guideline, when the information is presented in annex 2 of the current version of the guideline.	Accepted: The comment is endorsed and the text amended.
343	2	Comment: Footnote 17 is referred to (in relation to the Letter of Access Annex), but the wording of the footnote seems to refer to the wrong version of this guideline. Proposed change: "[17] see template in annex 2 of CH~~P~~MP/QWP/227/02 Rev.~~1~~3 (EMEA/CVMP/134/02 Rev.~~1~~3) *Guideline on active substance master file procedure* "	Accepted: The comment is endorsed and the text amended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
343 Annex 3	2	Comment: Box in line 343 describes documents which should be part of drug product dossier. ASMF is submitted to authorities by drug substance manufacturers and therefore list should be revised. Following is submitted to authorities by API manufacturers: - Transmittal letter - Letter of access - ASMF (Applicant's part, Restricted part, QoS for Applicant's part, QoS for Restricted part) - Responses to deficiency letters - Revised ASMF sections - Amendments describing changes - Correlation tables - Application forms (i.e. French, Swiss NA)	Not accepted: The comment is not endorsed.
343	4	It should be obvious that the template within this guideline should be used for issuing a Letter of Access. Proposal : Rephrase asterix 17 "see Annex 2".	Accepted: The comment is endorsed and text amended.
347	1	Would the Applicant/MAH be authorised to receive this table, with changes impacting the AP? It may be useful to ensure consistency with the variation's application form.	The Submissions Letter and Administrative Details (Annex 3) relates to ASMF submissions from the ASMF holder to a NCA/EMA. The applicant/MAH would be required to have knowledge about the various changes to an ASMF update in order to submit the MAV application. The AP ToC may be useful

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			in this respect; the RP ToC may contain confidential information.
347-357	2	Comment: It is still not clear how the EU numbering system will apply to ASMFs which are under different stages of review across multiple MAAs. (See general comment on the need for different versions of a unique ASMF).	Partially accepted: A separate document is being prepared re the EU numbering system for ASMFs to be used by competent authorities. This will not affect existing numbering systems used by ASMF holders but where relevant the comments made will be taken into account when developing the numbering system.
		The inclusion of a table outlining present and proposed CTD sections, and the wording *"If the changes have been previously authorised in a National or European procedure…."* suggests that different approved versions of individual CTD sections are possible, when in fact the EU numbering system means that only one version of each section should be in existence at any one time in the EU. It is requested that there is better clarification of how the EU numbering system will allow the existence of ASMFs which are under different stages of review across multiple MAAs. Proposed change:	Partially accepted: Separate documents are being prepared regarding a proposed worksharing system for ASMF assessment for ASMFs to be used by competent authorities. The comments made will be taken into account when developing the above documents.
347	4	From line 350 we conclude that the template "Table of Changes" is not to be part of the template submission letter, but needs to submitted as a separate document.	Accepted: A Word version of Annex 3 will be made available on the EMA website. ASMF holders

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		Proposal: Please separate both templates by creating Annex 3b for the template table.	can extract the ToC from this document so a separate annex is not required.
352-353	2	Comment: ASMF holder(s) might not have full overview of drug product registrations therefore "if available" should be added or the sentence should be omitted.	Not accepted: The comment is not endorsed. The ASMF holder should have full overview of the drug product registrations, particularly for updates, as they will have submitted LoA for the procedures and committed to inform applicants/MAHs of updates to the ASMF
356-357	3	Comment: It is proposed to allow updates of subsections instead of the proposed overall version number for the AP and the RP. Proposed change: ~~ASMF holder's RP and/or AP Version number~~ Subsection with ASMF holder's version number (CTD or NtA, as appropriate)	Partially accepted: The comment is endorsed but no change is made to the text. However, separate guidance on completing and submitting the Annexes 2, 3, & 4 are being prepared and these comments will be taken into account when drafting the above document
373-410 Annex 4 Template withdrawal of LoA	2	Comment: The introduction of Annex 4 will contribute to streamline regulatory documentation on API. The timeframe proposed for ASMF holders is 6 months. Although continuous relationship between ASMF holders and MA holders should allow earlier information, it is important to highlight that 6 months is a tight timeframe considering one would have to find an alternative supplier, manufacture new batches of finished product using the new API (produce	Accepted: The comment on the timing is endorsed and the text amended. Separate guidance on completing and submitting the Annexes 2, 3, & 4 are being prepared and these comments will be taken into account when drafting the above document

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		stability data) and have a variation filed and approved. This could lead to supply issues of medicinal products in the case only one ASMF is approved in a dossier (worst case scenario). We request that this timeline be revised to include a reference to the actual contract termination between the ASMF holder and the MAH. In addition, the practical consequences of LoA withdrawal also need to be clarified: Impact on bulk API available at the medicines manufacturing site: can batches be produced and released with the remaining API? This is particularly important in situations where a single API is registered in one MA. What is the timeframe to remove an API supplier from an MA (via variation)? Proposed change: The letter should ask for ASMF holders to detail when the MA holders was/were informed. The letter should also amend the last paragraph to read: 'The aforementioned Active Substance Master File holder also hereby confirms that they have previously informed [Name of Marketing Authorisation Holder/Applicant] of this decision ~~at least 6 months~~ before the date of this letter, i.e. at the time of the termination of the supply contract [dd/mm/yyyy].' The consequences of not informing the MA holders should be made clear in the core guidance document.	

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401-403	4	This paragraph implies that the decision to withdraw the LoA is always the ASMF holder's. The real problem is the applicants/MAHs who don't tell the ASMF holder when their applications/products have been withdrawn. Therefore it should be made clear that applicants/MAHs are obligated to do this.	Partially accepted: The comment is endorsed but no change is made to the text. Regular two-way communication between ASMF holder and MAH is encouraged.
402-403	4	Is 6 months a requirement or a recommendation? If the MAA holder agrees to have the LoA withdrawn sooner, Is there any reason to wait 6 months? Until now there was no such procedure, which means that there is a huge backlog. In practice, some applicants may not even exist anymore. How should this be handled? Proposal : '...of this decision at least 6 months before the date of this letter or a mutual agreement on this withdrawal exists."	Accepted: The comment on the timing is endorsed and the text amended.
402-403	5	Comment: Is 6 months a requirement or a recommendation? If the MAA Holder agrees to have the ASMF withdrawn sooner, is there is reason to wait 6 months? Proposed change: "… of this decision ~~at least~~ a recommended 6 months before the date of this letter."	Accepted: The comment on the timing is endorsed and the text amended.