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 were initially required to submit information on medicinal products 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, marketing-authorisation holders (MAHs) were required to complete previously submitted product data with additional information, bring this information up–to-date and improve the data quality by 31 December 2014. Thereafter, the 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 process

In July 2014, the EMA commenced the review of quality and integrity of 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 are expected to be quality controlled by the end of September 2015.

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

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

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[1] Changes are highlighted in red. Annex 3 included in rev. 5 of this document has been removed. Editorial changes are not highlighted.

latest version of the received medicinal product data is performed by checking each data element against the information stated in the provided Summary of Product Characteristics (SmPCs) 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 QPPV of the marketing-authorisation holder (MAH) organisation is informed by email with the request to review their 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 of the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) 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 (AMP) entity as *"Valid"* in the XEVMPD before their next maintenance related submission - *the MAH can always submit XEVPRMs with operation types 'Update (2)' or 'Invalidate MA (6)' 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:

- ~~A summary of changes made by the EMA to the medicinal product entities submitted by the MAH organisation are notified via an email to the QPPV within two weeks since the validation occurred.~~

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 2/13

- ~~The EMA will also provide the MAH organisation with an ad hoc and one-off comparison between the data validated by the Agency and the data submitted by industry. The comparison will be provided for information by mid October 2015.~~

- Since the electronic notification following the quality control process was implemented (i.e. 4 November 2015), the MAH organisation is informed of the outcome of the quality control process via the 3rd XEVPRM Acknowledgement.

- Should the MAH organisation either object to any of the changes/corrections made by the EMA or to request further clarifications on the performed amendments, an email should be submitted to the Article 57 Quality Control Inbox (Art57-QC@ema.europa.eu). The Art57-QC team will assess the comments or objections raised by MAHs 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.

- 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 has been 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 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.

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 3/13

Electronic notification following the quality control process

Phase I: process in use until 4 November 2015

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

Once the XEVPRM is processed by the EudraVigilance system, Gateway and WEB Trader users receive 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 as part of Phase II and was not used in the production environment before 4 November 2015.

Neither the operation type codes nor the acknowledgement message format has been amended.

Phase II: 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 described in Phase I, following the EMA quality control activity, 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.

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 4/13

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.

- 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.

  ~~Gateway user organisations can request testing of the 3rd XEVPRM Acknowledgement by following the process described in Annex 3: Test of receipt of the 3rd level XEVPRM Acknowledgement following the EMA quality control activity.~~

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

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 5/13

For further details related to the Extended EudraVigilance product report acknowledgement message please refer to Chapter 5: XEVPRM Acknowledgement of the user guidance.

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014
Page 6/13

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

Phase I

START

MAH submits a new AMP entity in the XEVMPD. Version number 1 is created.*
"Product validity" status is set to "**Not Assessed**". "Product pending" status is set to "**Not Assessed**".

2.2 Contact the QPPV and request for a valid document to be attached to the AMP entity

1. EMA retrieves the AMP to be validated

No

2.1
Is/are another document(s) that can facilitate the validation process attached?

No

2.
Is the latest valid SmPC attached to the AMP entity?

Yes

Yes

3. EMA validates the information in the AMP entity against the information listed in the attachment(s) and in accordance with the principles outlined in the QC Methodology document and Chapter 3.II: XEVPRM User Guidance

4.1 "Product validity" status is set to "**Valid**".
"Product pending" status is set to "**Assessed**".

The EMA version of the AMP is the same as the MAH's version

No

4. Were any corrections made as part of the validation?

Yes

Continue with step 8

5. New version (*version 2*) is created.

"Product validity" status is set to "**Valid**".
"Product pending" status is set to "**Assessed**".

The EMA version of the AMP is different from the MAH's version.

6. In due course, the QPPV of the MAH is provided with a Data Quality Report summarizing the results of the analysis performed by the Agency.
The MAH reviews the changes. If the MAH has any comments or objections regarding the performed changes, Art57-QC@ema.europa.eu should be contacted.

Continue with step 7

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

Quality Control of medicinal product data submitted as per the legal requirement introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014

Page 7/13

```
┌─────────────────────────┐                    ┌─────────────────────────┐
│           7.            │                    │ 7.1 In due course, the  │
│    Does/did the MAH     │                    │ MAH sends an XEVPRM     │
│ amend the AMP data in   │        No          │ with a maintenance      │
│ their internal database │ ─────────────────> │ related operation type  │
│ to correspond to the    │                    │ for the AMP as it is in │
│ EMA version with the    │                    │ their database (i.e.    │
│ corrected information?   │                    │ different version from  │
└─────────────────────────┘                    │ the EMA's version in    │
             │                                  │ the XEVMPD)             │
             │ Yes                              └─────────────────────────┘
             ▼                                               │
┌─────────────────────────┐                                 ▼
│ 8. In due course, the   │                    ┌─────────────────────────┐
│ MAH sends an XEVPRM     │        No          │           7.2           │
│ with a maintenance      │ <───────────────── │  Is the newly submitted │
│ related operation type  │                    │ version identical to    │
│ for the AMP as it is in │                    │ any of the versions     │
│ their database (i.e. the│                    │ previously submitted    │
│ same version as the EMA │                    │ by the MAH?             │
│ version in the XEVMPD)  │                    └─────────────────────────┘
└─────────────────────────┘                                 │
             │                                               │ Yes
             ▼                                               ▼
┌─────────────────────────┐                    ┌─────────────────────────┐
│ 9. New version (version │                    │ 7.3 The XEVPRM is       │
│ 3) of the AMP is created│                    │ rejected as the system  │
│ in the XEVMPD.          │ <───────────────── │ does not allow          │
│                         │                    │ duplicated versions to  │
│ "Product validity"      │                    │ be created.             │
│ status is set to        │                    │ At least one data       │
│ "Valid".                │                    │ element would need to   │
│ "Product pending"       │                    │ be changed within the   │
│ status is set to        │                    │ AMP.                    │
│ "Pending Update".**     │                    └─────────────────────────┘
└─────────────────────────┘
```

** 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.

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 8/13

Phase II

START
MAH submits a new AMP entity in the XEVMPD. Version number 1 is created.*
"Product validity" status is set to "**Not Assessed**". "Product pending" status is set to "**Not Assessed**".

2.2 Contact the QPPV and request for a valid document to be attached to the AMP entity

1. EMA retrieves the AMP to be validated

No

2.1
Is/are another document(s) that can facilitate the validation process attached?

No

2.
Is the latest valid SmPC attached to the AMP entity?

Yes

Yes

3. EMA validates the information in the AMP entity against the information listed in the attachment(s) and in accordance with the principles outlined in the QC Methodology document and Chapter 3.II: XEVPRM User Guidance

4.1 "Product validity" status is set to "**Valid**".
"Product pending" status is set to "**Assessed**".

The EMA version of the AMP is the same as the MAH's version

No

4. Were any corrections made as part of the validation?

Yes

4.2 The MAH is informed via a 3rd XEVPRM ACK that their medicinal product was successfully validated as submitted.

The EMA version of the AMP is the same as the MAH's version

5. New version (*version 2*) is created.

"Product validity" status is set to "**Valid**".
"Product pending" status is set to "**Assessed**".

The EMA version of the AMP is different from the MAH's version.

Continue with step 9

6. The MAH is informed via a 3rd XEVPRM ACK that their medicinal product was validated following an EMA edit of data. The list of changes is included in the 3rd ACK.

7. The MAH reviews the changes. If the MAH has any comments or objections regarding the performed changes, Art57-QC@ema.europa.eu should be contacted.

Continue with step 8

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

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 9/13

```
  ┌─────────────────────────┐                          ┌──────────────────────────────┐
  │           8.            │                          │ 8.1 In due course, the MAH   │
  │   Does/did the MAH      │         No               │ sends an XEVPRM with a       │
  │ amend the AMP data in   │──────────────────────────▶│ maintenance related operation│◀──┐
  │ their internal database │                          │ type for the AMP as it is in │   │
  │ to correspond to the EMA│                          │ their database (i.e. different│   │
  │ version with the        │                          │ version from the EMA's       │   │
  │ corrected information?   │                          │ version in the XEVMPD)       │   │
  └─────────────────────────┘                          └──────────────────────────────┘   │
              │                                                      │                      │
             Yes                                                     ▼                      │
              ▼                                         ┌──────────────────────────────┐   │
  ┌─────────────────────────┐                          │           8.2                │   │
  │ 9. In due course, the   │              No          │ Is the newly submitted       │   │
  │ MAH sends an XEVPRM with │◀─────────────────────────│ version identical to any of  │   │
  │ a maintenance related    │                          │ the versions previously      │   │
  │ operation type for the   │                          │ submitted by the MAH?        │   │
  │ AMP as it is in their    │                          └──────────────────────────────┘   │
  │ database (i.e. the same  │                                        │                      │
  │ version as the EMA       │                                       Yes                     │
  │ version is in the XEVMPD)│                                        ▼                      │
  └─────────────────────────┘                          ┌──────────────────────────────┐   │
              │                                         │ 8.3 The XEVPRM is rejected as │   │
              ▼                                         │ the system does not allow     │   │
  ┌─────────────────────────┐                          │ duplicated versions to be     │───┘
  │ 10. New version          │◀─────────────────────────│ created.                      │
  │ (version 3) of the AMP   │                          │ At least one data element     │
  │ is created in the XEVMPD.│                          │ would need to be changed      │
  │                          │                          │ within the AMP.               │
  │ "Product validity"       │                          └──────────────────────────────┘
  │ status is set to Valid.  │
  │ "Product pending" status │
  │ is set to Pending        │
  │ Update.**                │
  └─────────────────────────┘
```

┌───┐
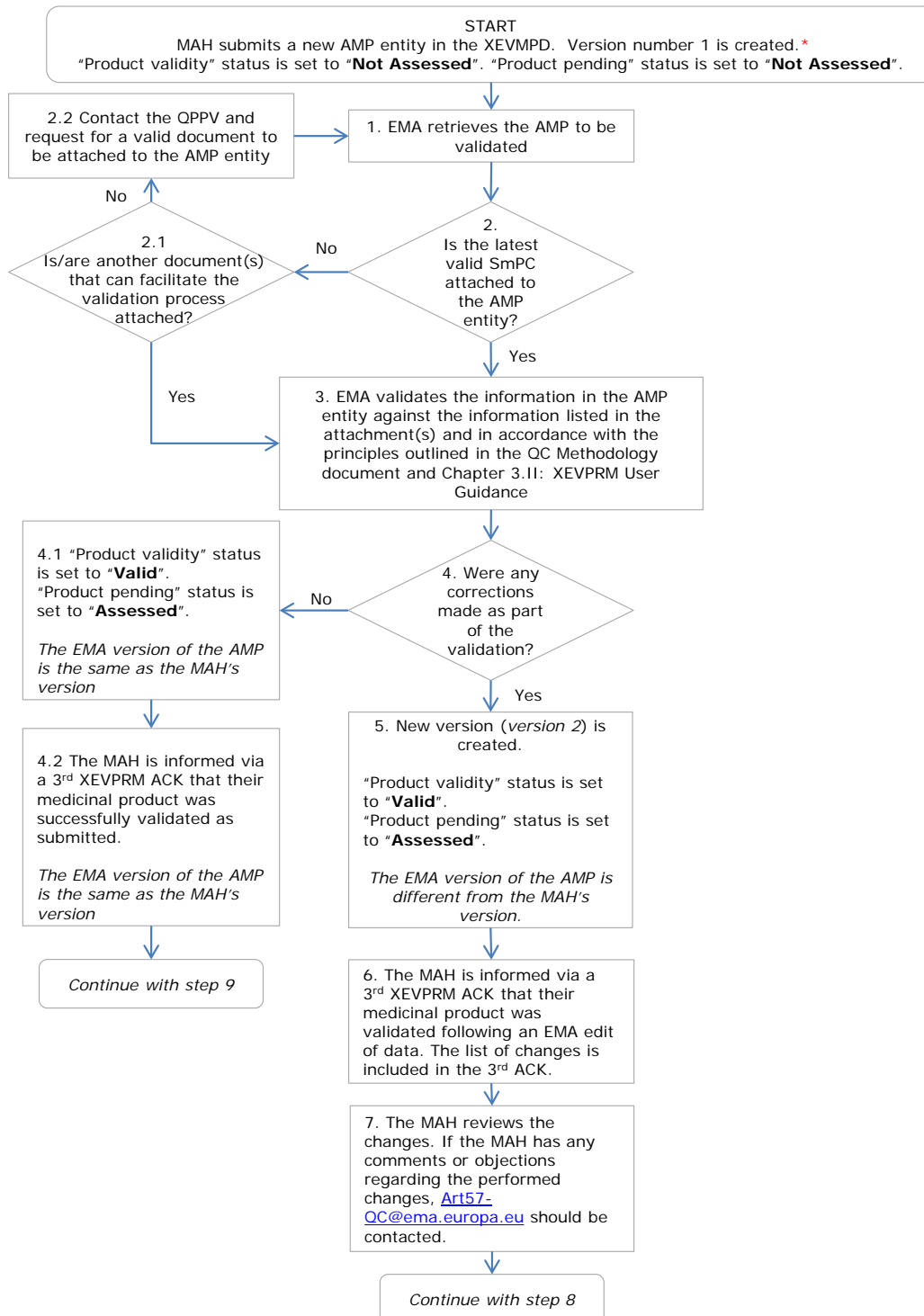│ ** Each time the MAH sends further updates as required, a new version is created.   │
│   │
│ Should the product be invalidated (i.e. operation type "Invalidate MA (6)" is applied) by │
│ the MAH, the MAH can no longer update [i.e. operation type "Update (2)] the (invalidated) │
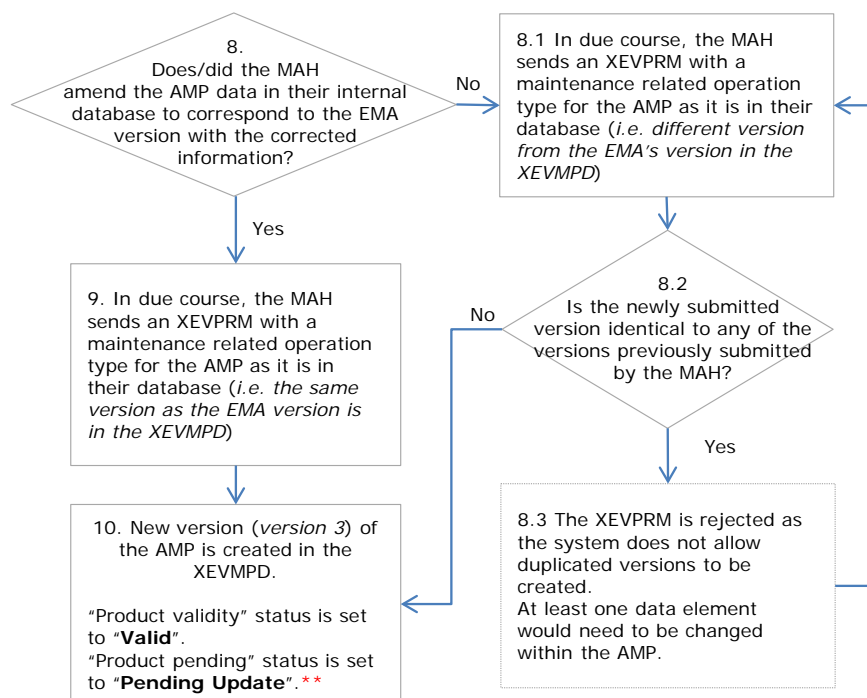│ AMP.   │
│   │
│ AMPs flagged as "Valid" can only be nullified by the EMA. Should the EMA nullify an AMP on │
│ behalf of the MAH, a new version number is assigned.   │
└───┘

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 10/13

Annex 2: 3rd Acknowledgement examples

Example 1: No changes were performed by the EMA

```xml
<?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 as submitted PRD329691 Version 6 / 2015/10/02
          11:37:32</messagenumb>
      <messagesenderidentifier>EVHUMAN</messagesenderidentifier>
      <messagereceiveridentifier>XXXXX</messagereceiveridentifier>
      <messagedateformat>204</messagedateformat>
      <messagedate>20151002113732</messagedate>
  </ichicsrmessageheader>
  <acknowledgment>
    <messageacknowledgment>
      <evmessagenumb>1683511</evmessagenumb>
      <originalmessagenumb>PRD329691 Version 6</originalmessagenumb>
      <originalmessagesenderidentifier>XXXXX</originalmessagesenderidentifier>
      <originalmessagereceiveridentifier>EVHUMAN</originalmessagereceiveridentifier>
      <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>
```

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 11/13

Example 2: Changes were performed by the EMA

```xml
<?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>XXXXX</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>
```

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 12/13

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: Most recent data available as recorded in the Article 57 database

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)

Quality Control of medicinal product data submitted as per the legal requirement
introduced by Article 57(2) of Regulation (EC) No 726/2004
EMA/661709/2014   Page 13/13