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[1] Delete once the reflection paper is adopted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Reflection paper on collecting and reporting information on off-label use in pharmacovigilance

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1. Scope

This paper outlines a proposal for the collection and reporting of information on off-label use by Marketing Authorisation Holders (MAHs) in relation to their pharmacovigilance obligations provided in Title IX of Directive 2001/83/EC. It follows questions raised by the European Federation of Pharmaceutical Industries and Associations (EFPIA) on the management of individual reports of off-label use not associated with harm to a patient (See Annex 3).The proposal distinguishes the situations where the off-label use of a medicinal product results in the occurrence of a suspected adverse reaction and those where it does not. It incorporates the feedback of the Pharmacovigilance Risk Assessment Committee (PRAC). Some Member States may already have put in place specific national guidance regarding the notification by MAHs of practices of off-label use of medicines at national level; the draft proposal presented here should not be interpreted as preventing the fulfilment by MAHs of national obligations.

2. Discussion

Art 23(2) of Directive 2001/83/EC (see Annex 1) states *"The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I.*

In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation".

An explanation on the utilisation of a medicinal product in off-label conditions is provided in Chapter VI.A.2.1.2 of the Good Pharmacovigilance Practices (GVP) Module VI in that off-label use *"relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information"*.

Off-label use may occur for various reasons. Examples of off-label use may refer to the intentional use of a medicinal product for medical purpose in a situation such as:

- A different indication in term of medical condition than the one described in the authorised product information;
- A different group of patients than the one described in the authorised product information;
- A different route or method of administration than the one described in the authorised product information;
- A different posology than the one described in the authorised product information.

Regarding the collection and reporting of reports of off-label use, the following two scenarios can be distinguished:

A. The off-label use of a medicinal product, which results in harm to a patient i.e. the occurrence of one or more suspected adverse reactions, and

B. The off-label use of a medicinal product, which does not result in harm to a patient.

These two scenarios are further outlined below, with a summary provided in Table 1.

A. Off-label use of a medicinal product, which results in harm to a patient i.e. the occurrence of one or more suspected adverse reactions

The obligations of MAHs in relation to the collection and reporting of information related to the off-label use of medicinal products resulting in harm, i.e. associated with the occurrence of suspected adverse reactions, can be summarised as follows:

- **Reporting of individual cases of off-label use associated with suspected adverse reactions**

In accordance with Article 107(1) and Article 107(3) of Directive 2001/83/EC and as further outlined in recital 5 of Directive 2010/84/EU, individual cases of off-label use, which result in the occurrence of suspected adverse reactions, shall be collected by MAHs and reported to competent authorities. This reporting is covered under the general pharmacovigilance obligation of reporting of any suspected adverse reaction related to the use of a medicinal product.

- **Periodic reporting of the clinical importance of risks related to the off-label use of a medicinal product**

In line with the guidance provided in Chapter VII.B.5.18.2 of GVP Module VII, the benefit-risk analysis evaluation presented in a Periodic Safety Update Report (PSUR) should take into account the clinical importance of a risk in relation to the off-label use of the concerned medicinal product where relevant and appropriate.

- **Risk management planning based on the quantification of off-label use in the context of particular risks and concerns**

With reference to GVP Module V revision 2 (currently in public consultation), it should be noted that the potential for off-label use should be discussed with a focus on any anticipated differences in safety concerns between the target and the off-label population. The monitoring of off-label use is particularly relevant for known safety concerns in the off-label population. The potential for use in other disease areas should also be considered where this is suspected to be related to a different safety profile. In such cases, potential or identified risks arising from the off-label use of the product should be considered for inclusion in the safety specifications.

B. Off-label use of a medicinal product, which does not result in harm to a patient i.e. without the occurrence of one or more suspected adverse reactions

Obligations of MAHs relevant to the collection of *"data on the use of the medicinal product where such use is outside the terms of the marketing authorisation"* are set out in Article 23(2) of Directive 2001/83/EC, which requires the MAHs 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"*.

Recital 12 of Directive 2010/84/EU clarifies that *"the marketing authorisation holder should be responsible for continuously monitoring the safety of its medicinal products, for informing the authorities of any changes that might impact on the marketing authorisation, and for ensuring that the product information is kept up to date. As medicinal products could be used outside the terms of the marketing authorisation, the marketing authorisation holder's responsibilities should include providing*

all available information, including the results of clinical trials or other studies, as well as reporting any use of the medicinal product which is outside the terms of the marketing authorisation (…)".

Some points that should be considered with regard to Article 23(2) are provided in Annex 2.

Further to the discussions at the PRAC and to concerns raised by industry associations, there is a need to clarify the handling of cases of off-label use which are not associated with the occurrence of suspected adverse reactions.

Whereas:

- Suspected adverse reactions occurring during off-label use are reported to the competent authorities in line with pharmacovigilance obligations;
- Where information on off-label use is considered by the MAH to influence the evaluation of the benefits and risks of the medicinal product, it is notified forthwith to the competent authorities in compliance with Article 23(2) of Directive 2001/83/EC;
- The MAH is required to continuously assess the benefits and risks of its products in the PSURs submitted to the competent authorities and address the clinical importance of any risk related to off-label use;

The most appropriate way to deliver a planned and risk proportionate approach to enable the monitoring of the use of specific medicinal products in routine clinical settings is through the risk management plan of the medicinal product concerned.

Where the potential for off-label use has been identified for a product, and such use is considered to raise a safety concern[2], the risk management plan should be used to clarify the obligations for the MAH:

- In terms of collection and follow-up of cases of off-label use (including cases not associated with suspected adverse reactions);
- In terms of additional structured investigations (drug utilisation studies, searches in databases).

In this context, it is expected that studies will only be imposed or required when the risk associated with the off-label use is included as important identified or important potential risk or as missing information in the safety specifications of the product. As part of risk management planning, the monitoring of off-label use should focus on collection and assessment of information which might influence the evaluation of the benefits and risks of the concerned medicinal product.

For products without a risk management plan, MAHs and competent authorities should consider whether off-label use constitutes a safety concern. If it does, then consideration should be given to requiring a risk management plan or a Post Authorisation Safety Study.

[2] As clarified in GVP Module V revision 2 (currently in public consultation), because there is a justified supposition that a potential risk might be associated with the long-term use, off-label use, or use in populations not studied (e.g. because similar effects have been seen with other products of the same class) and it is deemed important.

143 **Table 1: Overview of the collection and reporting of information on off-label use by MAHs**

Type of information	Required	Format
A. Collection and reporting of information on off-label use with harm		
Individual cases of off-label use associated with suspected adverse reactions	YES	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	YES	PSUR
Quantification of off-label use and implementation of risk minimisation measures when off-label use with harm is an important safety concern	YES	RMP
B. Collection and reporting of information on off-label use with NO harm		
Information on off-label use, which is brought to the MAH attention and which does not meet the criteria as set out under point A	Planned and based on a risk proportionate approach	Planned in the RMP

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3. Annexes

Annex 1 – Article 23 of Directive 2001/83/EC

"1. After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I.

In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

4. In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

The national competent authority may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest 7 days after receipt of the request."

Annex 2 – Points to consider regarding Article 23(2) of Directive 2001/83/EC on the collection and reporting of information on off-label use by MAHs

The main principle underlying Union pharmaceutical legislation is the protection of public health. Marketing authorisations for medicinal products are dynamic and not static and the dossier underlying a marketing authorisation must be regularly updated in order to ensure that scientific progress and new regulatory requirements are respected, in accordance with Article 23 of Directive 2001/83/EC, Annex I to Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004. In particular, any information which may influence the evaluation of the benefits and the risks of the medicinal product must be promptly supplied. (cf. Notice to applicants, Volume 2a, chapter 1)

Article 23 clarifies the responsibilities and obligations of the marketing authorisation holder. More in particular, Article 23(2) deals with the information that needs to be provided by the marketing authorisation holder to the national competent authorities.

Article 23(2) has two parts. In the first subparagraph it refers to the obligation to submit any new information to the competent authorities that may entail a variation:

"The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I."

The second subparagraph highlights then some specific information, which is covered by the first subparagraph and which needs to be provided to the competent authority. In view of the wording used in the second subparagraph, i.e. 'in particular', this is to be understood as a non-exhaustive list.

The following types of information are mentioned:

- Prohibition or restriction of the MA imposed by any competent authority (inside and outside the EU)
- Any other information that might influence the benefit/risk 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

Article 23(2) of Directive 2001/83/EC was first introduced in 2004 by Directive 2004/27/EC and subsequently further modified through Directive 2010/84/EC.

The purpose of the latest amendment is summarised in recital 12 of Directive 2010/84/EU: *"Experience has shown that the responsibilities of marketing authorisation holders with regard to pharmacovigilance of authorised medicinal products should be clarified. The marketing authorisation holder should be responsible for continuously monitoring the safety of its medicinal products, for informing the authorities of any changes that might impact on the marketing authorisation, and for ensuring that the product information is kept up to date. As medicinal products could be used outside the terms of the marketing authorisation, the marketing authorisation holder's responsibilities should include providing all available information, including the results of clinical trials or other studies, as well as reporting any use of the medicinal product which is outside the terms of the marketing authorisation (…)."*

It follows that it was the amendment of 2010 that introduced a specific reference to data on the use of a medicinal product outside the terms of the marketing authorisation (off-label use). This was in line with the general spirit of the 2010 amendments, which reinforced the obligation of marketing

authorisation holders and competent authorities to monitor the use of the product not only when it is used in the authorised indications, but also when it is used off-label.

However, questions have been asked what the obligation with regard to the submission of 'data on the use of the medicinal product where such use is outside the terms of the marketing authorisation' actually entails.

For answering this question it is important to clearly distinguish the obligations listed in Article 23(2) from the obligation of a marketing authorisation holder to report suspected adverse reactions in accordance with Article 107(1) of Directive 2001/83/EC provides. Article 107 provides for a separate, complete and comprehensive framework how individual case safety reports need to be submitted by the marketing authorisation holder to the competent authorities.

As also clarified by GVP Module VI – Management and Reporting of Adverse Reactions to Medicinal Products in Section VI.A.1 the obligation to submit individual case safety reports does not include *"the collection, management and reporting of events or patterns of use, which do not result in suspected adverse reactions (e.g. asymptomatic overdose, abuse, off-label use, misuse or medication error) or which do not require to be reported as individual case safety report or as emerging safety issues. This information may however need to be collected and presented in periodic safety update reports for the interpretation of safety data or for the benefit risk evaluation of medicinal products."*

It would therefore be wrong to expect the submission and/or collection of 'data on the use of a medicinal product outside the terms of the marketing authorisation' in accordance with Article 23(2) of Directive 2001/83/EC under procedures or systems that have been established to collate, collect and report individual case safety reports on adverse reactions in accordance with Article 107 of Directive 2001/83/EC.

This is further confirmed by the fact that the other types of information/data referred to in Article 23(2), like prohibitions/restrictions or results of clinical studies, are not supposed to be reported to the competent authorities through the reporting system for adverse reactions.

Instead, the obligation in Article 23(2) is linked to data/information, which may entail a variation of the marketing authorisation.

This could be data that directly influences the evaluation of the benefit/risk profile of the medicinal product in the authorised indications, but also other data, as specifically highlighted through the references in the second subparagraph to studies in non-authorised indications and to the data on the off-label use of the medicinal product. In justified cases, it might for example be necessary to include warnings and/or other information in the SmPC which goes beyond the authorised indications.

Moreover, data on off-label use or on research in non-authorised indications may also be used to allow the evaluation of the impact and gravity of individual signals if those signals arrive through individual case safety reports and relate to the use outside the terms of the marketing authorisation. Or, such data may be used to comply with the obligations under Article 34 of Commission Implementing Regulation (EC) 520/2012 to estimate in the context of a PSUR the exposure and actual use of the product, including the use in non-authorised indications.

Annex 3 – EFPIA problem statement and questions

Problem statement:

The lack of clarity in the Directive, GVP and Q&A documents have resulted in some pharmacovigilance Inspectors and MAHs interpreting this to mean that MAHs should be collecting all individual cases of off-label use without an adverse event that may be mentioned e.g. to a sales rep or come in as a Med info enquiry. In many instances MAH have put these on the safety database for lack of any other suitable repository. This practice in turn would imply a need for MAH to train our staff globally on the collection of off-label use with no AE. As promotion of off-label use is, of course, strictly prohibited, there is an apparent conflict in try to train sales staff in the collection of off-label information. In addition the practicalities of training Med Info or other call centre staff as to what exactly is meant by off-label use to be reported on to the safety department are difficult (e.g. is one puff of inhaler instead of 2 off-label use). The lack of clarity has resulted in very divergent and confusing practice in the different pharmaceutical companies.

We would like clarification as to the intent of the legislation surrounding off-label use. Our belief is that what is required of MAHs is to collect individual cases of suspected ADRs related to off-label use and not individual reports of off-label use where there was no associated adverse event. We believe MAH's should be aware of how their product is used in practice and if we become aware of off-label use in practice, from published literature or drug utilization studies then this should be presented in PSURs and (applicable) risk management plans. Furthermore, should a company decide to collect a report of off-label use with no AE that it is made aware of, there is no obligation to record that report on its safety database

We would propose that further Q&A on this topic be published by EMA and suitable language inserted in to the next revision of GVP VI to provide the necessary clarity for MAH and inspectors alike.

Questions:

Q1 – Do MAHs need to collect individual cases of off-label use without an adverse event?

Q2 – If an MAH receives a report of off-label use with no AE does it have to record the report on its safety database?

Q3 – Is there a requirement to train staff on collecting cases of off-label use without an adverse event?

Q4 - How should MAHs collect and monitor the information on off-label use that is required for PSURs and applicable risk management plans?