EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medical Literature Monitoring
Start-up Phase

Kick-off meeting

30 June 2015

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Overview

1. Start-up planning
2. Search strategies for top 50 chemical substance groups
3. Literature reports – reporting requirements for MAHs
4. MLM Search Results and MLM ICSRs tracking sheets
5. XML Sample Files
6. Questions

Overview

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1. START-UP PLANNING

- As of 1st July 2015, the service will become operational based on the top 50 substance groups with the aim to launch the full service (all 400 substance groups) in September 2015
- The Agency has prepared a Start-up Plan to provide a framework for the interaction with involved parties as well as the initiation of the operations and the optimal performance of the service
- The plan is published at the dedicated medical literature monitoring webpage of the Agency
- The start-up phase will run for a two months period until 31st August 2015 and will conclude on the basis of a closing report, which will summarise the outcome and findings based on the first two months of operational experience

1. START-UP PLANNING

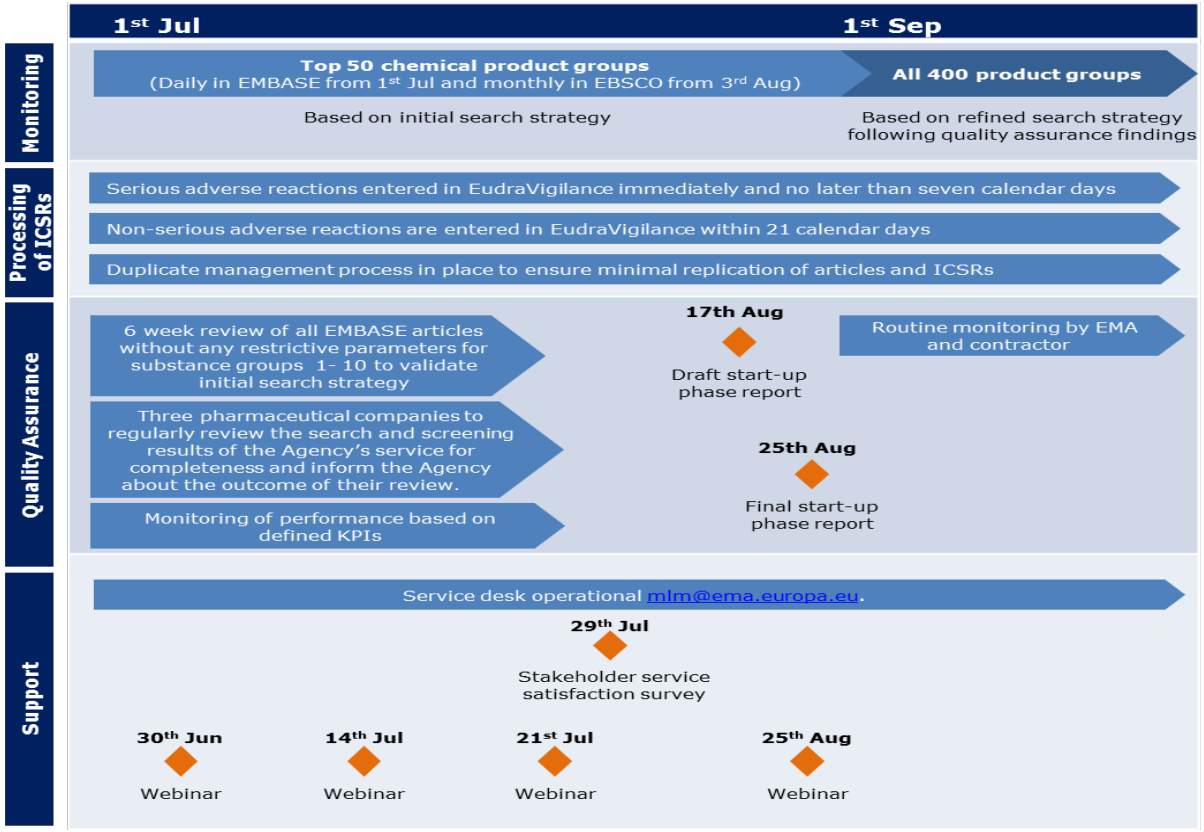
- First two months of the service will provide the opportunity to NCAs in EEA Member States, concerned MAHs, the Agency and the Agency's contractor to:
  - Execute against and where necessary fine-tune business processes outlined in the Detailed Guide and supporting documents
  - Achieve and ensure high 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

1. START-UP PLANNING

- **Concerned stakeholders during start-up phase**
  - All NCAs in EEA Member States
  - Around 2,370 MAHs
  - EMA

- **Scope**
  - Operate all business processes as outlined in the “Detailed Guide” and supporting documents

1. START-UP PLANNING



1. START-UP PLANNING

- **Interaction with concerned stakeholders**
  - Organisation of webinars: schedule published at dedicated medical literature monitoring webpage of the Agency
  - Service desk operation - contractor will provide Agency approved standardised responses to routine queries within two business days, 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:
    - 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

1. START-UP PLANNING

- **Search strategy refinement**
  - During the start-up phase, the contractor will apply “targeted search strings” designed for appropriate levels of precision and sensitivity to identify suspected adverse drug reactions (ADRs) including brand names, synonyms and translations of the active substances
  - 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
  - During the first six weeks of the start-up phase the contractor will also perform “broad search strings” in EMBASE for substance groups 1-10 without any targeted parameters to validate appropriate search sensitivity and precision

1. START-UP PLANNING

- **Search strategy refinement**
  - Three pharmaceutical companies (GSK, Merck Sharpe Dohme, Sanofi), which also operate extensive literature search and review processes, have volunteered to regularly review the search and screening results of the Agency's contractor of the Agency's service for completeness and inform the Agency about the outcome of their review
  - The contractor will cross reference the results from literature screening using the broad and targeted search to analyse whether any ICSRs were not accounted for by using the targeted approved search string and incorporate any stakeholder feedback obtained
  - The outcome of the analysis will be presented in the start-up phase closing report

1. START-UP PLANNING

- **Issue Escalation and Resolution**
  - The contractor will immediately assess, categorise and escalate to the Agency any issue, either from the internal quality activity or external feedback as required
  - An issue is categorised as either content, process, or contractual
  - If the Agency and contractor agree, it may be necessary to adjust business processes as a result of the feedback or as a result of Quality Assurance (QA) measures
  - 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.
  - The Agency will operate in liaison with the Pharmacovigilance Governance

1. START-UP PLANNING

- **Stakeholder Survey**
  - At the end of week four of the start-up phase, the contractor will conduct an Agency 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

1. START-UP PLANNING

- **Project Maintenance Group 1 (PMG 1)**
  - Will be regularly informed and consulted throughout the Start-up Phase on overall performance and potential content and process related issues to be resolved
  - Will also review and agree on the “Questions and Answers” to be published at the Agency’s dedicated MLM webpage, adaptations to the business processes and stakeholder surveys
- **Pharmacovigilance Inspectors Working Group (PVIWG)**
  - Has been briefed about the new activities
  - Acknowledges the fact 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
  - PVIWG will be kept informed and Agency will assist in the clarification of potential questions that may arise in the context of pharmacovigilance inspections

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1. START-UP PLANNING

- **Quality Assurance (QA)**
  - On a daily basis throughout the start-up phase, the contractor will undertake 100% Quality Assurance. 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 subject to continuous improvement measures
  - 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

1. START-UP PLANNING

- **Operational Oversight**
  - Pharmacovigilance Programme Board of the Agency and its contractor will meet at the end of the start-up phase to review the start-up phase report following discussion by Project and Maintenance Group 1 (PMG 1) with a view to ramping up to full production volumes on 1st September 2015.
  - Pharmacovigilance governance will be informed accordingly
  - The medical literature monitoring activities will 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. A first audit is planned to take place at the end of Q4 of 2015

1. START-UP PLANNING

- **Performance measure**
  - 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
  - These relate to all business processes as outlined in the Detailed Guide
- **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
  - A successful outcome for the start-up phase will be classified as meeting key performance indicator targets as outlined in the start-up plan and achieving steady state of the applicable business processes

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2. Search Strategy Definition

- As of 1st July 2015, the contractor will execute daily searches in EMBASE
- The search strategy has been devised based on GVP Module VI guidance
- Data from Art 57 database has been added to ensure the active substance variants, and trade names are accounted for when searching
- Throughout the start-up phase, the Agency and its contractor will continue to work together to further refine the search terms to perform daily searches with ever increasing precision and sensitivity

2. Search Parameters

The search parameters aim to identify and retrieve:

- Suspected adverse reactions originating from spontaneous reports and solicited reports in humans (see GVP module VI, chapter VI.B.1.1. and VI.B.1.2.) and
- Special situations such as lack of therapeutic efficacy, use of a medicinal product during pregnancy and breastfeeding, use of a medicinal product in a paediatric or elderly population, reports of off-label use, misuse, abuse, overdose, medication error as well as occupational exposure associated with suspected adverse reactions

2. Search parameters

Article 57 Data for active substance group AND ('adverse drug reaction'/exp OR 'adverse drug reaction' OR 'drug overdose'/exp OR 'drug overdose' OR 'drug misuse'/exp OR 'drug misuse' OR 'drug abuse' OR 'substance abuse'/exp OR 'substance abuse' OR 'pregnancy'/exp OR 'pregnancy' OR 'drug efficacy'/exp OR 'drug efficacy' OR 'drug withdrawal'/exp OR 'drug withdrawal' OR 'drug tolerance'/exp OR 'drug tolerance' OR 'medication error'/exp OR 'medication error' OR 'death'/exp OR 'death' OR 'drug interaction'/exp OR 'drug interaction' OR 'carcinogenicity'/exp OR 'carcinogenicity' OR 'off label drug use'/exp OR 'off label drug use' OR 'occupational exposure'/exp OR 'occupational exposure' OR 'toxicity'/exp OR 'intoxication' OR 'drug contraindication'/exp OR 'drug contraindication' OR 'congenital disorder'/exp OR 'congenital disorder' OR 'drug treatment failure'/exp OR 'drug treatment failure' OR 'lactation'/exp OR 'lactation' OR 'case report'/exp OR 'case report' OR 'environmental exposure'/exp OR 'environmental exposure' OR 'treatment contraindication'/exp OR 'treatment contraindication') AND humans/lim

2. Searches in literature reference databases

- The contractor will perform monthly searches in EBSCO (AMED, IPA) beginning on 03 Aug 2015 (to cover month of July)
- The searches are designed to be complimentary to the journals / active substances not covered in daily searches in EMBASE
- The same searching principles will apply, with products 1-10 undergoing broad searching and cross referencing against the specific safety terms added to the search strategy and to confirm any records containing potential ICSRs are appropriately retrieved

2. Continuous review and refinement

- Stakeholders are welcome to comment on the search strategies in order to refine and increase precision without compromising sensitivity for detecting ADRs
- The Agency and contractor will work to further develop the search strings in relation to the active substance data from Art 57
- Any updates to the search strategies will be published as updates on the EMA MLM website
- Feedback can be given through the MLM service desk (MLM@ema.europa.eu)

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3. Reporting Requirements- Literature Reports

- New version of "Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period" (EMA/411742/2015 Rev. 9) published
- Includes new chapter on Literature Reports
- During the interim period outlined in Article 2(4) and Article 2(5) of Directive 2010/84/EU and in line with national legislation and guidance where applicable, the following therefore applies to valid ICSRs originating from the literature:

3. Reporting Requirements- Literature Reports

a. For **active substances and literature not subject to the medical literature monitoring conducted by the Agency** pursuant to Article 27 of Regulation (EC) No 726/2004, the current reporting modalities apply (as outlined in Chapter 1 of the document (EMA/411742/2015 Rev. 9))

b. For active **substances subject to the medical literature monitoring conducted by the Agency** pursuant to Article 27 of Regulation (EC) No 726/2004 but when the **publication containing the relevant information is not included in the list of publications monitored by the Agency**, the current reporting modalities apply (as outlined in Chapter 1 of the document (EMA/411742/2015 Rev. 9))

3. Reporting Requirements- Literature Reports

c. For **active substances subject to the medical literature monitoring conducted by the Agency and when the publication containing the relevant information is included in the list of publications monitored by the Agency** pursuant to Article 27 of Regulation (EC) No 726/2004, the following reporting modalities apply ((as outlined in Table 5 of the document (EMA/411742/2015 Rev. 9).

3. Reporting Requirements- Literature Reports

Marketing authorisation procedure – substances subject to the service of the Agency	Origin Based on journals subject to the services of the Agency	Adverse reaction type	Destination	Time frame
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All serious[2]	• DE[1] when suspected adverse reaction occurred in this territory	15 days
		All non-serious[2]	• DE[1] when suspected adverse reaction occurred in this territory but only if requested individually in case of safety concerns	90 days
	Non-EU	All serious[2]	• DE[1] when suspected medicinal product is authorised in this territory	15 days

1 Federal Institute for Drugs and Medical Devices (BfArM)

2 Valid ICSRs are submitted by the Agency to the applicable Member State in line with chapter 1 of this document and as outlined in the Detailed Guide.

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4.1 Tracking sheets

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- **Every business day at 9.00 a.m. UK GMT two new tracking sheets will be published**
  - MLM Search results
  - MLM ICSRs
- **Published at secure area of EV website**
  - https://eudravigilance.ema.europa.eu/human/index.asp
  - Click “Production” to get to the secure area
    - You will need to be registered with Eudravigilance for this

4.1 Tracking sheets

- **MLM links in box on left**
  - Tracking sheets are top two links

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- **MLM links in box on left**
  - Tracking sheets are top two links
- **Tracking sheets are always at same URL**
  - This will allow you to automate downloading

4.2 MLM Search Results

- **Each literature record is presented on a separate unique row**
  - If a literature record refers to more than one monitored substance, it will appear once for each substance group
  - Duplicate ICSRs will not be created

- **Twelve fields provided for each literature record:**
  1. Substance group – the substance group searched for that returned the record
  2. Reference database – Embase (daily) or Ebsco (monthly)
  3. Date & time of search – in the format DD/MM/YYYY HH:MM
  4. Literature reference – in Vancouver Style
  5. Primary source country – the country of the lead author
  6. Lead Author

4.2 MLM Search Results

- **Twelve fields provided for each literature record:**
  7. Document object Identifier – a link to take you uniquely to the article
  8. Inclusion/exclusion criteria – if article contains valid case(s), populated with V; if no confirmed valid cases (yet), populated with a number matching the step in the inclusion/exclusion criteria flowchart
  9. Confirmed/ potential ICSRs – C = confirmed, P = Potential
  10. Serious? – “Y” if serious, “N” if not
  11. Full text request date – If applicable, the date the full text was requested, in the format DD/MM/YYYY
  12. Translation request date – If applicable, the date translation into English was requested, in the format DD/MM/YYYY

4.2 MLM Search Results

- **Contains all information on daily searching and screening activities**
  - Tracking sheet is saved with file name in the format “sum_screen_YYYY_MM_DD”
  - Only that day’s search and screening results are in that day’s sheet
  - Search and screening results from previous days are in the relevant spreadsheet in the archive
- **Published the following day**
  - One day’s spreadsheet is published the following day at 9.00 a.m. UK GMT
- **Once reviewed, records with potential or confirmed ICSRs appear in “MLM ICSRs” spreadsheet**
  - Decisions on whether or not the record contains ADRs & info on the case(s)

4.2. MLM ICSRs

- **Contains information on reviewed literature records & cases**
  - Every record reviewed on a given day, both with & without valid ICSRs
    - An article without valid ICSRs is considered closed
  - Every case which is not closed or has been closed on that day
    - A case is considered closed once one of the following criteria are met:
      - Case transmitted, 01 ACK received (for NCAs only), no follow-up (FU) required
      - FU received, FU version transmitted, 01 ACK received (for NCAs only), no further FU required
      - Date by which FU requested has passed and no FU received
  - Data exported at close of business as Excel spreadsheet
  - Tracking sheet is saved with file name in the format “sum_icsr_YYYY_MM_DD”
  - Articles/cases closed on previous days are in relevant spreadsheets in the archive

4.2. MLM ICSRs – reviews

- **Exclusion criteria published**
  - If a record has no valid cases, the exclusion criteria will be flagged
  - The reason for exclusion will be a number matching the step in the inclusion/exclusion document published on MLM webpage
- **Confirmed / potential ICSRs**
  - If a record definitely has valid ICSR(s), it will be flagged as “C” (Confirmed)
  - If a record may have valid ICSR(s) but clarification is needed, it will be flagged as “P” (Potential) and all the possibly applicable exclusion criteria will be provided and follow-up sought
- **Unique rows & data repetition**
  - Until ICSRs have been confirmed, each record will appear on a single row
  - Once ICSRs are confirmed, each ICSR appears on a single row, and a record will appear on as many rows as there are ICSRs associated with it

4.2. MLM ICSRs – reviews

- **The following 14 columns provide information on literature record reviews:**

- Substance group
- Reference database
- Date & time of search
- Literature reference
- Primary source country
- Lead Author
- Document object Identifier
- Inclusion/exclusion criteria
- Confirmed/ potential ICSRs
- Serious?
- Full text request date
- Full text receive date – If applicable, the date the full text was received, in the format DD/MM/YYYY
- Translation request date
- Translation receive date – If applicable, the date the English translation was received, in the format DD/MM/YYYY

Only the columns in red are not identical to the columns in the MLM search results spreadsheet

4.2. MLM ICSRs – case creation and management

- **Seventeen columns provide information on case creation, transmission & management:**
  - Suspect or interacting products/ substances (semicolon delimited) – all the suspect or interacting substances (with brand names where provided) in the case
  - WWID (A.1.10.1) – the worldwide unique case safety identifier of the case
  - Creation date – the date the case was created
  - Transmission date (EV) – the date the case was successfully transmitted to EV
    - If a case is transmitted but a 02 ACK is received and has to be retransmitted, this field will be populated with the latter date
    - The day after this, the case will be available to download from the ICSR export manager

4.2. MLM ICSRs – case creation and management

- **Seventeen columns provide information on case creation, transmission & management:**
  - Transmission date (NCA) – the date the case was successfully transmitted to the relevant NCA
  - FU to be initiated? (Y/N) – whether or not follow-up is to be initiated in accordance with the principles laid out in the detailed guide
  - Date FU initiated – if applicable, the date that FU was initiated
  - Date reply requested by – the date by which a reply was requested. This will normally be 4 weeks after the FU request was sent
    - If no FU received, the day after this date passes the case will be closed
  - Reply received? (Y/N) – If FU requested, this will be populated with N until such time as it has arrived

4.2. MLM ICSRs – case creation and management

- **Seventeen columns provide information on case creation, transmission & management:**
  - Date FU received – the date that any FU was received
    - This will normally be day zero for the relevant version of the ICSR
  - FU creation date – If applicable, the date the follow-up version was created
    - If a literature record had potential ICSRs & no case could be created until confirmation was received, then although the FU receive date will be populated, this field & the FU transmission fields will be blank
  - FU transmission date (EV) - the date the case was successfully transmitted to EV
  - FU transmission date (NCA) – if applicable, the date the FU was successfully transmitted to the relevant NCA

4.2. MLM ICSRs – case creation and management

- **Seventeen columns provide information on case creation, transmission & management:**
  - Duplicate? (Y/N) – If a case created by MLM service is detected as a duplicate of any other case in EV, this field will be populated with Y
    - Detection of a duplicate reopens a closed case
  - Master WWID; Other case numbers – Once detected, duplicates will be merged under a master case. The WWID of this master case & of all the duplicates will be provided in this field
  - Nullified? – If a case requires nullification, then this field will be populated with Y
  - Nullification date – if a case was nullified, the date on which it was nullified in the format DD/MM/YYYY

4.2. MLM ICSRs – case creation and management

- **Day zero**
  - If it is clear from the abstract that there are confirmed ICSRs, day zero will be the date that the search was performed
  - If it is only clear from the full text article that there are confirmed ICSRs, day zero will be the date the full text was received
  - If it is only clear on receipt of follow-up of missing information that there are confirmed ICSRs, day zero will be the date the follow-up was received
  - In all cases, day zero (whether for initial or follow-up versions) will be the receipt date (A.1.7b) in the downloaded ICSR.

NOTE: for **definition of Day Zero** please refer to GVP Module VI and further clarification provided in the Q&A document published at the dedicated medical literature monitoring webpage.

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5. Sample ICSR XML files

- Sample outputs of ICSRs in XML format, which are to be published routinely in the restricted area of the EudraVigilance website accessible by registered users, are made available on the dedicated webpage for reference:
- Sample ICSRs in XML format (both contain exactly the same individual fictive cases) (11 fake ICSRs from Japan).
  - MLM ICSR sample XML file (MLM EVWEB output)
  - MLM ICSR sample XML file (EudraVigilance ICSR Export Manager)

5. Sample ICSR XML files

- The message headers differ in the following ways
  - The EVWEB message header is blank
  - The ICSR Export manager message header is populated with the following values:
    - Message type = ichicsr
    - Message format version = 2.1
    - Message format release = 1.0
    - Message number = 0001
    - Message sender identifier = MLMSERVICE (all MLM ICSRs are sent by the sender MLMSERVICE & so this is the sender identifier for all messages downloaded from the ICSR export manager)
    - Message receiver identifier = EVTESTWT (this is the receiver identifier that was used to log on & download this file. This value will be populated with the receiver identifier of the user's organisation)
    - Message date format = 204
    - Message date = 20150629134703 (the precise date & time that the message was requested)

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Thank you for your attention

Further information

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