



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## Q&A on Off-Label Use

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Proposal in response to EFPIA paper of 3<sup>rd</sup> October 2014

EMA Industry Stakeholder Platform - Operation of EU Pharmacovigilance Legislation  
12 January 2015

Presented by Sabine Brosch (EMA) and Anja van Haren (MEB) on 12 January 2015

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## Overview

- For the recording and reporting of off-label use (without adverse reactions), EMA agreed at the September ISP meeting to develop a Q&A on this topic in collaboration with the EudraVigilance Expert Group (EV-EWG)
- A draft Q&A has been prepared and reviewed by the PhV Project and Maintenance Group 1 at their meeting on 7 January 2015
- An outline of the “[direction of travel](#)” is provided at the following slides



## Q1: Does a MAH need to collect individual cases of off label use without an adverse reaction? (1)

- Art 23 (2) of DIR 2001/83/EC requires the MAH to report to the competent authorities "*any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned*", including "*data on the use of the medicinal product where such use is outside the terms of the marketing authorisation*".



## Q1: Does a MAH need to collect individual cases of off label use without an adverse reaction? (2)

- In certain circumstances, it may be appropriate to actively monitor the use of the medicines e.g. through a drug utilisation study using electronic health records.
- As outline in chapter V.B.8.5.4 of GVP Module V, post-marketing updates to the safety specification should include information on EU off-label use (including use in non-authorised paediatric age categories).
  - Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. This includes drug utilisation studies which were requested by NCAs for purposes other than risk management.
  - When off label use is a safety concern or a concern has been raised by NCAs regarding off-label use, MAHs should attempt to quantify such use along with a description of the methods used to arrive at these figures.
  - Unless specifically requested, it does not include use outside the EU in an indication authorised in that territory which is not authorised in the EU.

## Q1: Does a MAH need to collect individual cases of off label use without an adverse reaction? (3)

- The guidance provided in question 8.2 of the Q&As to support the implementation of the PV legislation (EMA/228816/2012) emphasises that to be able to:
  - Conduct signal detection
  - Continuously monitor the benefit risk balance of medicinal products
  - Produce PSURs
  - Inform regulators of any changes to the benefit risk balancethe MAH should have procedures in place to collect and record relevant information including off label use.
- This applies where the MAH becomes aware of this information.



## Q2: If a MAH receives a report of off label use with no adverse reaction, does it have to record the report on its safety database?

- There is no legal requirement to record such report in the MAH safety database for the collection of Individual Case Safety Reports (ICSRs).
- Neither is there a requirement to submit ICSRs of off label use if not linked to a suspected adverse reaction, as referred to in question 8.2 of the Q&As to support the implementation of the PV legislation (EMA/228816/2012).
- However the information should be collected for the fulfilment of the pharmacovigilance tasks. In this aspect appropriate recording mechanisms should be in place to ensure that these reports are considered in signal management activities and included in the RMPs and in the PSURs (as necessary).



## Q3: Is there a requirement to train staff on collecting cases of off label use without an adverse reaction?

- Yes there is a requirement to train staff, as part of the routine operation of the pharmacovigilance system as referred to in Art 101 of DIR 2001/81/EC.
- This applies where the MAH becomes aware of this information.



## Q4: How should MAHs collect and monitor the information on off label use that is required for PSURs and applicable RMPs?

The expectations for the collection of off label use reports without adverse reaction are as follows:

- In response to enquiries about potential use of a medicinal product outside the term of its marketing authorisation, e.g. "Can product x be used in an unlicensed indication or manner?"
  - Where there is no confirmation/evidence that the product has actually been used in an off-label manner, there is no expectation for the MAH to collect and record this information or to follow-up with the enquirer at a later date to establish whether the product was actually used if an off-label way.





## Q4: How should MAHs collect and monitor the information on off label use that is required for PSURs and applicable RMPs? (2)

The expectations for the collection of off label use reports without adverse reaction are as follows:

- Confirmed reports of off-label use e.g. “Use in an unauthorised indication”:
  - These reports should be collected as part of the pharmacovigilance system in order that they may be easily collated for analysis and presentations during the production of a PSUR or RMP. In general, there is no expectation to follow-up on these reports except where they may be associated with an adverse reaction or on prospective reports of pregnancy.

Note: Guidance on the presentation and evaluation of off label use in PSURs and RMPs is provided in GVP V and VII.



## Next steps

- The EV-EWG will be consulted; the draft Q&A will be discussed at their meeting on 4 February 2015
- The Q&A will be finalised following consultation of the PRAC, the PhV Implementation Group and the ERMS-FG by end of 1<sup>st</sup> quarter 2015
- The Q&A will be published as part of the Q&As to support the implementation of the PV legislation (EMA/228816/2012) and the information integrated in the context of the next GVP update.



## Further information

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