EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines

Validation issues frequently seen with initial MAAs

This document provides a list of issues frequently seen during the administrative validation of initial MAAs. The document is intended to be used as guidance to facilitate the preparation of the dossier. The list is not exhaustive and does not preclude that during the actual validation of the submitted application the Agency may identify other issues that could impact the validation outcome.

Applications should be prepared in accordance with the relevant legal provisions in place.

Module 1 - Cover letter

The European Medicines Agency is standardising the administrative information required in cover letters for any submission concerning centralised procedures.

Cover letter annexes

GCP Compliance (see also Q.3.4.1 of the Pre-Authorisation guidance)

The applicant is asked to provide information in the application in order to facilitate the review and where needed the preparation of GCP Inspections.

The Applicant should provide the list of all the pivotal clinical studies (protocol number and title) and for each pivotal study:

- the study synopsis (or a mature draft with information at least on the design and conduct of the study),
- a short discussion of the GCP compliance status (listing any GCP non-compliance identified, any breach of GCP, providing information on any site excluded including the reasons etc.),
- list of investigators and their addresses,
- number of subjects enrolled at each site,
- information on study administrative structure,
- list of GCP inspections conducted/planned by any regulatory authority (indicating the site inspected/to be inspected, the date of inspection and the regulatory authority involved). Alternatively, a confirmation that no inspections had been requested nor taken place and that no inspections are planned.

GLP Compliance (see also Q.3.4.1 of the Pre-Authorisation guidance)

A summary table listing the non-clinical studies should be provided. Regarding GLP compliance, as per Notice to Applicant (Volume 2B), there should be a statement on the GLP status of the studies submitted in Module 2.4: Non-clinical Overview and Module 2.6: Non-clinical Summary.

Please also refer to the EMA published 'Pre-submission Guidance' for information regarding GLP

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compliance to be included in the application.

Which information do I need to provide in my marketing authorisation application regarding GCP Inspections and GLP Compliance?

For each relevant study, the applicant should indicate:

- study title;
- study code (Unique identifier assigned to the study);
- date of completion of the Final Report;
- test facility and test sites in which the study was conducted;
- complete address of the test facility (and test sites were applicable);
- period in which the test facility(ies) and/or test site(s) was(were) used indicating if in that period they were part of a European Union (EU) or an Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data (MAD) accepted GLP monitoring programme.

GLP compliance template

GMP Compliance (see also Q.3.4.1 of the Pre-Authorisation guidance)

Applicants should provide a declaration that information on the manufacturing sites listed in Module 3.2.P.3.1 and 3.2.S.2.1 (in terms of names, addresses and manufacturing activities) is consistent throughout the dossier (eAF, flow-chart, QP declaration, GMP certificates and MIAs or MIAs equivalent).

Electronic Application Form (eAF)

Correct version of the electronic **application form** (eAF) should be used i.e. the latest version available, as published in Eudralex Volume 2B on the e submission EMA website.

The 'Declaration and signature' page should be signed by the person authorised for communication on behalf of the Applicant or by a person identified in the proof of establishment as a valid signatory. The applicant's details should be consistent throughout the eAF (on the declaration and signature page under "applicant" and in section 2.4.1) and in the product information (SmPC section 7, Labelling sections 11 and 2, and PL section 6).

Product (invented) name: The invented name should have been agreed by the **Name Review Group (NRG)**. If not, the applicant may use one of the proposed (invented) names or the common name (or scientific name), together with a trademark or the name of the Marketing Authorisation Holder. In both cases, the NRG review is required. Once the NRG review outcome is available, the dossier may be updated as required. The applicant can contact the NRG at NRG@ema.europa.eu.

Please also refer to 'EMA pre-authorisation procedural advice for users of the centralised procedure'

How will I know if the proposed (invented) name of my medicinal product is acceptable from a public health point of view? and What are the dates for submission of (invented) name requests?

The **product name** should be consistent throughout the eAF (on the declaration and signature page and in section 2.1.1.) and in the product information e.g. in lower case or upper case and the spelling should be the same throughout the dossier.

The **active substance** (AS) should be consistent throughout the eAF (on the declaration and signature page and in sections 2.2.1 and 2.6.1), with the exception of section 2.1.2 where priority is given to the INN only.

The active substance should be indicated in the eAF as follows:

- Declaration and signature page
  - AS including salt/solvate (e.g. hydrate) if applicable
- Section 2.1.2
  - Recommended INN accompanied by its salt or hydrate form if relevant (in brackets)
- Section 2.2.1
  - Active moiety as INN only, used for expression of strength
- Section 2.6.1
  - active substance as active moiety (INN) in the 'strength' field and corresponding value of x mg of salt/solvate in the composition field titled 'name of active substance'
  - for chemical compounds, the complete AS name should be given, i.e. the INN + the salt or hydrate etc.
  - active substance as active moiety (INN), in the footnote "*corresponds to x mg of salt/solvate" (e.g. irbesartan 75 mg, corresponding to 86.11 mg of irbesartan hydrochloride)

For guidance on how to complete the eAF, you may consult the EMA/CMDh guidance on Module 1: Administrative information Application form and eAF Q&A, specially the point on "How do I add 'salt/hydrate' form in to section 2.1.2 and/or 2.6.1? (H+V)".

The **applicant's/proposed MAH's details** should be consistent throughout the eAF (on the declaration and signature page under "Applicant", and in section 2.4.1) and in the product information (SmPC section 7 and PL section 6).

The **person authorised for communication** on behalf of the applicant should be consistent throughout the eAF (on the declaration and signature page, and in section 2.4.2) and in Annex 5.4. Please also note that personalised email addresses are required for eAF sections 2.4.1, 2.4.2 and 2.4.3. In addition, contacts listed under these sections should be duly registered in the EMA Account Management Database. To request user access roles, users need to have an active EMA account or request it by registering via EMA registration platform https://register.ema.europa.eu

The **billing address** in 2.4.1 must always be completed.

Annex 5.3 (related to section 2.4.1)

The proof of establishment of the applicant in the EEA must be provided and:
- must have the same name and address (if mentioned) as in section 2.4.1 of the eAF;
- the address must be in the EEA;
- should not be older than 6 months.

Annex 5.4 (related to section 2.4.2 and 2.4.3)

A letter of authorisation should be provided on headed paper, signed and with a recent date. The details of the person in Annex 5.4 should be the same as in section 2.4.2 and 2.4.3 (if applicable) of the eAF.

Annex 5.7 (related to section 2.4.1)

If **SME** status has been assigned by the EMA, Annex 5.7 and a valid SME number should be provided.

Annex 5.8 the flowchart (related to section 2.5.2 and 2.5.3)

Should list all manufacturing sites with their respective activities, be consistent with the application form, Modules 3.2.P.3.1 and 3.2.S.2.1, and the QP declaration.

Annex 5.12 (related to CEPs for the AS, excipients and/or reagents etc. of animal or human origin)

Should be submitted in Module 1.2 and also in Module 3.2.R (only applicable if CEP(s) are submitted

and section 2.6.2 is completed), and should be consistent with the eAF, section 2.6.2, 3.2.R and where any other relevant section of the dossier.

Annex 5.22: A QP declaration (related to section 2.5.3) needs to cover:
- in Part A all the active substance and active substance intermediate manufacturers, including manufacturers of the MCB/WCB in case of biological active substance;
- in Part B all EEA sites responsible for manufacture of the finished product and batch release;
- in Part C audits conducted on the sites listed in Part A.

Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture

QP declaration template

Annex 5.23

If New Active Substance is claimed, a justification should be provided.

ATC code

Pharmacotherapeutic group: the ATC code should be indicated in section 2.1.3. Alternatively, the applicant should tick the box to confirm that an application for an ATC code has been made and provide the first three characters.

Qualitative and quantitative composition

The qualitative and quantitative composition in terms of the active substance(s) and the excipient(s) in section 2.6.1 should be consistent with the composition presented in Module 3.2.P.1 and point 6.1 of the SmPC. Substance(s) used in the manufacturing process that are not present in the finished product should appear in the application form and in 3.2.P.1. They should not appear in the SmPC.

In case of Informed Consent applications, the composition should be consistent with what is stated in Mod. 3.2.P.1 of the reference product and point 6.1 of the SmPC.

For liquids, the concentration per 1 ml should be given in addition to the container size/volume of the product.

For ingredients which are mixtures of other ingredients e.g. coating agents such as Opadry etc., the qualitative and quantitative composition must be provided, even if the mixture is purchased from a supplier and should be consistent with 3.2.P.1. The ingredients should be listed in the SmPC without their quantities.

Module 1

1.3.1 The **product information** (SmPC, Anne II, Labelling and Package Leaflet) should be provided in English for all the pharmaceutical forms and strengths applied for. The latest QRD template should be used.

A Word version of the product information should be provided outside the eCTD structure.

1.3.4 The **Consultation with Target Patient Groups** (also called user tests) should be included. Alternatively, a commitment that the results will be submitted together with the day 121 responses, or a justification for its absence, should be provided. For procedures undergoing Accelerated Assessment, full results should be provided at the time of submission.

Please also refer to the EMA Pre-authorisation Guidance'.

Submission and assessment of information on user consultation

1.3.6 Braille should be provided or a justification of exemption.

1.4.1, 1.4.2 and **1.4.3** The **Quality, Non-clinical and Clinical expert** statement should be provided:

- on the correct template
- signed and dated
- with a CV of the expert

The statements must include the sentence: "According to his/her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC".

Applicants are referred to the Notice to Applicants Volume 2B for the templates (pages 17, 18 and 19 of Module 1).

1.5.4 Exceptional circumstances: if requested, the applicant should include a justification in this section, covering the following aspects:

1. A claim that the applicant is unable to provide comprehensive non-clinical or clinical data on the efficacy and safety under normal conditions of use.
2. A listing of the non-clinical or clinical efficacy or safety data that cannot be comprehensively provided.
3. Justification on the grounds for approval under exceptional circumstances.
4. Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information).

1.5.5 Conditional MA: if requested, the applicant should include a justification in this section, covering the following aspects:

1. Evidence that the product falls under Article 3(1) or 3(2) of Regulation (EC) No 726/2004 and belongs to one of the categories set-out in Article 2 of Commission Regulation (EC) No 507/2006;
2. Evidence that the product satisfies the requirements laid down in Article 4 of Commission Regulation (EC) No 507/2006;
3. Applicant's proposal for completion of ongoing studies, conduct of new studies and/or collection of pharmacovigilance data (as appropriate), in accordance with Article 4(1)(b) of Commission Regulation (EC) No 507/2006.

1.6 The **Environmental Risk Assessment** (ERA) should be provided, or a justification for its absence. Both documents should be signed and dated by the expert and have the expert's CV attached to it.

1.8.1 The Summary of the Pharmacovigilance System should be provided including:

- Statement that the applicant has at his disposal a qualified person for PhV (QPPV);
- The EEA member states in which the QPPV resides and carries out his/her tasks;
- The contact details of the QPPV;
- A statement dated and signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC;
- Reference to the location where the PhV system master file (PSMF) for the medicinal product is kept.

1.8.2 A product specific **Risk management Plan** (RMP) should be provided and:.

- It should refer to the correct invented name and active substance(s) on the cover page.
- It should show the RMP version number and date.
- The correct template should be used.

1.9 For all **Clinical trials conducted outside the EEA** the applicant should provide:

- A listing of all trials (protocol number) and all involved countries outside the EEA.
- A statement regarding the ethical conformity as per Art.8(ib) of Directive 2001/83/EC, which should state "Clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC".

1.10 Paediatrics: When applicable, the full Paediatric Investigation Plan (PIP) decision (with all annexes) should be submitted and not only the Opinion. The compliance letter should also be provided. In the eAF the decision number (P/0xxx/YY) should be stated and not the PIP procedure number (EMEA-000xxx-PIPxx-YY). In case of class waiver, the applicability letter and the last class waiver decision should be submitted (currently CW/X/XXXX).

The PIP compliance check should be carried out **before** submitting a marketing-authorisation application and a positive PDCO opinion should be available at the time of submission. If said check is carried out as part of the validation of the application, it will unequivocally require the application to be suspended at this stage until the PDCO opinion is adopted.

This is in line with Art. 7(1) of Regulation (EC) No 1901/2006 which clearly states:
"An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:
(a) the results of all studies performed, and details of all information collected in compliance with an **agreed** paediatric investigation plan;
[…]
For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application.

and Art. 23(2)(a), which additionally clarifies that:

"[…] 2. The Paediatric Committee may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan:
(a) by the applicant, **prior** to submitting an application for marketing authorisation or variation as referred to in Articles 7, 8 and 30, respectively; […]

In the case of point (a), **the applicant shall not submit its application until the Paediatric Committee has adopted its opinion, and a copy thereof shall be annexed to the application**.

Good Manufacturing Practice (GMP)

All sites mentioned throughout the dossier (section 2.5 of the eAF, annex 5.8 (the flowchart), annex 5.22 (QP declaration), Mod. 3.2.S.2.1, Mod. 3.2.P.3.1 and PI) must be consistent regarding their names, detailed addresses and activities. The actual manufacturing site address must be provided for all sites, not the administrative/legal address of the site which may be different. P.O boxes are not acceptable and should not be provided.

A Manufacturing and Importation Authorisation (MIA) should be submitted for all sites located in the EEA (except for Contract Laboratories which do not hold a separate MIA, in which case a valid GMP certificate will suffice). Alternatively, the EudraGMDP reference should be indicated in the eAF (preferred option).

A document equivalent to a manufacturing authorisation in accordance with Article 8.3(k) of Directive 2001/83/EC must be provided (annex 5.6) for MRA (Mutual Recognition Agreements) sites, ACAA

partners and all other sites located outside the EEA. For sites located in the USA, submission of either the "Drug License" issued by the relevant State (if available) or a screenshot of the FDA Drug Establishments Current Registration Site website showing the site name, address, activities and DUNS number of the site is required. If the site has previously been inspected by an EEA authority, please submit the latest GMP certificate or a valid EudraGMDP reference number in the relevant field. Alternatively, at least one of the following documents should be included: the 90 days decisional letter, a screenshot of the FDA Inspection Classification Database, the Establishment Inspection Report or a Certificate of Pharmaceutical Products.

Please also refer to 'Good manufacturing practice'

Module 2

2.4 Non-clinical overview and GLP compliance statement

Any missing eCTD section in Module 4 should be justified in the Non-clinical overview in Module 2.4.

According to the Notice to Applicants, the Non-Clinical Overview should include a statement regarding GLP compliance. If the statement is provided as a stand-alone document, it should be signed by the non-clinical expert.

2.5 Clinical overview and GCP compliance statement

Any missing eCTD section in Module 5 should be justified in the clinical overview in Module 2.5.

According to the Notice to Applicants, the Clinical Overview should include a statement regarding GCP compliance. If the statement is provided as a stand-alone document, it should be signed by the clinical expert.

Modules 3, 4 and 5

Statements justifying absence of data or specific eCTD sections should be provided in the relevant Quality overall summary, non-clinical/clinical overviews respectively in Module 2.3, 2.4 and 2.5. Should any of these documents require updating, the relevant expert's declaration in Module 1.4 will also need to be updated.

A statement indicating that the information has not been provided does not constitute a valid justification. Scientific justifications giving the reason(s) why it is not needed should be included. This applies to all missing studies/data in the overviews as appropriate.

ASMF (2.5.3 eAF/Module 3.2.S) - When an Active Substance Master file (ASMF) is used, the applicant should ensure that it has been submitted by the ASMF Holder to the Agency no later than the submission deadline (see also "How should I submit an active-substance master file (ASMF)?") in order to proceed with the validation of the dossier. For submission requirements please refer to the Guideline on Active substance master File Procedure.

3.2.R Regional information (for EU)

All CEPs (for AS, excipients etc.) should be included here in addition to Annex 5.12 of the eAF in Module 1.2.

Table A, B or C should be provided if, in section 3.2.P.4.5, excipients of animal or human origin are specified. It should be consistent with the eAF section 2.6.2.

Please ensure that all CEPs are listed and that the actual name and address of the manufacturer (not of the CEP Holder) is included.

GCP – for pivotal studies
The **signature of a principal or coordinating investigator**, as required by ICH E3 and Directive 2001/83/EC as amended, should be provided. The sponsor's medical officer may sign only if the study is on-going and still blinded.