9 June 2015
EMA/262834/2015
Information Management Division

Process description for managing duplicates in the context of the Medical Literature Monitoring (MLM) service

In support of the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency

Draft prepared by Project and Maintenance Group 1 "Collection of key information on medicines" (PMG 1) of the governance structure for pharmacovigilance	18 May 2015
Consultation of the EudraVigilance Expert Working Group (EV-EWG)	29 May 2015
Finalised by Project and Maintenance Group 1 (PMG1)	2 June 2015

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

The duplicate management process applied in EudraVigilance is defined in the Guideline on detection and management of duplicate individual cases and Individual Case Safety Reports (ICSRs)[1] (Doc. Ref. EMA/13432/2009).

The process description for the duplicate management in the context of the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency (MLM service) in accordance with Article 27 of Regulation (EC) 726/2004 is further described in this document.

Until the launch of the MLM service, the EMA, via EudraVigilance, had only been receiving ICSRs and had thus managed confirmed duplicates exclusively by creating a master case. This is based on merging the data from the underlying duplicates into the master in accordance with section 2.3.1.2 of the Guideline on detection and management of duplicate individual cases and ICSRs.

Following the launch of the MLM service, the EMA is also creating and making available ICSRs. Therefore a process of managing duplicates concerning MLM related ICSRs needs to be put in place.

This document outlines the process that the EMA will follow taking into account different sources of duplicates in EudraVigilance.

2. General principles

2.1. General

- This document describes the duplicate management process applied in accordance with the reporting requirements of ICSRs as outlined in GVP Module VI[2].
- Information on individual cases is processed in accordance with personal data protection requirements as outlined in GVP Module VI[3].

2.2. MLM Service

- Only ICSRs created and sent by the sender MLMSERVICE are available for marketing authorisation holders to download.
- Only ICSRs created and sent by the sender MLMSERVICE are sent to National Competent Authorities in European Economic Area (EEA) Member States.
- All versions of MLMSERVICE individual case reports will be made available to all senders and will always retain their original world-wide unique case identifiers.
- When a duplicate of an MLMSERVICE individual case is detected and confirmed, the MLMSERVICE case will always be updated in EudraVigilance with the information from the other duplicative case,

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/06/WC500129037.pdf
[2] GVP Module VI.B.8 Reporting modalities; GVP Module VI.C Operation of the EU Network; GVP Module VI, Appendix 3 Modalities for reporting and Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period (17 October 2013, EMA/321386/2012 Rev.8 or later if applicable)
[3] GVP Module VI.C.6.2.2.8. What to take into account for data privacy laws; GVP Module VI.C Operation of the EU Network

in line with data protection requirements, so that it will contain essentially the same information as the master case.

- Information on duplicates related to MLMSERVICE individual cases will be captured in both the report duplicates section of the MLM individual cases and the “MLM ICSRs” tracking tables published at the dedicated area of the EudraVigilance website.
- Masters are not made available by the MLMSERVICE to marketing authorisation holders via the MLM EVWEB area and the EudraVigilance ICH ICSR Export Manager. They are also not transmitted to the National Competent Authorities in EEA Member States, however they are available in EudraVigilance in support of pharmacovigilance activities to all stakeholders in line with the EudraVigilance Access Policy.

2.3. Duplicate management

- EMA needs to manage and remove duplicates in EudraVigilance.
- Within EudraVigilance, an individual case is defined as a combination of “sender (organisation) identifier” (ICH M.1.5) and the “worldwide unique case identification number” (ICH E2B(R2) A.1.10). Two ICSRs sent by two **different** organisations with the **same** worldwide unique case identification number are two individual cases, unless both are merged under a master by the EMA.
- Each individual case is owned by its sender.
- The EMA **never** nullifies a case sent by another organisation.
- Once a master case is created, it is visible in the pharmacovigilance queries of EVDAS (the underlying duplicates are not visible).
- The underlying duplicates of a master individual case remain live for administrative purposes and follow-up by sender organisations.
- Master cases have all underlying duplicates cross-referenced in the report duplicate section “Other case identifiers in previous transmissions” (ICH E2B(R2) A.1.11) and the links are visible in the cluster information in EVWEB.

3. Sources of duplicate information

3.1. MLM individual case identified as a duplicate of another MLM individual case (originating from a different article but referring to the same individual case)

a. EMA identifies potential duplicates of two MLM individual cases (**case A** & **case B**);

b. EMA informs its MLM service provider;

c. MLM service provider validates potential duplicates and confirms or rejects the duplicates;

d. If duplicates are confirmed, then the MLM service provider updates **case A** with the information from **case B**, nullifies **case B** and updates the relevant “MLM ICSR” tracking sheets;

e. Both individual cases (i.e. updated case A and nullified case B) are transmitted to EudraVigilance and National Competent Authorities (as applicable);

f. All versions of **case A** will remain available in EVDAS, the MLM EVWEB area and the EudraVigilance ICSR Export Manager;

g. The latest version of **case B** (the nullified case report) will be available in the EudraVigilance ICSR Export Manager, whereas the earlier versions will no longer be available;

h. **Case B** will no longer be available in EVDAS; however all versions of **Case B** will still be available in the MLM EVWEB area.

3.2. MLM individual case retransmitted to EudraVigilance without (significant) new information by other sender

a. Either:

   i. Where the retransmitted individual case is identical, these will be automatically merged by the EudraVigilance Automaster algorithm; or

   ii. Where the individual cases are not identical, but the changes made by the re-transmitter are not based on new information, these will be merged manually by the EMA's duplicate management service provider;

b. The tracking tables will be updated;

c. If the individual cases are completely identical (with the exception of the sender identifier (M.1.5) or sender section (A.3.1)), including the case numbers, then no update will be made to the MLM case;

d. If there is any different information in the individual cases, including the world-wide unique case identifications number from the other sender, then the MLM case will be updated;

e. EMA will contact the re-transmitter to stop the resubmission of MLM individual cases;

f. The MLM case will remain available as it previously was in the MLM EVWEB area and via the ICSR Export Manager;

g. The master case will remain in EVDAS for pharmacovigilance purposes (the underlying duplicates are not visible); it will not be transmitted to National Competent Authorities in EEA Member States and will not be made available to marketing authorisation holders.

3.3. MLM individual case is a duplicate of another pre-existing ICSR which contains significant new information to that in the MLM individual case

a. EMA identifies confirmed duplicates including one **MLM case**;

   i. If the duplication is detected at the time of data entry, then the MLM case will be based on the pre-existing case;

   ii. If there is only one pre-existing case, then the MLMSERVICE case shall be created as though it was a follow-up. The world-wide unique case safety identifier (ICH E2B (R2) A.1.10) and the receive date (ICH E2B(R2) A.1.6) of the pre-existing case will be retained.

   iii. The receipt date will be the date the literature record was retrieved with the four minimum reporting criteria available and the sender's unique (case) safety report identifier (ICH E2B(R2) A.1.0.1) will be created as an MLMSERVICE number. Personal data that is not in the public article will be redacted;

b. EMA merges the **MLM case** with the duplicate under a master;

c. Duplicate management service provider updates **MLM case** with information from the duplicate, including case numbers in report duplicates section, and updates the relevant tracking sheets;

d. The updated version of the **MLM case** is transmitted to EudraVigilance and National Competent Authorities in EEA Member States (as applicable) via the usual follow-up procedures;

e. The **MLM case** will still be available as it previously was in the MLM EVWEB area and via the EudraVigilance ICSR Export Manager;

f. The master case will be available in EVDAS. It will **not** be transmitted to National Competent Authorities in EEA Member States and will **not** be made available to marketing authorisation holders.

3.4. Follow-up information on an existing MLM individual case obtained by an organisation other than MLMSERVICE

For individual cases resulting from the MLM service specific security and access rules apply. Even if the worldwide unique case identification number is the same, follow-up reports sent by a different organisation than MLMSERVICE will be considered as a different individual case, in line with current case management rules. Therefore these cases from other sender organisations will not be made available as MLMSERVCE cases.

EMA has to merge these individual cases sent to Eudravigilance by different senders, under a master case. When one of the duplicates is a case from MLMSERVICE, the EMA will update the MLMSERVICE case with additional information from the duplicate(s).

a. National Competent Authority/marketing authorisation holder (organisation other than MLMSERVICE) receives new information about a pre-existing **MLM case**;

b. National Competent Authority/marketing authorisation holder creates follow-up report based on MLM individual case and transmits it to EudraVigilance (Note: This ICSR will not be available to other organisations via the MLMSERVICE tools at this point);

c. Within one calendar day, the EMA duplicate management service provider merges the updated **MLM case** with the National Competent Authority/marketing authorisation holder **follow-up report** under a master case;

d. Later that same calendar day, the EMA MLM service provider updates the **MLM case** with information from the National Competent Authority/marketing authorisation holder **follow-up report** and updates the MLM ICSR tracking sheet;

e. The **updated MLM case** is transmitted to EudraVigilance via usual follow-up;

f. The **updated MLM case** is only transmitted to the National Competent Authority if:

   i. Initial MLM individual case was sent to the National Competent Authority and

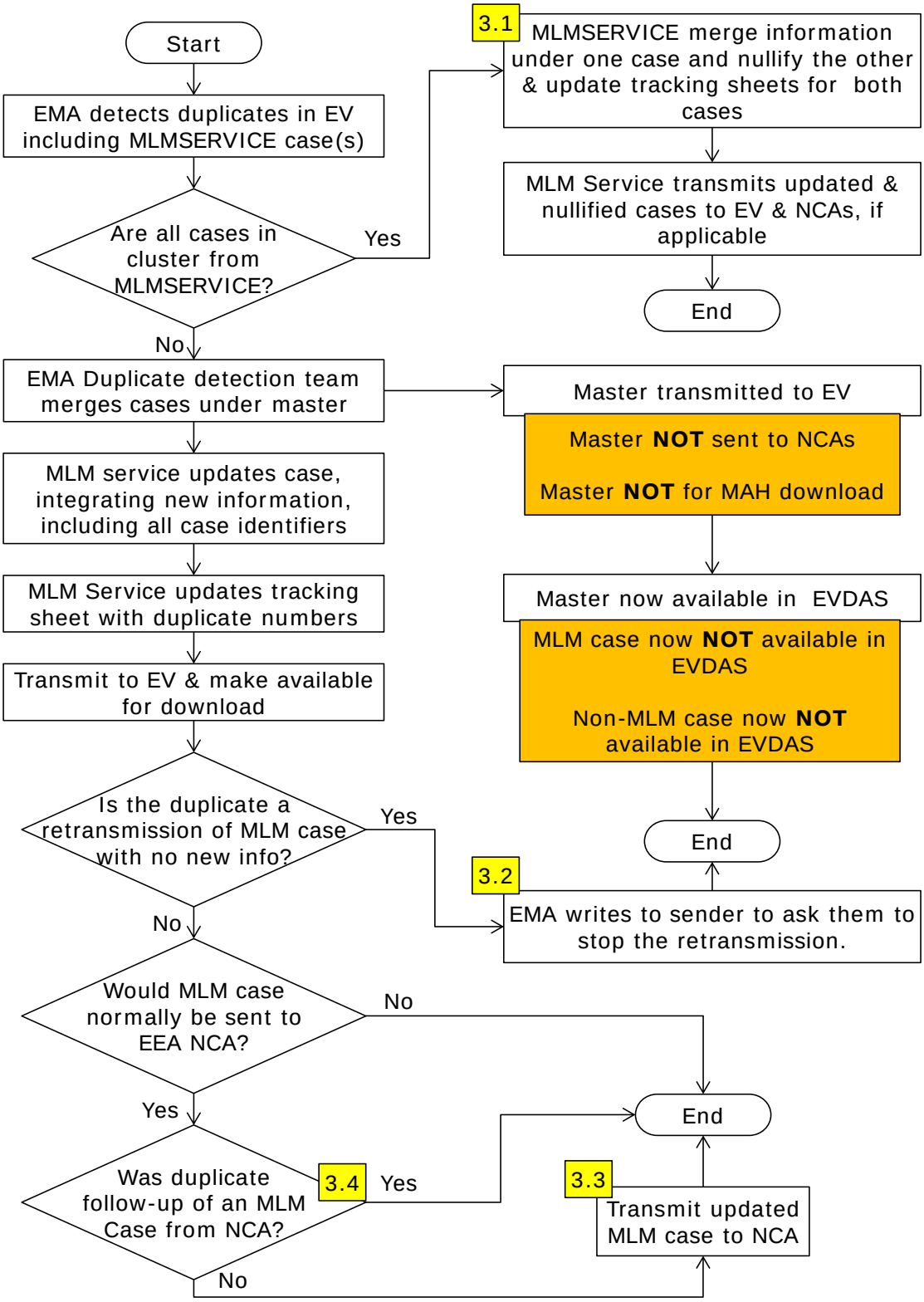
   ii. The sender organisation that sent the follow-up to EudraVigilance was NOT that NCA;

g. The **MLM case** will still be available as it previously was in the MLM EVWEB area and via the EudraVigilance ICSR Export Manager;

h. The master case will be visible in EVDAS for pharmacovigilance purposes (the underlying duplicates are not visible); it will **not** be transmitted to National Competent Authorities and will **not** be made available to marketing authorisation holders.

4. Flowchart

The flowchart below shows the interrelation of the scenarios detailed above. The numbers in yellow boxes refer to the number of the relevant scenario at that point.


Start
EMA detects duplicates in EV including MLMSERVICE case(s)
Are all cases in cluster from MLMSERVICE?
Yes
3.1
MLMSERVICE merge information under one case and nullify the other & update tracking sheets for both cases
MLM Service transmits updated & nullified cases to EV & NCAs, if applicable
End
No
EMA Duplicate detection team merges cases under master
Master transmitted to EV
Master NOT sent to NCAs
Master NOT for MAH download
MLM service updates case, integrating new information, including all case identifiers
MLM Service updates tracking sheet with duplicate numbers
Master now available in EVDAS
MLM case now NOT available in EVDAS
Non-MLM case now NOT available in EVDAS
Transmit to EV & make available for download
Is the duplicate a retransmission of MLM case with no new info?
Yes
End
3.2
EMA writes to sender to ask them to stop the retransmission.
No
Would MLM case normally be sent to EEA NCA?
No
End
Yes
Was duplicate follow-up of an MLM Case from NCA?
3.4
Yes
3.3
Transmit updated MLM case to NCA
No