



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Collecting and Reporting Information on Off-label Use

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7th Industry Stakeholder platform on operation of EU  
pharmacovigilance legislation– 4<sup>th</sup> April 2016

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# Objectives

- To address questions raised by EFPIA about management by MAHs of reports of off-label use of medicinal product, which do not result in harm to a patient.
  - Do MAHs need to collect and record in safety database individual reports of off-label use not associated with suspected adverse reaction?
  - Do MAHs need to train staff on collecting those reports?
  - How should MAHs collect and monitor the information on off-label use for PSURs and applicable risk management plans?
- To highlight main aspects detailed in discussion paper on collecting and reporting information on off-label use drafted in consultation with PRAC, based requirements Art 23(2) Dir 2001/83/EC.
  - Position includes specific legal advice from European Commission services on interpretation of Art 23(2) Dir 2001/83/EC.

## Legal interpretation Art 23(2) Dir 2001/83/EC

- Art 23 clarifies responsibilities & obligations of MAH on informing NCAs:
  - Regularly update marketing authorisation (MA) dossier in order to ensure that scientific progress and new regulatory requirements are respected.
  - Continuously monitor safety of medicinal products (within/outside MA terms), for informing competent authorities of any changes that might impact on MA, and for ensuring that product information is kept up to date.
- Art 23(2) deals with MAH obligation to submit to competent authorities any new information that may entail variation, particularly on:
  - Prohibition or restriction of MA imposed by any competent authority (inside and outside EU),
  - Any other information that might influence product benefits/risks evaluation,
  - Positive and negative results of clinical trials or other studies in all indications and populations, even outside the MA,
  - Data on the off-label use of the product.

## Legal interpretation Art 23(2) Dir 2001/83/EC

- Distinguish obligations on submission of data on off-label use between:
  - Art. 23(2) linked to data/information, which may directly influence product benefits/risks evaluation and may entail a variation of MA, (e.g. prohibitions/restrictions of MA, results of clinical trials or other studies) and
  - Art. 107 which provides for separate, complete and comprehensive framework on how MAH should collate, collect and report to competent authorities ICSRs on suspected adverse reactions.
- Data on off-label use or on research in non-authorised indications may also be useful:
  - To allow the evaluation of the impact and gravity of individual signals if those signals arrive through ICSRs of reactions and relate to the use outside the terms of the marketing authorisation.
  - To comply with obligations under Art 34 IR (EU)520/2012 to estimate in context of a PSUR the exposure and actual use of product, including use in non-authorised indications.

## MAH obligations on collection and reporting off-label use when associated with harm (i.e. suspected adverse reactions)

- Report suspected adverse reactions occurring during off-label use to competent authorities.
- Continuously assess benefit-risk of its products in PSURs and address clinical importance of any risk related to off-label use.
- Detail in RMP measures to quantify off-label use and to minimise risks when off-label use is important safety concern (i.e. associated to particular risks or concerns raised by competent authorities).
- Notify as emerging safety issues (in compliance with Art 23(2) Dir 2001/83/EC) information on off-label use considered by MAH to influence evaluation of benefits and risks of medicinal product.

### Proposal for MAH obligations on collection and reporting off-label use when no harm

- Tools set in place pursuant Art 107 Dir 2001/83/EC to collect and report suspected ADRs are not applicable to monitor off-label use with no harm.
- RMP is most appropriate way to deliver planned and risk proportionate approach for monitoring off-label use in routine clinical settings.
- Where potential for off-label use is identified for product and such use is considered important safety concern (e.g. justified supposition that potential risk might be associated to off-label use), RMP should be used to clarify MAH obligations.

- RMP should clarify MAH obligations
  - In terms of collection and follow-up of individual reports of off-label use (including those not associated with suspected adverse reactions);
  - In terms of additional structured investigations (drug utilisation studies, searches in databases) when risk is considered important safety concern.
- As part of risk management planning, monitoring of off-label use should focus on collection and assessment of information which might influence evaluation of benefits and risks of concerned medicinal product.
- For products without RMP, MAHs and competent authorities should consider whether off-label use constitutes safety concern. If it does consideration should be given to requiring RMP or PASS.

Type of information	Format
<b>A. Collection and reporting of information on off-label use with harm</b>	
Individual cases of off-label use associated with suspected adverse reactions	ICSR
Benefit-risk analysis taking into account the clinical importance of a risk in relation to the off-label use of the concerned medicinal product	PSUR
Quantification of off-label use and implementation of risk minimisation measures when off-label use with harm is important safety concern	RMP
<b>B. Collection and reporting of information on off-label use with NO harm</b>	
Where potential for off-label use have been identified and such use is considered important safety concern: <ul style="list-style-type: none"><li>▪ Risk management plan used to quantify and monitor off-label use focussing on collection and assessment of information which might influence evaluation of benefits and risks of concerned medicinal product.</li></ul>	RMP





## Next steps

- Public consultation launched in April 2016 based on the points presented here.
- Pharmaceutical industry and other stakeholders invited to comment.
- Final paper will likely be published as stand alone and, overtime, integrated in relevant GVP documents.

# Thank you for your attention

## Further information

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