



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Information Management

Quality Control of medicinal product data submitted as per the legal requirement introduced by Article 57(2) of Regulation (EC) No 726/2004

As per Article 57(2) requirements, marketing-authorisation holders (MAHs) were initially required to submit information on medicinal products authorised for human use by 2 July 2012.

From July 2012, marketing-authorisation holders are required to submit information on new marketing authorisations granted in the EEA within 15 calendar days from the date of notification of the granting of the marketing authorisation by the competent authority.

As of 16 June 2014, MAHs were required to complete the previously submitted product data with additional information, bring this information up-to-date and improve the data quality by 31 December 2014. Thereafter, industry is required to keep the medicinal product information up to date and notify the European Medicines Agency (EMA) of any variation to the terms of marketing authorisation within 30 calendar days of the date of approval of the changes.

Outlines of the quality control (QC) process

In July 2014, the EMA commenced the review of quality and integrity of the medicinal product information submitted in line with the amended eXtended EudraVigilance Product Report Message (XEVPRM) format and specifications effective as of 16 June 2014. Authorised medicinal products (AMPs) with a valid marketing authorisation (i.e. marketing authorisation status is equal to "Valid" or "Suspended") submitted prior to 1 February 2015 were expected to be quality controlled by the end of September 2015.

Medicinal products submitted after 1 February 2015 were aimed to be quality controlled within six months since their submission, providing that no exceptionally large submissions are made within the validation period.

Since January 2024, the EMA aims to perform the validation of newly submitted authorised medicinal product records within 2 weeks since their submission in the Article 57 database of the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) by the marketing authorisation holders.

¹ Changes are highlighted in red and strike-through text.



There is no defined timeline for a subsequent validation of the AMP records following an update of the AMP information. This is due to large volumes of data and prioritisation of newly entered product records. Therefore, re-validation of previously validated AMPs is performed as needed, and generally within 2 years since the last validation was performed.

The above stated timelines are not applicable in exceptional cases (e.g. regulatory procedures and/or triggered by safety concerns).

The EMA performs data integrity assessments and, where necessary, revisions in accordance with the principles outlined in the published [Data Quality Control methodology](#). Systematic assessment of the latest version of the received medicinal product data is performed by checking each data element against the information stated in the **provided supporting document(s), such as** Summary of Product Characteristics (SmPCs), **extract of Module 3** or equivalent document that facilitates the data quality assurance process by the EMA. Rational assessment of the validity of the submitted data based on expert knowledge and a sense check against other relevant fields within the database is also part of the assessment.

- If the EMA cannot perform the data quality control because incorrect or invalid document(s) was/were provided during the submission process, the Qualified Person Responsible for Pharmacovigilance (QPPV) of the MAH organisation is informed by email with the request to review the medicinal product entity/entities and attach a valid reference document(s) or additional document(s) that allow the data quality assurance process within 15 calendar days as per paragraph 6(b) of the [Legal Notice on the Implementation of Article 57\(2\) of Regulation \(EC\) No. 726/2004](#).
- If correct and valid document(s) is/are attached, the EMA performs the quality control process on the latest (i.e. current) version of the medicinal product available in the Article 57 database at the time of assessment.
- Provided that the medicinal product entity was submitted by the MAH correctly and in line with the information stated in the attached document(s) and principles outlined in the [Data Quality Control methodology](#) and [Chapter 3.II: XEVPRM User Guidance](#), the EMA flags the assessed version of the medicinal product entity as "Valid".

Each MAH organisation maintains full ownership of their medicinal product entity, irrespective of the ongoing validity assessment process. The MAH is not required to wait for the EMA to flag their authorised medicinal product record in the Article 57 database as "Valid" before their next maintenance related submission; **the MAH can always submit XEVPRMs with maintenance related operation types irrespective of the validity assessment status.**

- All versions of the AMP entity are visible to the users registered under the ID of the owner organisation in the XEVMPD Data-Entry Tool (EVWEB).
- Only the versions flagged as "Valid" are visible to other EVWEB users as per the applicable visibility rules.
- The version of the medicinal product entity flagged as "Valid" is used to support signal management activities (e.g. codification of ICSRs). For detailed information on the use of AMP versions from Art57 database see *Annex 3: Use of AMP versions from Art57 database*.
- If the medicinal product entity was not submitted correctly by the MAH organisation, the EMA performs an operation type 'Update (2)' on the medicinal product entity and corrects the submitted information so that it is in line with the information stated in the attached document(s)/principles

outlined in the [Data Quality Control methodology](#) and [Chapter 3.II: XEVPRM User Guidance](#). This action results in a new version (EMA version) being created and flagged as "Valid" and becomes the current version of the medicinal product entity in the database.

Follow-up actions after Quality Control process

Once the product version has been quality controlled by the Agency:

- the MAH organisation is informed of the outcome of the quality control process via the **3rd XEVPRM Acknowledgement** (since 4 November 2015).
 - Should the MAH organisation object to any of the changes/corrections made by the EMA an email should be submitted to the ~~Article 57 Quality Control Inbox (Art57-QC@ema.europa.eu)~~ a [Request \(for\) XEVMPD/Art.57 Services](#) should be submitted via the [EMA Service Desk](#).
 - Should the MAH organisation wish to request further information or clarifications on the performed amendments, email should be submitted to the ~~Article 57 Quality Control Inbox (Art57-QC@ema.europa.eu)~~ a [Request for Information](#) should be submitted via the [EMA Service Desk](#). In the 'Service' section of the form "SPOR" should be selected and in the 'Service Offering' section of the form "XEVMPD/Art.57" should be selected.

The Art57-QC team will assess the comments, questions or objections raised by MAH and provide explanation on the rationale of the changes made by the EMA. If corrective actions need to be taken by the EMA, the Art57-QC team will perform an amendment of the AMP information in the Article 57 database by creating a new version of the AMP entity and then inform the MAH. Art57-QC team responds to the received queries within 15 working days requests for services within 5 working days and to the received requests for information within 22 working days since the raised ticket was assigned to them.

- The system will automatically flag any newly submitted product version as "Valid" if the notified amendments do not require additional quality control by the Agency (e.g. change in the QPPV field);
 - The list of fields that can be automatically validated includes: QPPV, Master File location, PhV enquiry phone, PhV enquiry email, MRP/DCP number, excipient strength information, Product Attachment.
- To optimize the process and the parser activity, the system has been modified to reject any XEVPRM in which the product information is completely identical to the previous version that was changed by the EMA as part of the quality control process outlined above.

If a medicinal product entity was amended by the EMA during the quality control process, no further action needs to be performed by MAH organisations using **WEB Trader** until their next maintenance submission is performed (e.g. to reflect any changes to the terms of the marketing authorisations following variation, transfer, renewal, suspension, revocation or withdrawal of the marketing authorisation procedure or to nullify the entity).

If an organisation submitting product information via the WEB Trader functionality also maintains a local database, the users are advised to review and retrieve the medicinal product entities in which information was amended by the EMA using the [XEVMPD Product Export tool](#) and amend this information in their internal systems prior to their next maintenance submission due to changes to the terms of the marketing authorisations.

Gateway users are advised to review and retrieve the medicinal product entities in which information was amended by the EMA using the [XEVMPD Product Export tool](#) and update this information in their internal systems prior to their next maintenance submission due to changes to the terms of the marketing authorisations.

See *Annex 1: Medicinal product quality control activity performed by the Agency* for further information.

Electronic notification following the quality control process

Process used until 4 November 2015

Following the submission of an XEVPRM, Gateway users (only) automatically received an MDN acknowledgement generated automatically by the Agency's ESTRIM Gateway.

Once the XEVPRM was processed by the EudraVigilance system, Gateway and WEB Trader users received an XML message acknowledgement confirming the result of the load of the message (i.e. '01' if the XEVPRM has been processed successfully, '02' if the XEVPRM has not been processed successfully) and displaying the applicable operation result code (so called 2nd level Acknowledgement).

The file name of the 2nd Acknowledgement is in the format "[ack_](#)" + [<file name sent by the MAH without .zip>](#) + ".xml".

The description text was amended to include additional information on the quality control activity performed by the EMA and informing on:

- The applicable version number
 - Medicinal product submitted in an XEVPRM with an operation type 'Insert (1)' is assigned with a version number (i.e. version number 1). Any subsequent amendment(s) to the medicinal product entity via an operation type 'Update (2)', 'Invalidate MA (6)' or 'Nullification (4)' lead to a new version number being assigned,
 - MAHs can view each individual version available for the EV Code of their AMP entity in the sections "Previous Versions"/"Subsequent Versions" within the AMP entity.
- The quality control activity that the EMA will perform
 - i.e. *"The product will be validated by the EMA in due course. When validated you will receive a further acknowledgement with the message number: "Product Validated XXXX Version [Version Number] / [Date and Time]"."*

Please note that "...further acknowledgement..." referenced in the above message was implemented only after 4 Nov 2015 and was not used in the production environment before 4 November 2015.

Neither the operation type codes, nor the acknowledgement message format was amended.

Process in use from 4 November 2015

The below process was endorsed at the Article 57 Implementation Working Group (IWG) teleconference meeting on 6 May 2015.

In addition to the 2nd level acknowledgement, once the EMA quality control activity was performed on an AMP entity in the Article 57 database, the EMA notifies the outcome of the quality control activity for **each medicinal product** (i.e. one AMP entity per XEVPRM XML Acknowledgement) by sending an additional XEVPRM XML Acknowledgement message (so called 3rd Acknowledgement) to the sender's organisation ID. The technical specifications of the 3rd Acknowledgement are identical to the current [XEVPRM XML ACK schema](#) of the 2nd Acknowledgement.

For MAH organisations using **WEB Trader** (for both EVWEB application users and users posting via the 'EV-Post function'), the 3rd level Acknowledgement is available within their WEB Trader Inbox and therefore no technical enhancements were required by these MAH organisations.

For MAH organisations using in-house solutions (i.e. **Gateway Users**), the minimum technical requirement was that the system should be enhanced to allow the receipt of the 3rd Acknowledgement, which has the same format as the 2nd Acknowledgement but is generated per each individual validated version of the AMP, whilst the 2nd Acknowledgement is generated per each XEVPRM message.

- If **no changes were performed by the EMA on an authorised medicinal product entity submitted by the marketing-authorisation holder**, the file name of the 3rd Acknowledgement is in the format "validated-" + <Sender ID of the Validated Version> + "-" + <EV Code> + "-" + <Validated Version Number> + "-" + <Date and Time>.

The operation result description contains the text *"Product validated successfully as submitted"*.

See Annex 2: 3rd Acknowledgement examples, Example 1: No changes were performed by the EMA for details.

- If **changes were performed by the EMA on an authorised medicinal product entity submitted by the marketing-authorisation holder**, the file name of the 3rd Acknowledgement is in the format "ackval" + "_" + <EV Code> + "_" + <New Version Number> + ".xml".
 - The Message Number (messagenumb) is in the format:
"Product validated following EMA edit of data " + <EV Code> + " Version " + <Validated Version Number> + " / " + <Date and Time>;
 - The Original Message Number (originalmessagenumb) is be in the format:
"EMA edit of data " + <EV Code> + " Version " + <Version Number used as base for the Changes>.

These naming conventions enable MAHs to understand which product EV Code and which of the product's version was validated (with changes) by the Agency.

The operation result description contains the text *"Entity updated successfully"*. The list of changes made to each field is included.

See Annex 2: 3rd Acknowledgement examples, Example 2: Changes were performed by the EMA for details.

The timeline for the roll-out of the automatic notification via the 3rd XML Acknowledgement was set to 4 November 2015 following dialogue with the Article 57 Implementation Working Group.

- WEB Trader users did not need to perform any further testing as their acknowledgements are automatically stored in their WEB Trader Inbox.

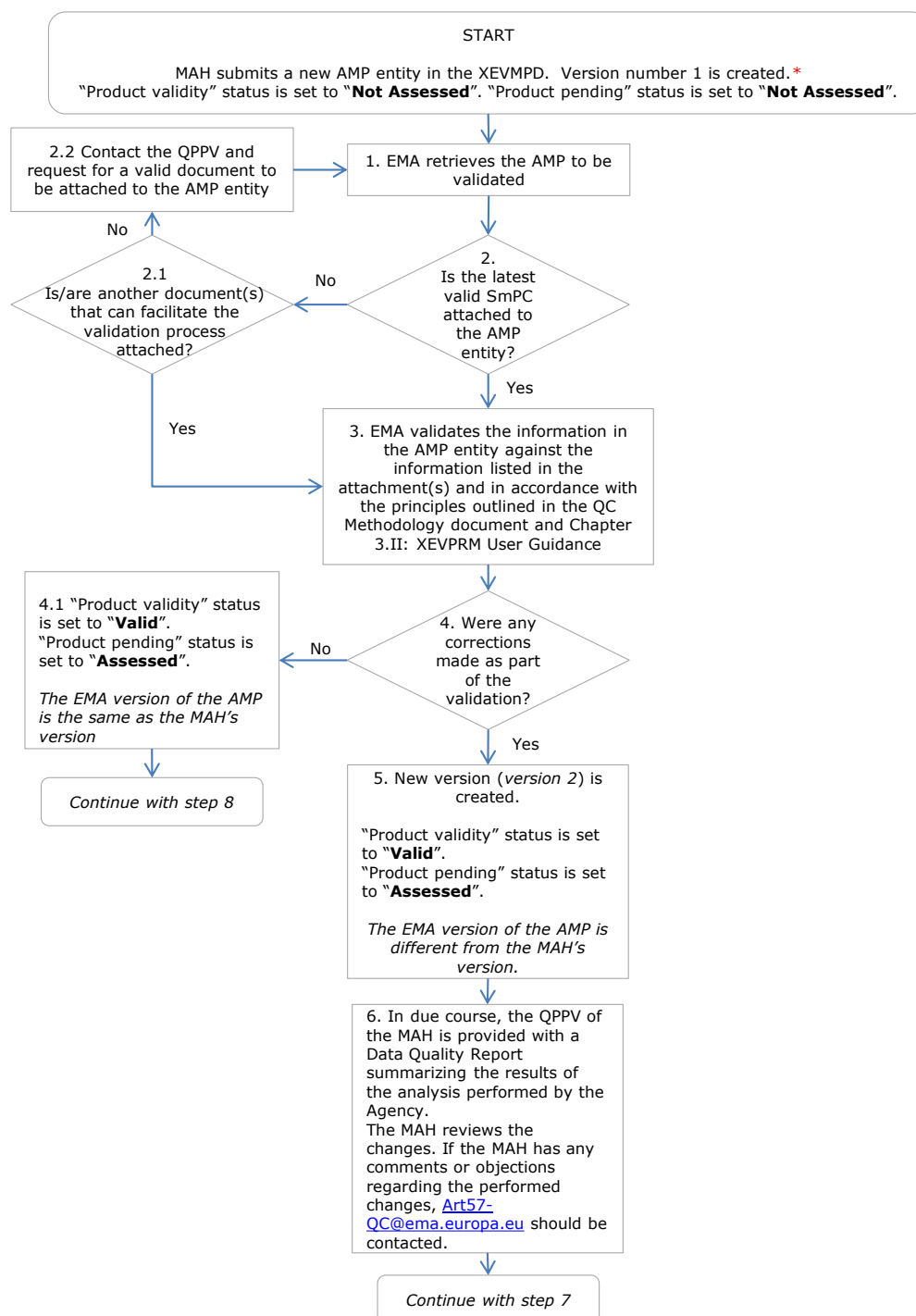
- The EMA offered the possibility to test the receipt of the 3rd level acknowledgment by Gateway users in the External Compliance Testing environment (XCOMP) between 1 July 2015 and 4 November 2015.

Thereafter, if a gateway provider is performing testing of the receipt of the 3rd level acknowledgement on behalf an MAH organisation in the XEVMPTD test environment (XCOMP), the gateway provider can request validation of an AMP EV Code available in XCOMP, which will generate this acknowledgement, by submitting a [Request \(for\) XEVMPTD/Art.57 Services](#) via the [EMA Service Desk](#). The EV Code of an AMP record, which is not flagged as nullified or invalidated in the XCOMP environment must be included in the request.

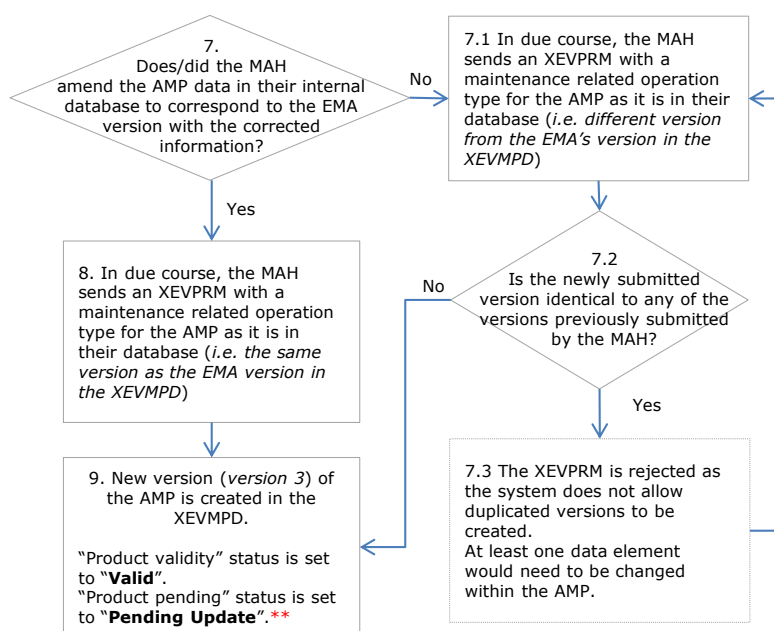
For further details related to the Extended EudraVigilance product report acknowledgement message please refer to [Chapter 5: XEVMPTD Acknowledgement](#) of the user guidance.

Annex 1: Medicinal product quality control activity performed by the Agency

Process used until 4 November 2015



*Following the initial submission, if the MAH performed any updates to their submitted AMP, the version number will be higher than 1

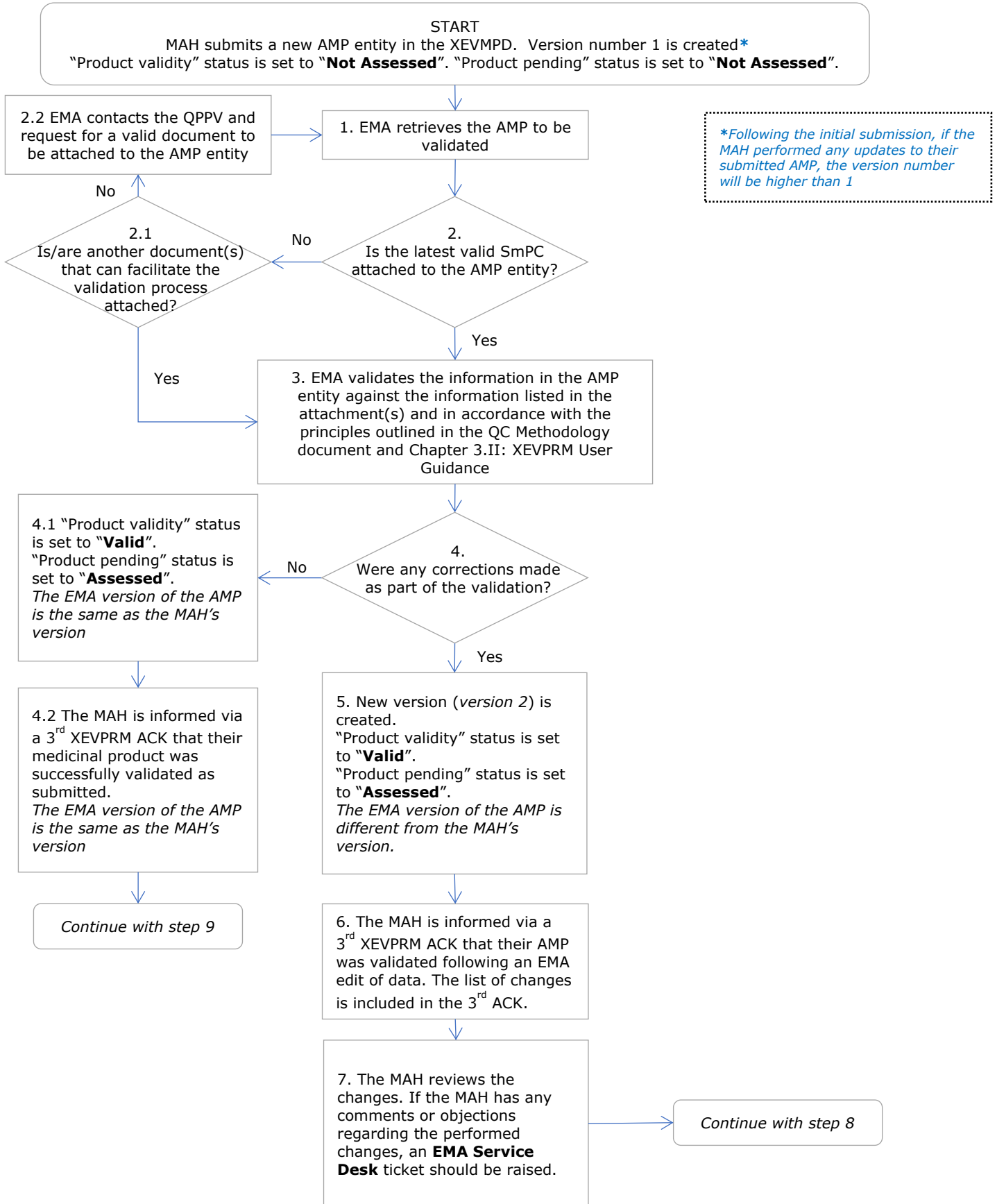


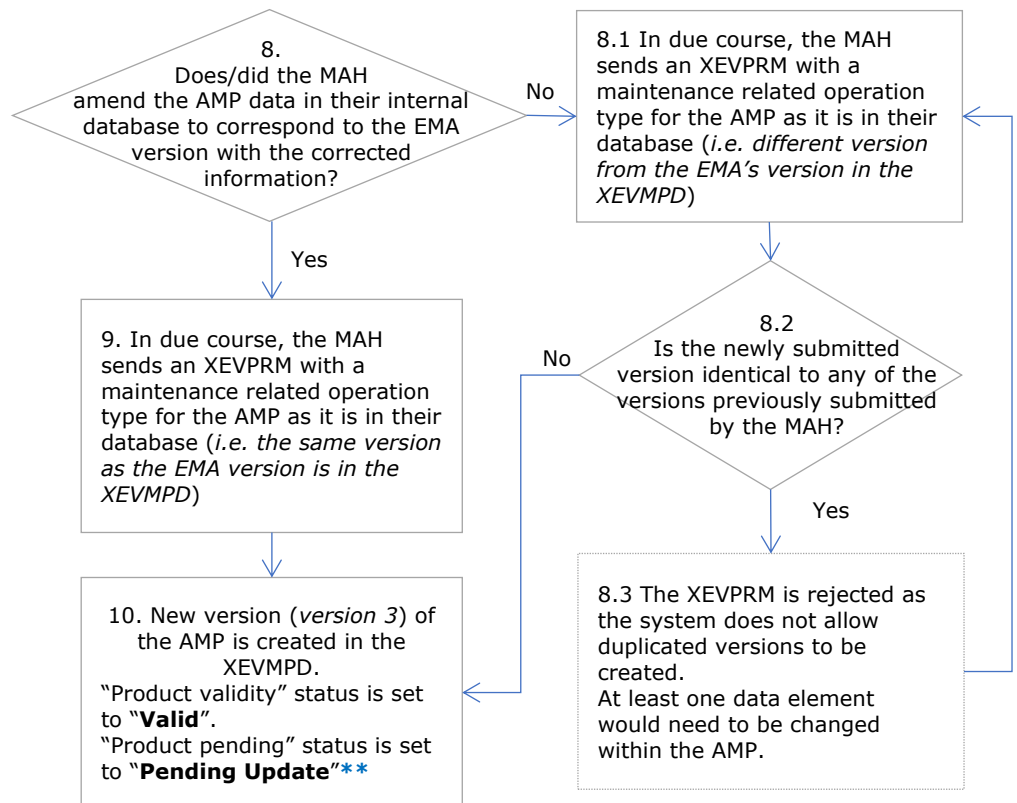
** Each time the MAH sends further updates as required, a new version is created.

Should the product be invalidated (i.e. operation type "Invalidate MA (6)" is applied) by the MAH, the MAH can no longer update [i.e. operation type "Update (2)"] the (invalidated) AMP.

AMPs flagged as "Valid" can only be nullified by the EMA. Should the EMA nullify an AMP on behalf of the MAH, a new version number is assigned.

Process in use from 4 November 2015





**** Each time the MAH sends further updates a new version is created.**
Should the product be invalidated (i.e. operation type "Invalidate MA (6)" is applied) by the MAH, the MAH can no longer update [i.e. operation type "Update (2)] the (invalidated) AMP.
AMPs flagged as "Valid" can only be nullified by the EMA. Should the EMA nullify an AMP on behalf of the MAH, a new version number is assigned.
AMPs that were invalidated or nullified are not subject of any future validation.

Annex 2: 3rd Acknowledgement examples

Example 1: No changes were performed by the EMA

```
<?xml version="1.0" encoding="UTF-16"?>
- <evprmack
xsi:noNamespaceSchemaLocation="http://eudravigilance.ema.europa.eu/schema/ackxevmprack.xsd"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance">
  - <ichicsrmessageheader>
    <messagetype>EVPRACK</messagetype>
    <messageformatversion>1.0</messageformatversion>
    <messageformatrelease>1.0</messageformatrelease>
    <messagenumb>Product Validated as submitted PRD329691 Version 6 / 2015/10/02
      11:37:32</messagenumb>
    <messagesenderidentifier>EVHUMAN</messagesenderidentifier>
    <messageceiveridentifier>XXXXXX</messageceiveridentifier>
    <messagedateformat>204</messagedateformat>
    <messagedate>20151002113732</messagedate>
  </ichicsrmessageheader>
  - <acknowledgment>
    - <messageacknowledgment>
      <evmessagenumb>1683511</evmessagenumb>
      <originalmessagenumb>PRD329691 Version 6</originalmessagenumb>
      <originalmessagesenderidentifier>XXXXXX</originalmessagesenderidentifier>
      <originalmessageceiveridentifier>EVHUMAN</originalmessageceiveridentifier>
      <originalmessagedateformat>204</originalmessagedateformat>
      <originalmessagedate>20141006141650</originalmessagedate>
      <transmissionacknowledgmentcode>01</transmissionacknowledgmentcode>
    </messageacknowledgment>
    - <reportacknowledgment>
      <reportname>AUTHORISEDPRODUCT</reportname>
      <localnumber/>
      <ev_code>PRD329691</ev_code>
      <operationtype>9</operationtype>
      <operationresult>601</operationresult>
      <operationresultdesc>Product validated successfully as
        submitted.</operationresultdesc>
    </reportacknowledgment>
  </acknowledgment>
</evprmack>
```

Example 2: Changes were performed by the EMA

```
<?xml version="1.0" encoding="UTF-16"?>
- <evprmack
  xsi:noNamespaceSchemaLocation="http://eudravigilance.ema.europa.eu/schema/ackxevmpd.xsd"
  xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance">
  - <ichicsrmessageheader>
    <messagetype>EVPRACK</messagetype>
    <messageformatversion>1.0</messageformatversion>
    <messageformatrelease>1.0</messageformatrelease>
    <messagenumb>Product validated following EMA edit of data PRD116098 Version 2 /
      2015/10/13 17:02:06</messagenumb>
    <messagesenderidentifier>EVTEST</messagesenderidentifier>
    <messagereceiveridentifier>XXXXXX</messagereceiveridentifier>
    <messagedateformat>204</messagedateformat>
    <messagedate>20151013170204</messagedate>
  </ichicsrmessageheader>
  - <acknowledgment>
    - <messageacknowledgment>
      <evmessagenumb>EU-EC-M-137432</evmessagenumb>
      <originalmessagenumb>EMA edit of data PRD116098 Version 1</originalmessagenumb>
      <originalmessagesenderidentifier>EVTESTWT</originalmessagesenderidentifier>
      <originalmessagereceiveridentifier>EVTEST</originalmessagereceiveridentifier>
      <originalmessagedateformat>204</originalmessagedateformat>
      <originalmessagedate>20151013165926</originalmessagedate>
      <transmissionacknowledgmentcode>01</transmissionacknowledgmentcode>
    </messageacknowledgment>
    - <reportacknowledgment>
      <reportname>AUTHORISEDPRODUCT</reportname>
      <localnumber/>
      <ev_code>PRD116098</ev_code>
      <operationtype>2</operationtype>
      <operationresult>4</operationresult>
      <operationresultdesc>Entity updated successfully Version 2 Product validated
        following EMA edit of data. Please note that your product data was not deemed
        valid as submitted and was edited as part of the validation process as follows:
        Product Versions Changes Section: Presentation # Changed: Product Short
        Name</operationresultdesc>
    </reportacknowledgment>
  </acknowledgment>
</evprmack>
```

Annex 3: Use of AMP versions from Art57 database

The table below defines which version of the data is used by the various processes relying on the Article 57 database.

Latest Version:

Art57 Business Use		AMP version used from Art57 database
Perform data analysis:		
• EudraVigilance Data Analysis System (EVDAS)		All versions
• Signal Management		Latest EMA version
• Establish a complete list of medicinal product and active substance information to support the coding of such information reported in Individual Case Safety Reports (ICSRs)		Latest EMA version
Facilitate medicines regulation and fulfil regulatory actions and legal obligations:		
• Referrals		Latest version (MAH or EMA)
• PSUR repository		Latest version (MAH or EMA)
• PSUR single assessment		Latest version (MAH or EMA)
• Medical Literature Monitoring		Latest version (MAH or EMA)
• Calculation of pharmacovigilance fees (Annual and Procedural)		Latest version (MAH or EMA)
• Art57 Data Warehouse (notifications of QPPV/MFL to NCAs) – In development		Latest version (MAH or EMA)
Communicate effectively with Agency stakeholders		
• Targeted Pharmacovigilance Risk Assessment Committee (PRAC) communications		Latest version (MAH or EMA)