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30 March 2010

European Medicines Agency
Compliance and Inspection, London
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European Commission
Pharmaceuticals Unit, Brussels
entr-gmp@ec.europa.eu

Ref: Explanatory notes for pharmaceutical manufacturers on the preparation of a Site Master File and content of a Site Master File;
ENTR/F2/MT/AM/jr D (2009), 10 December 2009
Deadline for comments: 31 March 2010

To: Responsible Person: European Commission, Pharm. Unit
Responsible Person: European Medicines Agency, Inspections Sector

PDA is pleased to provide comments on the *Explanatory notes for pharmaceutical manufacturers on the preparation of a Site Master File and content of a Site Master File*, dated 10 December 2009. Our comments were prepared by an international group of volunteer experts with experience in GMP and regulatory affairs. Our comments consist of five general comments, covered in this letter, and a series of more detailed technical comment found in the attached EMA matrix format.

General comments:

1. New Part III: PDA recommends this document be published as an Annex to the EU GMP, and not as a new Part III of the GMP. The creation of a new Part III is a major step which may have long term consequences poorly understood by the affected stakeholders including inspectorates. We understand all content of EudraLex to be the binding regulations in the EU. The addition of informational guidance documents may be inconsistent with the purpose of EudraLex. We suggest approaching the European Commission to request that creation of a new GMP Part III be subject to broader discussion before implementation.
2. Product Related Information: We recommend that the SMF exclude, to the extent practicable, individual product related filing and CMC information. This includes references to PAT, Quality by Design, real time release, and parametric release. To include product information in the SMF renders it unmanageable in size and complexity as well as repeating the content of the CTD. Excluding product specific information will not reduce the usefulness of the SMF for its primary purpose – efficient planning and undertaking of GMP inspections.

3. Format: We recommend the format of the document be reconsidered and amended. It is currently structured similar to the content of a company's quality manual. This may not the best way to organize information for a manufacturing site. In addition, the current format results in some redundancy, e.g. contractors addressed in sections 4.2, 8, and Appendix 8.
4. Glossary: There are occasional references to acronyms and abbreviations, e.g. DUNS. These should be explained in an Appendix entitled Glossary.
5. Size of SMF: As written, there is a risk that the size of the SMF could easily exceed 30 pages. Many of our suggestions, e.g. deletion of product information, will help keep the SMF to a reasonable and useful size.

As referenced in our first General Comment, PDA believes the creation of a new Part III of the GMP should be subject to more discussion by affected stakeholder, including industry and inspectorates. We are willing to help with the creation of a public discussion forum or other means of achieving that discussion.

If you have any questions please contact me, or James Lyda of the PDA staff (lyda@pda.org) who managed this project.

With very best regards,

Georg Roessling, Ph.D.
Senior VP, PDA Europe
Roessling@pda.org

cc: S. Schmitt, S. Rönninger, S. Mendvil, J. Lyda, R. Levy, R. Dana,

European Medicines Agency

PDA COMMENTS ON SITE MASTER FILE
PDA Contact: James Lyda, lyda@pda.org

GENERAL COMMENTS	
1	New Part III: PDA recommends this document be published as an Annex to the EU GMP, and not as a new Part III of the GMP. The creation of a new Part III is a major step which may have long term consequences poorly understood by the affected stakeholders including inspectorates. We understand all content of EudraLex to be the binding regulations in the EU. The addition of informational guidance documents may be inconsistent with the purpose of EudraLex. We suggest approaching the European Commission and requesting that creation of a new GMP Part III be subject to broader discussion before implementation.
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SPECIFIC COMMENTS ON TEXT			
No	**Line no[1]. + para no.**	**Comment and Rationale**	**Proposed change (if applicable)**
6	Title of	The current title of the document is long and can be shortened with	Reduce the current title to the following: "Explanatory notes for

[1] Where available

SPECIFIC COMMENTS ON TEXT			
No	**Line no[1]. + para no.**	**Comment and Rationale**	**Proposed change (if applicable)**
	document	no loss of clarity.	pharmaceutical manufacturers on the preparation **and content** of a Site Master File ~~and content of a Site Master File~~"
7	Table of Contents	ToC only covers 3 pages of the document.	Expand ToC to include the Annex/Content and Appendices
8	1.Intro 1.1	Incorporating the policies and activities should be restricted to the site, not the company.	Change text, "...policies and activities of the **site** ~~company~~, the production..."
9	1.Into 1.1	The SMF will not address quality management policies but rather systems. Clarification of text.	Revise in line 2, "...information about the quality management ~~policies~~ **system** and..."
10	1.Intro 1.3	The SMF should not stipulate the size of paper used	Delete reference to 'A4' paper
11	1.Intro 1.3	There seems to be a missing word, "A Site Master File should be detailed enough..." Enough for what?	Revise text to read, "A Site Master File should ~~be detailed enough~~ **contain adequate information**, but should not....."
12	1.Intro S 1.4	Paragraph 1.4 says the SMF "should have an edition number and effective and expiry dates." The requirement for an expiry date is prescriptive as revision of the document should be based on need. An edition number is not necessary when there is an effective date. It should be possible to update the Appendices independently from the main body of the document in order to simplify the maintenance. This would further make an edition number impractical.	Revise text to read, the SMF "should have ~~an edition number and~~ an effective date ~~and expiry dates~~. The Site Master File should be reviewed regularly and updated in cases of major changes of the business, of key processes, or of the organizational set-up. Each Appendix can have an individual effective date, allowing for independent updating"
13	1.Intro 1.4	The last sentence of this section is a clear instruction that the SMF should follow the format of the explanatory notes. This sentence should be made a clear instruction in a new section 1.6.	Move last sentence of 1.4 into new section 1.6.
14	1.Intro 1.5	The SMF should not stipulate the size of paper used.	Delete reference to 'A4' paper

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15	3. Scope	The second sentence of the first paragraph reads, "Refer to national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File and supply it and version updates to the Supervisory Authority." This is a different issue than scope and should be made into a separate section.	Create new section, "4. Authority" or similar, and move the referenced sentence to this section. The remaining text of 3. Scope, can be combined into a single paragraph.
COMMENTS BELOW RELATE TO THE ANNEX ON 'CONTENT OF THE SITE MASTER FILE'			
16	Format	The bullet format makes it difficult to reference the text of the SMF	Replace bullets format with format where different lines can be identified and referenced, e.g. a.b.c.....or 1.2.3.
17	1.1	'buildings and production units' are listed later in the SMF	Delete, '~~building and production units'~~
18	1.1	GPS and DUNS	Define in glossary
19	1.2	Bullet points 3 to 6 are listed in later parts of the document	Delete points 3 to 6.
20	1.2	The GMP license of the competent authority reflects the decisions originating from GMP inspections. No details on authority inspections should be requested in the SMF.	Replace: ~~Information of supervision of competent authorities, dates and outcome of latest GMP inspections. A copy of current GMP certificate (Appendix 3) or reference to EudraGMP, should be included, if available.~~ With: "Copy of current GMP certificate or reference to EudraGMP or equivalent (e.g. PIC/S), should be included in Appendix 3, if available".
21	2.1	Bullet point 3, information need only be included on GMP related accredited and certified activities. Clarity.	Add the term "GMP related" to bullet point 3.
22	2.2	Bullet point 3. Validation policies are addressed in section 4.2.2.	Revise bullet point 3 to remove reference to validation.

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No	**Line no[1]. + para no.**	**Comment and Rationale**	**Proposed change (if applicable)**
		Redundancy.	
23	2.3	First bullet point. We recommend listing names of all persons, e.g. QP, as an Appendix to the SMF as there are occasional changes. Clarity.	Create new Appendix for authorized persons, responsible persons and/or qualified persons, and change first bullet point to refer to appendix.
24	2.3	Third bullet point. Per our general comments, we recommend deletion of all product related and CMC filing topics from the SMF. This includes information relating to PAT, real time or parametric release.	Delete bullet point 3.
25	2.3	Fifth bullet point. These roles are required by the respective Annex in the EU GMPs. No need for repetition here.	Delete bullet point 5.
26	2.3	QP	Define in glossary
27	2.4	It will be helpful to clarify, as in bullet point 3, that this section relates primarily to 'critical' activities. Clarity.	Add word 'critical' to title of section 2.4 to read, "Qualification policy for contractors providing GMP critical services or materials and...."
28	2.4	QRM and API	Define in glossary
29	2.4	The first bullet point is part of the Section 2.5 requirements	Delete bullet point 1 and combine with section 2.5
30	2.4	The third bullet point. Contractors are covered in Section 8.	Delete bullet point 3.
31	2.5	Title should reference QRM methodology, not policy.	Change title to "Quality Risk Management ~~Policy~~ methodologies"
32	2.5	Bullet point 1. Same issue.	Bullet point 1. Change policy to 'methodologies'
33	2.5	QRM is not currently a requirement of any EU GMP document. ICH	Bullet point 2: Revise to read, "Scope and focus of QRM activities,"

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		Q9 does not suggest or support the need for a QRM organisation. Bullet point 2 is suggesting a level of detail inappropriate for the SMF. The use of the word 'any' (any activities, any application) is open-ended and out of scope for the SMF.	delete all remaining text. Delete bullet points 3 & 4.
34	2.6	Suggest deletion of section 2.6 and incorporation of necessary information into section 5. Clarity & redundancy.	Delete section 2.6.
35	4.1.1	This section would normally be described as HVAC.	Change title of 4.1.1. to "Brief description of heating, ventilation and air conditioning (HVAC) systems"
36	4.1.1	The information requested in this section is very detailed and technical in nature, and inconsistent with the purpose of the SMF. This level of information can be obtained during the inspection as a normal part of the audit.	Recommend deleting bullet points 1 – 3.
37	4.1.2	Similar comment. Leave the title of this section as is, but eliminate the technical detail.	Recommend deleting bullet points 1-3.
38	4.2	Equipment. Consistent with risk-based approaches, equipment or lab instruments are considered as critical based on risk classification.	Revise bullet point 1 to read, "Listings of major production....with critical equipment **identified according to risk classification** should be provided in Appendix 7."
39	4.2.3	Cleaning and sanitation, bullet point 3, requires 'brief description of cleaning methods and frequency for the, air handling system, dust extraction system, production areas and critical equipment'. This might not be applicable in all cases.	Revise bullet point 3 to add, "...if applicable" to the end to the statement.
40	5.	Insert reference to off-site records to be moved from 2.6.	Insert new bullet point to read, 'Records retention, off-site storage facilities'
41	6.1	Bullet point 1. A company/site may have multiple IMPs. Detailed IMP information should be available on dedicated documents. The SMF	In bullet point 1, replace: - description of investigational medicinal products which are

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		should include reference to those documents and/or include their copies in a dedicated Appendix.	manufactured including the detailed information of production areas and personnel responsible and stage of development of IMP if different than commercial manufacturing processes With: - description of investigational medicinal products which are manufactured. Detailed information of production areas and personnel responsible and stage of development of IMP, if different than commercial manufacturing processes, should be included in Appendix (x) or the corresponding document(s) should be referenced.
42	6.1	Bullet point 5: In Pharmaceutical Development, the concept of QbD and Design Space is an approach that is aimed for the majority of future submissions. To list details on these projects and their manufacturing process for a development organization appears to be inconsistent with the concept of the SMF.	Delete bullet point 5.
43	6.2	Bullet point 1. 'Continuous validation approach' is a future concept. It is not a commonly used term, and is not yet implemented in official guidelines. Delete this portion of the bullet point.	Delete 'continuous validation approach' from bullet point 1.
44	7.	CA	Define in glossary
45	8.	Change title to reflect analysis information in this section.	Change title to read, "Contract manufacturing and analysis"
46	8.	Bullet point 3. There could easily be hundreds of incoming and out-going materials and activities. This could result in a Site Master File greater than 100 pages if "comprehensive flow charts" are required.	In bullet point 3,, change "Comprehensive flow charts of supply-chains..." to "Brief description of supply-chains..."
47	8.	Bullet point 4. The technical agreement is not always referred to as a contract.	Change bullet point 4 to read, "...details of the technical contract/agreement between..."

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48	9.1	Bullet point 1. This information is usually regarded as protected trade information, is not directly relevant to GMP review, and is not important for content in the SMF.	Delete bullet point 1.
49	9.1	Bullet point 2. Same comment as above.	Delete bullet point 2.
50	9.1	Bullet point 5 (last point). Same comment as above.	Delete bullet point 5.
51	Appendix 3	Compliance with requirement for a valid GMP certificate cannot be guaranteed. For example some API sites do not have this because FDA does may not issue for the entire site.	Revise statement, "Copy of valid GMP Certificate, if issued."
52	Appendix 7	We understand that requalification is an issue, and there is no standard frequency for this activity. To list all these details will make the document exceed the required size. There are risk-based approaches. Alternative wording is suggested.	Revise statement, "… production and laboratory equipment used **indicating the approach to frequency for requalification."**
	END		

Please feel free to add more rows if needed.

These comments and the identity of the sender will be published on the EMEA website unless a specific justified objection was received by EMEA.