



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medical Literature Monitoring

5th Industry Platform on the implementation of EU pharmacovigilance legislation



Presented by Tom Paternoster-Howe on 15 September 2015
EMA/Information Management/Data Standardisation & Analytics

An agency of the European Union





- 1 • **Service setup**
- 2 • **Launch phase achievements**
- 3 • **Full Production**
- 4 • **Optimisation of MLM Service**
- 5 • **Customer Service Mailbox Update**
- 6 • **Key Performance Indicators**
- 7 • **Management of Follow-up**
- 8 • **Future benefits**

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- 11 May 2015: signed Framework Contract with contractors (Kinapse)
- 01 June 2015: started setup phase
- Setup phase achievements:
 - Contractors recruited & trained 24 staff members
 - Created SOPs & WINs for all aspects of the service
 - Created search parameters for 50 substance groups in 2 literature databases
 - Created tracking tool to:
 - record search results,
 - publish tracking sheets
 - Perform case management, including submission tracking, follow-up, QA & nullifications
 - Created service desk
 - Created launch plan
- 1 July 2015: Launch phase started



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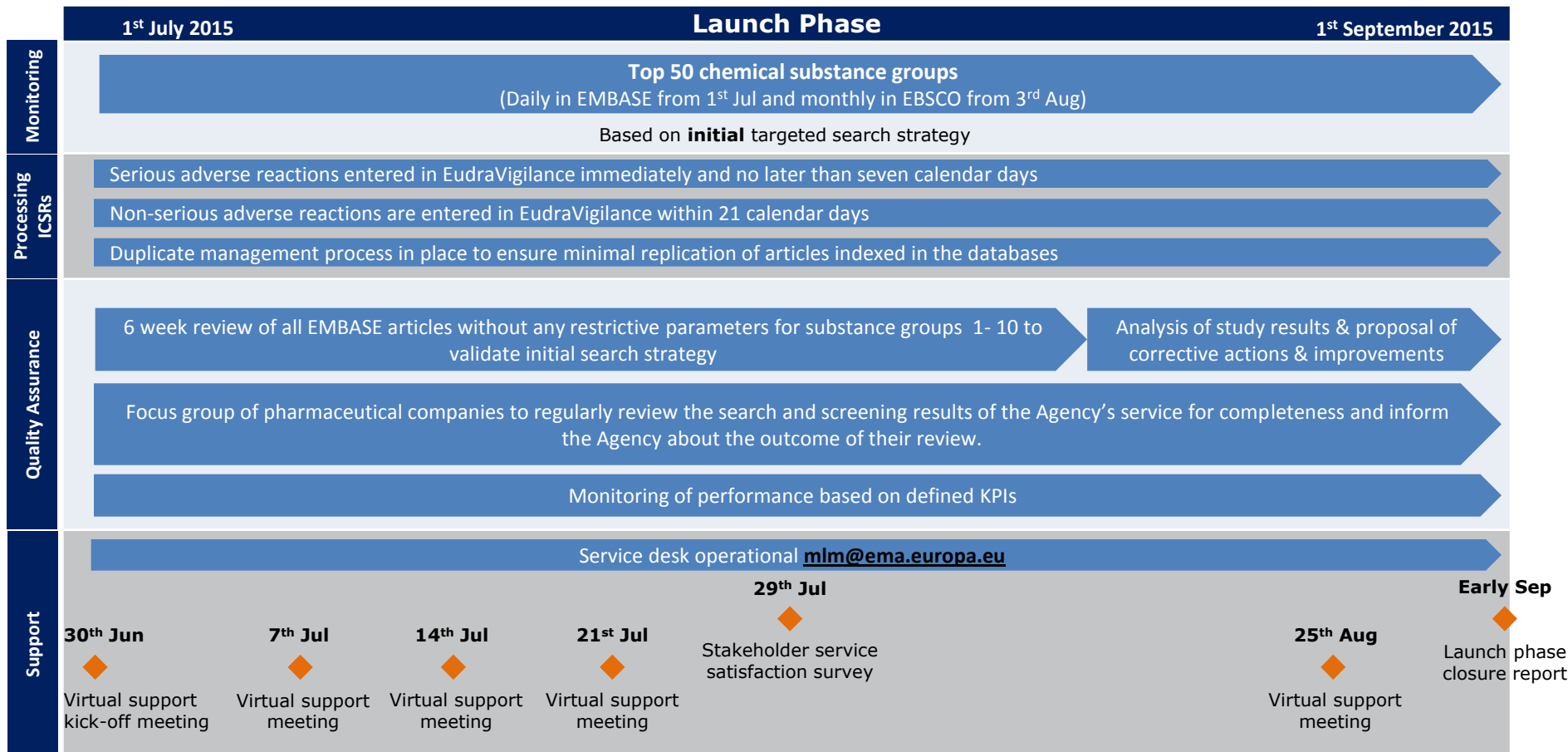


- Perform MLM work for top 50 substances
- Interaction with concerned stakeholders
- Search strategy refinement
- Issue Escalation and Resolution
- Stakeholder Survey
- Quality Assurance (QA) processes refined
- Performance measures refined
- Launch phase closing report

Launch phase achievements



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Full Production



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1st September 2015

Full Production

2016

Monitoring

100 Herbal substance groups and 300 chemical substance groups
(Daily in EMBASE and monthly in EBSCO)

Based on **refined** targeted search strategy

Processing ICSRs

Serious adverse reactions entered in EudraVigilance immediately and no later than seven calendar days

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

Duplicate management process in place to ensure minimal replication of articles indexed in the databases

Quality Assurance

Continue review of all EMBASE articles without any restrictive parameters for substance groups 1- 10 to validate initial search strategy & update of refined search strategy

Dec 2015

Audit

Monthly review of refined search strategy with expert panel to address any missed ICSRs

Monitoring of performance based on defined KPIs

Support

Service desk operational mlm@ema.europa.eu

Jan 2016

Stakeholder service satisfaction survey

Virtual support meetings

1st Sep

15th Sep

29th Sep

27th Oct

24th Nov

22nd Dec

8th Sep

22nd Sep

13th Oct

10th Nov

8th Dec





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Optimisation of MLM Service



Issue mitigation activities

| Launch-Up Phase | | Full Production | | | | | | | | | | | | | | | | | | | |
|--|-----|--|-----|-----|-----|---------|--|--|--|--|--|--|--|--|--|--|---|--|--|--|--|
| Jul | Aug | Sept | Oct | Nov | Dec | Q1 2016 | | | | | | | | | | | | | | | |
| Additional inclusion exclusion criteria added to tracking sheet | | 1st Sept <ul style="list-style-type: none"> ◆ Day zero published on sum_icsr spreadsheet ◆ Updated user manual published to include sum_icsr spreadsheet changes ◆ Updated Q&A published ◆ Updated search strategy published | | | | | <ul style="list-style-type: none"> ◆ Resolution of helpdesk IT issues ◆ Automated helpdesk responses updated | | | | | <ul style="list-style-type: none"> ◆ Revised tracking sheet published | | | | | | | | | |
| Tracking tool updated to ensure full conformance to Vancouver reference style | | | | | | | | | | | | | | | | | | | | | |
| Tracking sheet updated to state where no literature references have been retrieved in the daily / monthly search | | | | | | | | | | | | | | | | | | | | | |
| Delivery of additional training to contractor to reduce number of cases to be resubmitted with updated information | | | | | | | | | | | | | | | | | | | | | |
| Technical amendments made to EudraVigilance to ensure ICSRs transmitted on a given day are available for same day download | | | | | | | | | | | | | | | | | | | | | |
| User manual updated with additional information on EVWEB, export manager & tracking sheets | | | | | | | | | | | | | | | | | | | | | |
| Monthly collated tracking sheets initiated | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | Ongoing quality assurance and delivery of additional training to contractor where necessary to reduce number of cases which need to be resubmitted with updated information. Amendment to process to move EMA QA step before submission | | | | |
| | | | | | | | | | | | | | | | | | Precision improvement to search strategy, date of publication limited to 2015 | | | | |
| | | Sensitivity improvement to search strategy, addition of terms to the search strategy to address any identified missing ICSRs | | | | | | | | | | | | | | | | | | | |
| | | Continue with review of all EMBASE articles without any restrictive parameters for substance groups 1- 10 to validate refined search strategy | | | | | | | | | | | | | | | | | | | |
| | | Monthly review of refined search strategy with expert panel to address any missed ICSRs | | | | | | | | | | | | | | | | | | | |

Key ■ Completed actions ■ Actions to be undertaken

In addition to the improvements outlined on the previous slide, the following improvements have already been made & actions taken following specific requests from industry:

- Day zero added to spreadsheet
- Update to EV to ensure that all ICSRs appearing in the tracking sheet are available in EV the same day
- Updated user manual with more information & tips on how to get the best results
- Monthly collated tracking sheets
- Q&A document updated
- Amended export manager to change the way MedDRA version is displayed when version is x.0
- Amended primary source section so that only one primary source is captured to help users of particular databases
- Presented implementation of MLM Service to inspectors, to enable them to understand the service, how it impacts MAHs & asked inspectors to be understanding with MAHs regarding this during the first few months of operation



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- New mailbox was setup by EMA
- Contractors access via VPN & reply on behalf of EMA
- Technical issues with mailbox meant that a number of queries did not get seen by staff and thus were not responded to
- Backup plan implemented and now all queries are responded to within 2 business days
- Issue has been identified and a resolution is being worked-on
- The problem will be fixed within a few days



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Key Performance Indicators during launch phase



| Key Performance Indicator | Target Performance | Actual | Corrective actions |
|--|--------------------|--------|--|
| Daily screening of all 50 active substance | 100% | 100% | - |
| Publication of search and screening results (MLM Search Results) by 9am (UK time) the following day | 100% | 90% | <ol style="list-style-type: none"> 1. Additional training 2. Automated checks at EMA to ensure that if a file isn't uploaded, it will be spotted immediately |
| Response to all emails in MLM Service Desk within two business days | 95% | 83% | <ol style="list-style-type: none"> 1. Improved process for response approval 2. Additional training |
| Consistent and accurate assessment of literature references | >99% | 99.8% | - |
| Timely Entry of Serious ICSR in EudraVigilance within seven calendar days | 100% | 83% | Almost all late ICSRs due to corrections. QA process refined to move EMA QA step before submission to minimise need for corrections |
| Timely Entry of non-serious ICSR (occurrence within the EEA) in EudraVigilance within 21 calendar days | 100% | 100% | - |
| Daily provision of listing of ICSRs generated following literature screening and publication on EudraVigilance website | 100% | 90% | <ol style="list-style-type: none"> 1. Additional training 2. Automated checks at EMA to ensure that if a file isn't uploaded, it will be spotted immediately |
| Correct and timely follow-up of all suspected adverse reactions | >99% | 100% | - |



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- 74 Follow-up requests sent out between 01 July and 08 September
- Eight responses received to date
- 11% response rate is broadly in-line with expectations
- After end-September, we will assess the overall results
- Questionnaires will be reassessed and may be amended to see if response rates can be improved



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The service has already improved significantly during the launch phase & is continuing to improve: quality, consistency & timeliness are improving week-on-week

Over the coming months and years, we expect to see all stakeholders benefitting from:

- A significant reduction in duplicate literature reports within EudraVigilance
- A harmonised approach to the entry of adverse drug reactions originating from literature articles
- An efficiency in Marketing Authorisation Holder (MAH) business processes by holding the Agency accountable for the resource intensive screening and reviewing of literature
- A gradual streamlined pharmacovigilance function as literature review and case processing of articles is transitioned to the Agency
- Creation of a gold standard for literature searching



Thank you for your attention

Further information

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Additional slides answering specific questions & latest KPI figures

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Key Performance Indicators during **September**



| Key Performance Indicator | Target Performance | Actual | Corrective actions |
|--|--------------------|--------|---|
| Daily screening of all 50 active substance | 100% | 100% | - |
| Publication of search and screening results (MLM Search Results) by 9am (UK time) the following day | 100% | 100% | |
| Response to all emails in MLM Service Desk within two business days | 95% | >90% | <ol style="list-style-type: none"> 1. Service desk error resolution in September has impacted timelines for start of September 2. Should be >95% by month-end |
| Consistent and accurate assessment of literature references | >99% | >99% | - |
| Timely Entry of Serious ICSR in EudraVigilance within seven calendar days | 100% | 87% | Initial cases 97.5%. Corrections from launch phase processed in early September were >7 days. Only 1 case >15 days By contrast, industry average within 15 days: 91% (89% for initial cases) |
| Timely Entry of non-serious ICSR (occurrence within the EEA) in EudraVigilance within 21 calendar days | 100% | 100% | - |
| Daily provision of listing of ICSRs generated following literature screening and publication on EudraVigilance website | 100% | 100% | |
| Correct and timely follow-up of all suspected adverse reactions | >99% | 100% | - |

- EMA to clarify the position of the EMA case identifier for cases with already existing world-wide unique case identifier
 - Process for managing duplicates published. If EMA identify one pre-existing case in EV for that article prior to data entry, then WWID will be retained & the MLMSERVICE number entered into Safety Report ID field. If there are already multiple cases, then the MLMSERVICE number will be WWID as a master would have to be created anyway
- Provide industry with clarity on EMA/inspectors view of how different industry sectors should use the MLM service
 - Industry is free to use the service or not, but should not transmit to EV cases which would be duplicates of the MLMSERVICE cases. EMA has discussed with inspectors and asked for a degree of flexibility/understanding during the first few months as process changes are implemented
 - EMA-inspectors dialogue will continue and inspectors' views on how they see MAHs using the service will be sought and shared, where provided

- Define an implementation period and then state that compliance will only be measured after that period
 - The launch phase can be considered as an implementation period, however the EMA has contacted, and will continue to contact, MAHs that retransmit MLMSERVICE reports to EV not in compliance with the requirements
- Suggestions on the timing and content of the published results of the searches
 - The results of the searches and ICSRs created will all be made available at 9am the day after the work has been performed (searches run and screened & ICSRs transmitted to EV)
 - Details on how to understand the tracking sheets are provided in User manual published on the MLM webpage
- Publish a list of enhancements
 - A full list of requested enhancements will be collated and published during October, including their status (implemented, in progress, rejected)

- Service to follow the published workflows (e.g. timelines for lists and cases)
 - This is now being done – initial teething troubles have been overcome
- Improve response to queries
 - The technical issue which led to the problems will be resolved shortly.
 - Backup procedures were put in place once EMA was aware of the nature of the problem
- Improve presentation and accuracy of the lists
 - Improvements already made, more to follow, including automated queries to ensure 100% accuracy and internal consistency in lists
- Harmonise between EV-Web, ICSR Export Manager and search results listings
 - This has been done – EV systems updated to remove bottlenecks and ensure that cases transmitted on one day are available the next