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Inspections and Human Medicines Pharmacovigilance Division

Monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency

Start-up Plan

Draft prepared by Project and Maintenance Group 1 "Collection of key information on medicines" (PMG 1) of the governance structure for pharmacovigilance	2 June 2015
Consultation of the EudraVigilance Expert Working Group (EV-EWG)	15 June 2015
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Table of contents

1. Introduction and purpose

In accordance with Article 27 of Regulation (EC) No 726/2004, the European Medicines Agency (EMA) is in the process of starting the monitoring of selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances and of entering into EudraVigilance the relevant information. The list of active substances and the medical literature subject to this monitoring have been defined and are published on the dedicated MLM webpage.

The Detailed Guide prepared by the Agency in consultation with the Commission, Member States and interested parties defines the activities and business processes related to the monitoring of medical literature and the entry of relevant information into EudraVigilance. The Detailed Guide is complemented by the following supporting documents:

- Inclusion/exclusion criteria for processing Individual Case Safety Reports
- Process description for managing duplicates in the context of the medical literature monitoring service
- Search parameters for the top 50 chemical substance groups

As of 1st July 2015, the medical literature monitoring activities to be performed by the Agency will become operational based on the top 50 chemical substance groups of the list published at the MLM webpage and will be extended to the full scope of 400 substance groups in September 2015. The first two months of the activities will provide the opportunity to National Competent Authorities (NCAs) in European Economic Area (EEA) Member States, concerned marketing authorisation holders (MAHs) and the Agency, as well as the Agency's contractor, to:

- Execute against and where necessary fine-tune business processes outlined in the Detailed Guide and supporting documents;
- Achieve and ensure high quality and adequate performance of the activities, which will be monitored through a robust quality assurance process;
- Clarify questions;
- Identify potential issues and take corrective measures where necessary.

The Agency has prepared this Start-up Plan to provide a framework for the interaction with involved parties and the initiation of the operations including an optimal performance of the new activities based on Article 27 of Regulation (EC) 726/2004.

The start-up phase is scheduled from 1st July until 31st August 2015 and will conclude on the basis of a closing report, which will summarise the outcome and findings based on the initial operational experience.

2. Concerned stakeholders

The parties concerned by the launch of the Agency's literature monitoring activities based on the 50 top active chemical substance groups are as follows:

- All NCAs in EEA Member States
- Around 2,370 MAHs
- EMA

3. Scope and activities of the start-up phase

The scope of the start-up phase includes:

1. Daily[1] search of the scientific and medical literature reference database Embase™ as of 1 July 2015. Embase is manually indexed by Embase indexers against the full text article, with the indexed terms being available for searching to ensure precision. Indexing is controlled against the Emtree thesaurus, which is mapped to Medical Subject Headings (MeSH) by including all MeSH synonyms in Emtree to ensure indexing and searches are transposable across different vocabularies. Emtree is updated three times a year and is updated in synchrony with MeSH updates to ensure continuous retrieval.

2. A monthly search[2] of the scientific and medical literature reference database International Pharmaceutical Abstracts (IPA) and the Allied and the Complementary Medicine Database (AMED) as of 3 August 2015. This search covers the previous month (period of 30 June to 31 July 2015). A duplicate management process is in place to ensure minimal replication of articles indexed in the databases being searched. AMED thesauruses contain over 2,500 terms based on MeSH for indexing. AMED and IPA are both abstracting and indexing (A&I) databases, which within EBSCO are "SmartLinked" to call back the full text record from Medline full text.

3. Publication[3] of the "MLM Search Results" tracking sheets at the dedicated area of the EudraVigilance website.

4. Review and initial assessment (screening) of each literature record resulting from the literature search against the inclusion/exclusion criteria within one calendar day[8] following the conduct of the search (i.e. citation details, abstract and full text article if available/ordering of full text article if not available and translation as applicable) and tracking of the screening outcome.

5. Publication of the "MLM Search Results" and "MLM ICSRs" each calendar day following the review activities on the restricted area of the EudraVigilance website.

6. Follow-up of missing information of potential ICSRs, tracking of the follow-up status and outcome as well as publication of the status as part of "MLM ICSRs".

7. Entering of valid Individual Case Safety Reports (ICSRs) in EudraVigilance for all suspected adverse reactions within the EEA and suspected serious adverse reactions originating outside the EEA as an outcome of the screening activities and in line with the timelines specified below:

    a. Serious adverse reactions are entered in EudraVigilance immediately and no later than seven calendar days[4];

    b. Non-serious adverse reactions are entered in EudraVigilance within 21 calendar days.

8. Updating and publishing the "MLM ICSRs" tracking sheet and making the ICSRs available for download by MAHs in the MLM EVWEB area or via the EudraVigilance ICSR Export Manager.

[1] Daily refers to calendar days with the exception of weekends (Saturday and Sunday)
[2] Monthly refers to updates of the database as issued by the database provider every calendar month.
[3] At the next calendar day following execution of the search
[4] Day zero for the timelines related to the entry in EudraVigilance is the date on which the contractor becomes aware of a publication containing the minimum information for an ICSR to be reportable. Refer to GVP module VI, chapter VI, App 2.7

9. Transmitting electronically the ICSRs entered in EudraVigilance within one calendar day to the NCAs in EEA Member States in accordance with the reporting requirements of ICSRs as outlined in GVP Module VI.[5].

10. Initiating appropriate follow-up of confirmed ADRs and publishing of the updates to the MLM "ICSR tracking" table as applicable.

11. Processing of any new follow-up information, maintaining and publishing the "MLM ICSRs" tracking sheet accordingly and creating follow-up ICSRs within:

    a. seven calendar days for suspected serious adverse reactions;

    b. 21 calendar days following receipt of new information related to suspected non-serious adverse reactions.

12. Updating the "MLM ICSRs" tracking sheet in line with the outcome of the EudraVigilance duplicate management.6 process and initiation of ICSR processing (including nullification) where applicable.

13. Operating the Medical Literature Monitoring Tracking Tool (MLTT) to support the tracking of all activities and the creation and publication of the "MLM Search Results" and "MLM ICSRs" Excel files.

14. Operation of the service desk.

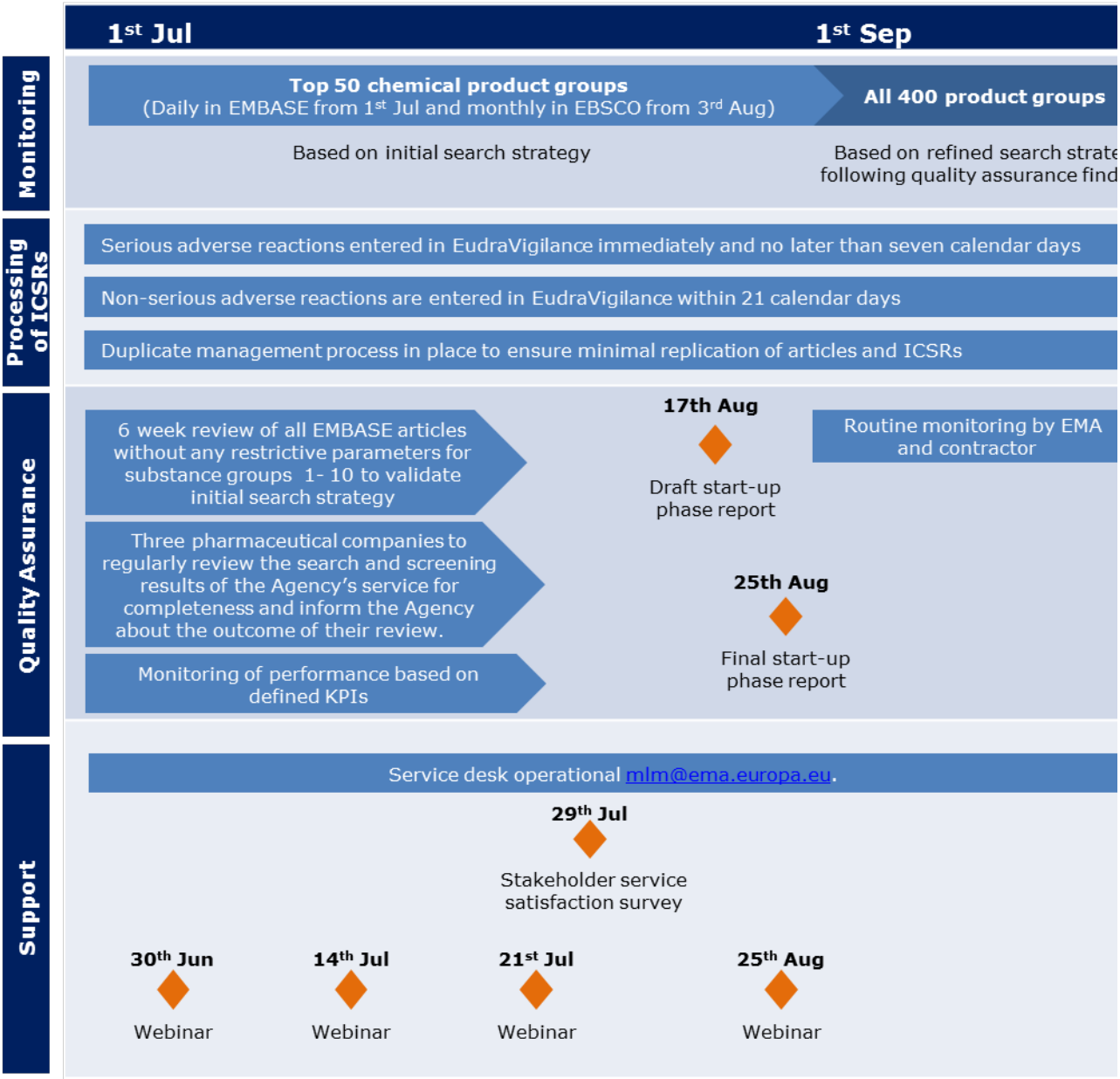
Please refer to the MLM Detailed Guide and supporting documents for an exhaustive description of all activities and processes.

4. Start-up phase planning

A summary of the key activities and related timeframes are outlined in figure 1 and further described in this document.

[5] 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 (EMA/321386/2012 Rev.9 or later if applicable)
[6] Process Description for managing duplicates in the context of the medical literature monitoring (MLM) Service

Figure 1. Medical Literature Monitoring (MLM) Service Start-up Phase



5. Interaction with concerned stakeholders

To facilitate openness and transparency during the start-up phase, the Agency and its contractor offer the opportunity to provide feedback on the MLM business processes using the MLM service desk mailbox mlm@ema.europa.eu and will host meetings to provide updates on the service performance and evolution.

5.1. Webinars

The Agency and its contractor will host webinars throughout the start-up phase. The purpose of these meetings is to communicate progress against the start-up plan and performance against key

performance indicators in line with expectations to ramp up production to 400 active substances on 1 September 2015 and to provide support to stakeholders throughout this period of change.

Metrics to be shared include:

- Volume of literature references screened and reviewed;
- Volume of full text articles ordered;
- Volumes of translations performed;
- Volume of confirmed ICSRs entered in EudraVigilance;
- Volume of potential ICSRs with follow-up requested;
- Volume of follow-up for confirmed ICSRs and responses received;
- Volume of duplicates identified;
- Volume of ICSRs transmitted to NCAs in EEA Member States;
- Volume of emails received by the MLM Service Desk and typical response time to resolution.

The virtual meetings will also include an overview of frequently asked questions, potential issues and challenges faced, a summary of pertinent feedback received through the MLM service desk, and any amendments to process taken as corrective and preventative action. All questions are to be submitted to mlm@ema.europa.eu. Questions to be included for discussion must reach the service desk 5 calendar days before each webinar.

At the end of the start-up phase, one webinar will be dedicated to summarising the experiences of the service to date and confirmation that the service is fit for purpose to move to full production of 400 active substances.

Due to the potential large numbers of attendees, the webinars will be independently moderated to ensure minimal disruption to conversation. All webinars will be held via Adobe Connect using a 200 capacity seminar room. Lecture Mode or 'listen only' mode will be used to prevent background noise and echo. A questions pod will be included to allow participants to post questions and comments in writing. Detailed instructions will be sent to the remote participants in advance of the meetings.

Those interested to attend one or more meetings need to send an e-mail to mlm@ema.europa.eu indicating the date for each event of interest. Every virtual meeting is restricted to a maximum of 200 attendees and a First-come, first-served (FCFS) policy will be applied.

The scheduled dates of the virtual meetings are as follows:

Date	Meeting
30th June 2015, 10.00 to 11.00 a.m. UK GMT	Kick-off meeting
07th July 2015, 10.00 to 11.00 a.m. UK GMT	Support meeting
14th July 2015, 10.00 to 11.00 a.m. UK GMT	Support meeting

Date	Meeting
21st July 2015, 10.00 to 11.00 a.m. UK GMT	Support meeting
25th August 2015, 10.00 to 11.00 a.m. UK GMT	Summary meeting

5.2. Service Desk

The Agency and its contractor encourage feedback and escalation of potential issues through the dedicated MLM service desk (mlm@ema.europa.eu). The service desk is established to assist enquiries from MAHs and NCAs in EEA Member States (e.g. case processing issues, assessment queries, compliance issues).

The service desk operated by the Agency's contractor will be in operation from 1st July 2015 and will be actively monitored during the Agency's business hours[7]. The working language of the mailbox is English. The contractor will provide Agency approved standardised responses to routine queries within two business days[7], and Frequently Asked Questions (FAQ) which will be maintained, detailing the service desk activity and responses.

E-mails received through the MLM Service Desk will be categorised based on the nature of the query.

These categories will include:

- Questions on the search activities;
- Questions of the screening and assessment of medical literature;
- Questions of the validity or quality of an ICSR;
- Standard MLM Process questions;
- General information, no response required.

Any e-mail containing a question on the review of a literature article, or an issue in relation to timelines, the validity or quality of a specific MLM ICSR will be investigated by the contractors' programme management and where a correction is needed, this will be initiated immediately.

Where the contractors' assessment remains in conflict with the initiator of the feedback, the issue will be escalated to the Agency for adjudication. Where this is necessary, the expected time for response will be two business days.

The service desk team will post the outputs of the previous day's literature screening and ICSRs processing in the format of the "MLM Search Results" and the "MLM ICSRs" in the restricted area of EudraVigilance by 09:00 a.m. UK GMT.

[7] European Medicines Agency Business hours and holidays http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000247.jsp&mid=WC0b01ac05800293ff

5.3. Issue Escalation and Resolution

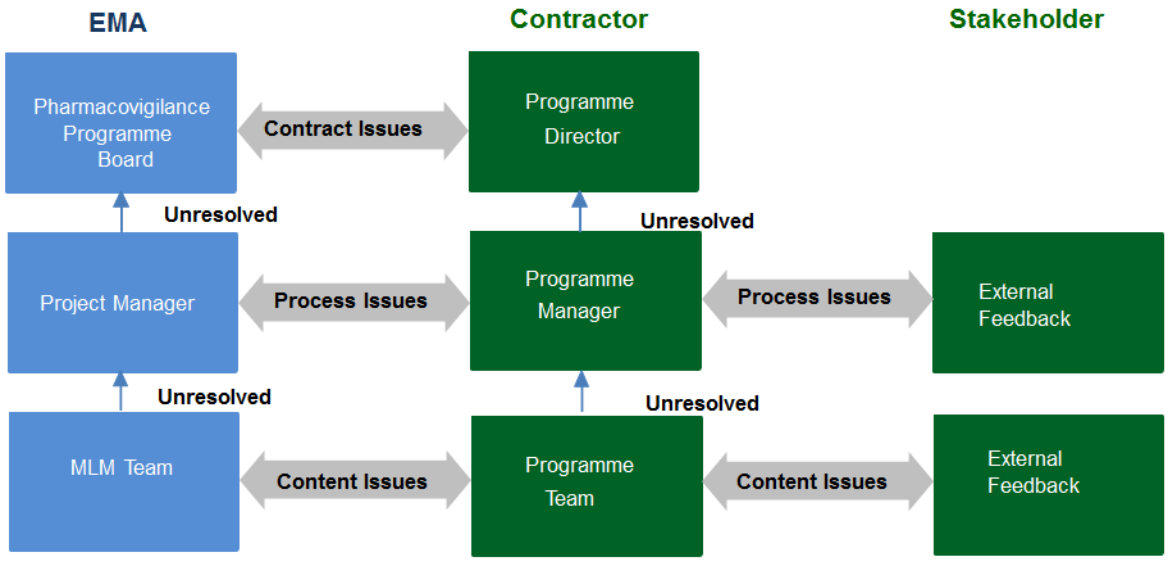
Where the contractor becomes aware of an issue, either from the internal quality activity or external feedback, it will immediately assess, categorise and escalate to the Agency as required. An issue is categorised as either content, process, or contractual.

An example of a content issue is where a stakeholder reviews the daily screening outputs on the EudraVigilance website and disagrees with the assessment as to whether a valid ICSR is present in the literature reference. In this scenario, the contractor's programme team would assess the feedback and if necessary escalate to the Agency's project manager for oversight and agreement. If the origin of the issue was feedback through the MLM service desk, a complete response will be sent to the initiator detailing the adjudication process and rationale.

If the Agency[8] and contractor agree, it may be necessary to adjust business processes as a result of the feedback either from cumulative content feedback or direct process feedback from stakeholders or as a result of Quality Assurance (QA) measures. An example, of a process issue would be the search strings deemed inaccurate for capturing literature references that meet inclusion criteria (see chapter 6) or feedback on the validity and or quality of MLM ICSRs produced.

Any changes in the process will be reflected through updating SOPs, WINs or literature search, screening and ICSR management processes. All updates to processes will be published on the EMA website and discussed at the MLM service update meetings.

Figure 2. MLM Service Issue Escalation Pathway



[8] The Agency will operate in liaison with the Pharmacovigilance Governance as outlined in chapter 5.5 of this document.

5.4. Stakeholder Survey

At week four of the start-up phase, the contractor will conduct an Agency[9] approved service satisfaction survey of the concerned stakeholders (MAHs and NCAs in EEA Member States). The survey will examine the ability of the contractor to meet appropriate levels of quality and accuracy in the work performed on behalf of the Agency. This process will subsequently be repeated at six monthly intervals.

5.5. Pharmacovigilance Governance

Project Maintenance Group 1 (PMG 1) on "Collection of Key Information on Medicines" will be invited to all webinars and will be regularly informed and consulted throughout the start-up phase on the overall performance as well as the potential content and process related issues to be resolved. PMG1 will also review and agree on the "Questions and Answers" to be published at the Agency's dedicated medicial literature monitoring webpage, adaptations to the business processes and stakeholder surveys.

5.6. Pharmacovigilance Inspectors Working Group

The Pharmacovigilance Inspectors Working Group (PVIWG) has been briefed about the new activities and the fact that during the set-up phase MAHs may need to further adapt and fine-tune their business processes in line with those operated by the Agency in line with Article 27 of (EC) Regulation 726/2004. The Agency will keep the PVIWG informed and assist in the clarification of potential questions that may arise in the context of pharmacovigilance inspections and the operation of the medical literature monitoring activities.

6. Search Strategy Refinement

During the start-up phase, the contractor will search the medical literature based on their targeted search parameters (Doc. Ref. EMA/403865/2015) designed for appropriate levels of precision and sensitivity to identify suspected adverse drug reactions (ADRs), including brand names, synonyms and translations of the top 50 chemical substance groups. The search strategies for each substance group are published at the Agency's dedicated webpage and have been subject to an initial validation by the contractor based on a small validation study. Feedback on proposed refinements is welcomed through the MLM service desk throughout the duration of the service.

For an initial phase of six weeks during the start-up phase and to further demonstrate the suitability of the designed search parameters to retrieve literature records with potential and confirmed ICSRs, the contractor will also perform a broad systematic daily review of all records indexed in Embase without any targeted parameters for substance groups 1-10. The validation of the search strategy in Embase will serve to demonstrate the concepts of the searching applied to Embase (including Medline) for daily screening and AMED and IPA as part of the monthly searches have appropriate sensitivity and precision.

[9] The Agency will operate in liaison with the Pharmacovigilance Governance as outlined in chapter 5.5 of this document.

In addition, three pharmaceutical companies[10] which also operate extensive literature search and review processes, have volunteered to regularly review the search and screening results of the Agency's contractor for completeness and inform the Agency about the outcome of their review.

The contractor will cross reference the results from literature screening using the targeted and broad search to analyse whether any ICSRs were not accounted for by using the targeted search string and incorporate any stakeholder feedback obtained. The outcome of the analysis will be presented in the start-up phase report and search parameters refined as necessary.

7. Quality Assurance and Control

The contractor will produce a suite of process governance documents supporting the service. This includes SOPs governing the screening and review process and the processing of all suspected adverse reactions as ICSRs, and dedicated Work Instructions (WINs) to describe the processes in detail for the MLM service desk management, duplicate management, screening and reviewing of literature, ICSR processing and quality assurance.

On a daily basis throughout the start-up phase, the contractor will undertake 100% Quality Assurance (QA) throughout the start-up phase. This will include:

- Confirmation of all literature references from search results tracked accurately;
- Review of literature references against inclusion and exclusion criteria to confirm the correct assessment;
- Review of ICSRs to ensure complete and accurate data entry against source information.

All QA findings will be addressed immediately pertaining to incorrect assessments and ICSRs. All QA findings will be discussed regularly with the Agency and continuous improvement measures taken as appropriate.

The Agency will supplement the QA measures of the contractor by performing routine sample QA of literature reference assessments and 100% QA of ICSRs processed.

8. Reporting and Communication

Reporting by the contractor to the Agency will take place weekly and the webinar summaries and actions will be recorded as part of a weekly report, which will include:

- A statistical summary of the work done during the period, cumulatively since the beginning of the contract and compared with the previous quarter;
- A statistical report of the resources expended during the period, cumulatively since the beginning of the contract and compared to the previous quarter;
- An analysis of performance against the key performance indicators;
- An analysis of the significant issues encountered and their resolution;

[10] GSK, Merck Sharpe Dohme, Sanofi

- A listing of open issues, noting in particular any that have remained unresolved for longer than two weeks.

9. Operational Oversight

The Pharmacovigilance Programme Board of the Agency and its contractor will review the start-up phase summary report following review by Project and Maintenance Group 1 (PMG 1) of the governance structure for pharmacovigilance with a view to ramping up to full production volumes on 1st September 2015. The pharmacovigilance governance will be informed accordingly.

The medical literature monitoring activities will also undergo a two yearly, independent audit of the contractor's internal quality management and control systems and of the services provided to assess their effectiveness with a view to bringing about continuous improvements. The first audit is planned to take place at the end of Q4 of 2015.

10. Performance indicators

The critical success factors for the service will be to ensure timely and adequate daily screening and tracking of the medical literature with publication in EudraVigilance. Once identified, the ICSRs are to be processed in a timely manner, with appropriate and timely follow-up performed. The contractor will also ensure timely responses to all queries received through the MLM service desk.

Below are Key Performance Indicators (KPIs) which will be used by the Agency and its contractor to monitor performance based on continuous assessment throughout the start-up phase.

Key Performance Indicator.[11]	Target performance
Screening of all top 50 active substance groups within one calendar day.[12] following the conduct of the targeted search Screening of the top 10 active substance groups part of the additional validation step within one calendar day.[13] following the conduct of the broad search	100% 80%
Publication of search and screening results (MLM Search Results) by 9 a.m. UK GMT the following calendar day	100%
Response to all e-mails in MLM Service Desk no later than two business days.[14] (with the exception of issues, which require discussion and agreement at the level of PMG 1).	95%

[11] The timelines and definition of calendar days as outlined in the Detailed Guide apply accordingly.
[12] Bank holidays are considered as calendar days
[13] Bank holidays are considered as calendar days
[14] Working hours are the same as EMA business hours

Consistent and accurate assessment of literature references	>99%
ICSRs related to suspected serious adverse reactions originating from the EEA and in third countries are entered in EudraVigilance immediately and no later than seven calendar days from day zero	100%
ICSRs related to suspected non-serious adverse reactions originating from the EEA are entered in EudraVigilance within 21 calendar days from day zero	100%
Daily provision of listing of ICSRs generated following literature screening and publication on EudraVigilance website[15]) and publication by 9 a.m. UK GMT the following calendar day	100%
Correct and timely follow-up of all suspected adverse reactions[16]	>99%
Submission of ICSRs related to serious and non-serious adverse reactions within one calendar day to the concerned NCA in accordance with the interim reporting requirements of ICSRs as outlined in GVP Module VI[17].	100%

11. Start-up phase closing report

The start-up phase scheduled from 1st July until 31st August 2015 will conclude on the basis of a closing report, which will summarise the outcome and findings based on the initial operational experience.

A successful outcome for the start-up phase will be classified as meeting key performance indicator targets as outlined in chapter 10 of this start-up plan and achieving steady state of screening and reviewing medical literature, entering all valid ICSRs into EudraVigilance as well as transmitting the ICSRs to NCAs in EEA Member States within the defined timelines and in line with the GVP Module VI reporting modalities including making cases available in a timely manner for download by MAHs.

[15] Bank holidays are considered as calendar days
[16] As outlined in chapter 3.3 of the Detailed Guide (EMA/161530/2014)
[17] 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 (EMA/321386/2012 Rev.9 or later if applicable)