1 8 December 2015
2 EMA/118465/2012 Rev 1 Draft for public consultation

3 Guideline on good pharmacovigilance practices (GVP)

4 Module XV – Safety communication (Rev 1)

Date for coming into effect of first version	24 January 2013
Draft Revision 1* finalised by the Agency in collaboration with Member States	17 November 2017
Draft Revision 1 agreed by the European Risk Management Facilitation Group (ERMS FG)	24 November 2015
Draft Revision 1 adopted by Executive Director	8 December 2015
Release for consultation	15 December 2015
End of consultation (deadline for comments)	29 February 2016
Anticipated date for coming into effect	Q2 2016

5

6 *Note: Revision 1 contains the following:

7 - Introduction of the concept of core EU DHPCs for the situation where a common DHPC prepared at EU
8 level may not be suitable because of differences in the DHPCs required at the level of Member States
9 (e.g. differences in available alternative treatments) and the PRAC/CHMP therefore agree(s) on core
10 messages only (changes in XV.A., XV.B.2., XV.C.2.1. and XV.C.2.2.);

11 - Introduction of the option that one marketing authorisation holder may act on behalf of other
12 marketing authorisation holders with a goal of disseminating one single DHPC in situations where
13 several marketing authorisation holders are concerned (changes in XV.C.2.2.);

14 - Adjustments of references to other GVP Modules, given the recently revised GVP structure (see page
15 6 of GVP Introductory Note of 15 December 2015);

16 - Editorial improvements throughout the Module (changes in particular in XV.A., XV.B.2., XV.B.3,
17 XV.B.5., XV.B.5.1., XV.B.5.2., XV.B.6., XV.C.1., XV.C.1.1., XV.C.1.2.);

18 - The revised GVP Annex II – DHPC template (EMA/36988/2013) and the new GVP Annex II – DHPC
19 Communication Plan template (EMA/334164/2015) have been replicated at the end of the Module for
20 ease of reference.

21

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu.

Note for public consultation:

The public consultation is restricted to the yellow highlighted revised texts (i.e. replaced by new texts with deletions and additions) or deleted texts (i.e. not replaced). However, if revisions or deletions impact or contradict other existing text, comments on such non-highlighted texts will be processed and taken into account for the finalisation process. Comments on the GVP Annex II templates should be provided separately (see EMA/36988/2013 and EMA/334164/2015).

Table of contents

XV.A. Introduction

This Module provides guidance to marketing authorisation holders, competent authorities in Member States and the European Medicines Agency on how to communicate and coordinate safety information concerning medicinal products authorised in the EU, in particular to support achieving the quality objectives of pharmacovigilance ~~Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions and contributing to the protection of patients' and public health~~ (see Module I).

Safety communication is a broad term covering different types of information on medicines, including statutory information as contained in the product information (i.e. the summary of product characteristics (SmPC), package leaflet (PL) and the labelling of the packaging) and public assessment reports. Although some principles in this Module (i.e. Section XV.B.1 and B.2.) apply to all types of safety communication, the module itself focuses on the communication of 'new or emerging safety information', which means new information about a previously known or unknown risk of a medicine which has or may have an impact on a medicine's risk-benefit balance and its condition of use. Unless otherwise stated, the term 'safety communication' in this Module should be read as referring to emerging safety information.

Experience so far has demonstrated the need to coordinate safety communication within the EU regulatory network. High levels of public interest are anticipated when new safety concerns arise and it is important that clear and consistent messages are provided across the EU in a timely manner. The new legislation on pharmacovigilance therefore includes a number of provisions to strengthen safety communication and its coordination[1].

Communication of important new safety information on medicinal products should take into account the views and expectations of concerned parties, including patients and healthcare professionals, with due consideration given to relevant legislation. This Module addresses some aspects of the interaction with concerned parties ~~and supplements the specific guidance given in GVP Module XI on public participation as well as the guidance on communication planning in relation to safety-related action given in GVP Module XII~~.

Communication is distinct from transparency, which aims to provide public access to information related to data assessment, decision-making and safety monitoring performed by competent authorities. The new EU legislation on pharmacovigilance envisages an unprecedented level of transparency. Transparency provisions applicable to each pharmacovigilance process are provided in the relevant GVP Modules.

XV.B. of this Module describes principles and means of safety communication. XV.C. provides guidance on the coordination and dissemination of safety communications within the EU network. Both sections give particular consideration to direct healthcare professional communications (DHPCs), and provide specific guidance for preparing them. This is because of the central importance of DHPCs in targeting healthcare professionals and because of the level of coordination required between marketing authorisation holders and competent authorities in their preparation.

Throughout this Module, legal obligations are referred to as stated in the GVP Introductory Cover Note and are usually identified by the modal verb 'shall' (e.g. 'the marketing authorisation holder shall').

[1] Directive 2010/84/EU amending Directive 2001/83/EC (the latter is referenced as DIR), Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (the latter is referenced as REG) and in the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (the Implementing Regulation is referenced as IR).

When guidance is provided on how to implement legal provisions, the modal verb 'should' is used (e.g. 'the marketing authorisation holder should').

XV.B. Structures and processes

XV.B.1. Objectives of safety communication

Safety communication aims at:

- providing timely, evidence-based information on the safe and effective use of medicines;
- facilitating changes to healthcare practices (including self-medication practices) where necessary;
- changing attitudes, decisions and behaviours in relation to the use of medicines;
- supporting risk minimisation behaviour;
- facilitating informed decisions on the rational use of medicines.

In addition to the above effective, high quality safety communication can support public confidence in the regulatory system.

XV.B.2. Principles of safety communication

The following principles of safety communication should be applied:

- Safety communication should deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.
- Safety communication should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.
- The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process, and should be part of the considering options for safety-related action ~~risk assessment (see GVP Module XII)~~.
- There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. competent authorities, other public bodies and marketing authorisation holders).
- ~~Safety communication should deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.~~
- ~~Safety communication should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.~~
- Information on risks should be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and, if available, expected time to recovery.
- Safety communication should address the uncertainties related to a safety concern. This is of particular relevance for emerging information which is often communicated while competent

authorities are conducting their evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.

- Information on competing risks such as the risk of non-treatment should be included where appropriate.
- The most appropriate quantitative measures should be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; for risk comparisons, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the risk-benefit balance may also be ~~used~~considered.
- Patients and healthcare professionals should, where possible, be consulted and messages pre-tested early in the preparation of safety communication, particularly on complex safety concerns.
- Where relevant safety communication should be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations.
- The effectiveness of safety communication should be evaluated where appropriate and possible (see XV.B.7.).
- Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

XV.B.3. Target audiences

The primary target audiences for safety communication issued by regulatory authorities and marketing authorisation holders should be patients, carers and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

As primary target audiences, healthcare professionals play an essential role in ensuring that medicines are used as safely as possible. Effective safety communication enables them to give clear and useful information to their patients, thereby promoting patient safety and confidence in the regulatory system. Both healthcare professionals in clinical practice and those involved in clinical trials should be provided with appropriate information on any safety concern at the same time.

Patient, consumer and healthcare professional organisations can play a role as multipliers as they can disseminate important safety information to target audiences.

The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on medicines. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from the competent authorities in addition to the information they receive from other sources, such as from the marketing authorisation holders.

XV.B.4. Content of safety communication

Taking into account the principles in XV.B.2., safety communication should contain:

- important emerging information on any authorised medicinal product which has an impact on the medicine's risk-benefit balance under any conditions of use;
- the reason for initiating safety communication clearly explained to the target audience;
- any recommendations to healthcare professionals and patients on how to deal with a safety concern;

- when applicable, a statement on the agreement between the marketing authorisation holder and the competent authority on the safety information provided;
- information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL));
- a list of literature references, when relevant or a reference to where more detailed information can be found;
- where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

The information in the safety communication shall not be misleading and shall be presented objectively [DIR Art 106a(1)]. Safety information should not include any material or statement which might constitute advertising within the scope of Title VIII of Directive 2001/83/EC.

XV.B.5. Means of safety communication

Communication tools and channels[2] have become more numerous and varied over time, offering the public more information than was previously possible. ~~The use of this increasing variety of~~Various means should be considered when issuing safety communication in order to reach the target audiences and meet their growing expectations. Different communication tools and channels are discussed below in XV.B.5.1. to XV.B.5.9..

XV.B.5.1. Direct healthcare professional communication (DHPC)

A direct healthcare professional communication (DHPC) is ~~defined in this document as~~ a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorisation holder or a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals~~, nor are they meant as educational material for routine risk minimisation activities~~.

The preparation of DHPCs involves cooperation between the marketing authorisation holder and the competent authority. Agreement between these two parties should be reached before a DHPC is issued by the marketing authorisation holder. The agreement will cover both the content of the ~~information~~ DHPC (see XV.B.4.) and the communication plan (see GVP Annex II), including the intended recipients and the timetable for disseminating the DHPC.

Where there are several marketing authorisation holders of the same active substance for which a DHPC is to be issued, a single consistent message should normally be delivered.

Whenever possible, it is advised that healthcare professionals' organisations or learned societies are involved as appropriate during the preparation of DHPCs to ensure that the information they deliver is useful and adapted to the target audience.

A DHPC may be complemented by other communication tools and channels and the principle of providing consistent information should apply (XV.B.2.).

A DHPC may be an additional risk minimisation measure as part of a risk management plan (see GVP Modules V and XV).

[2] For the purpose of this Section tools and channels are presented without distinction as they often overlap and there is no general agreement on their categorisation.

A DHPC should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicinal product:

- suspension, withdrawal or revocation of a marketing authorisation for safety reasons;
- an important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;
- a restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.

Other situations where dissemination of a DHPC should be considered are:

- new major warnings or precautions for use in the product information;
- new data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- ~~substantiated knowledge~~ new evidence that the medicinal product is not as effective as previously considered;
- new recommendations for preventing or treating adverse reactions or to avoid misuse or medication error with the medicinal product;
- ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC should encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimise the potential risk).

A competent authority may disseminate or request the marketing authorisation holder to disseminate a DHPC in any situation where the competent authority considers it necessary for the continued safe and effective use of a medicinal product.

XV.B.5.2. Documents in lay language

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. It can also help healthcare professionals to communicate better with their patients. Lay language documents should contain the competent authority's recommendations and advice for risk minimisation for patients and healthcare professionals in relation to the safety concern, and should be accompanied by relevant background information.

Lay language documents are generally useful to members of the public who have an interest in the subject but do not have a scientific or regulatory background. Reference should be made to other communication materials on the topic to direct readers to where they can find further information.

Competent authorities publish lay language documents on their national medicines web-portals and may additionally disseminate them to relevant parties such as patients and healthcare professionals' organisations.

Whenever possible, it is advised that patients and healthcare professionals are involved during the preparation of lay language documents to ensure that the information they deliver is useful and adapted to the target audience.

XV.B.5.3. Press communication

Press communication includes press releases and press briefings which are primarily intended for journalists.

Competent authorities may send press releases directly to journalists in addition to publishing them on their websites. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with the authority's scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system.

Press releases may also be prepared and published by marketing authorisation holders. Their press releases may reflect the position of the marketing authorisation holder on a safety topic but should also make reference to any regulatory action taken by the competent authority. Relevant ongoing reviews should be mentioned in any communication by the marketing authorisation holder.

Although aimed at journalists, press releases will be read by other audiences such as healthcare professionals, patients and the general public. Reference should therefore be made to related communication materials on the topic. In cases where a DHPC is also prepared, healthcare professionals should ideally receive it prior to or around the same time of the publication or distribution of a press release so that they are better prepared to respond to patients.

Press briefings with journalists should be considered by competent authorities for safety concerns or other matters relating to the safety of medicinal products that are of high media interest or when complex or public-health-sensitive messages need to be conveyed.

XV.B.5.4. Website

A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on medicinal products. Competent authorities as well as marketing authorisation holders should ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up-to-date, with any information that is out-of-date marked as such or removed.

The new legislation on pharmacovigilance foresees the creation of an EU medicines web portal which will contain information on all medicines authorised in the EU [REG Art 26]. This web portal will become a key tool for communicating up-to-date safety information to EU citizens and will contain information in all EU official languages. Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the EU medicines web-portal. [DIR Art 106a]. Until the web portal is fully established and into operation, the Agency's website will be acting as an interim platform to convey this important up-to-date safety information.

XV.B.5.5. Other web-based communications

Online safety information may also be disseminated via other web tools. When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised. Communication practices should take into account emerging communication tools used by the various target audiences.

XV.B.5.6. Bulletins and newsletters

Bulletins and newsletters provide at regular intervals new information about medicines and their safety and effectiveness. Competent authorities can reach a large audience with these tools by using web-based and other available means.

XV.B.5.7. Inter-authority communication

When one competent authority takes regulatory action on a particular safety concern, other competent authorities usually need to respond to enquiries or communicate on the same issue. The use of inter-authority communication material, such as lines-to-take should be considered. Lines-to-take are documents specifically prepared by a competent authority to assist its own staff and those of co-operating authorities in responding to external enquires or communicating on a specific safety issue.

XV.B.5.8. Responding to enquiries from the public

Competent authorities and marketing authorisation holders should have systems in place for responding to enquiries about medicines from individual members of the public. Responses should take into account the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by competent authorities. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

In this respect, Article 86(2) and Article 98(1) of Directive 2001/83/EC apply to marketing authorisation holders.

XV.B.5.9. Other means of communication

In addition to those discussed above, there are other tools and channels such as publications in scientific journals and journals of professional bodies.

Some tools and channels may be used in the context of risk management; risk minimisation measures often include specific programmes for risk communication. Tools used in such programmes, such as patient alert cards or healthcare professional safety guidance, are outside the scope of this module and are described in more detail in GVP Module XVI.

XV.B.6. Effectiveness of safety communication

Safety communication is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. ~~Adequate~~ Where possible, mechanisms should be introduced in order to measure the effectiveness of the communication ~~based on clear objectives~~. Measuring effectiveness allows lessons to be learned and helps in making decisions on prioritising and adapting tools and practices to meet the needs of the target audiences. A research-based approach will normally be appropriate in order to establish that safety communications have met the standard of XV.B.2.. This approach may measure different outcomes, including behaviour, attitudes, and knowledge. When evaluating the effectiveness of safety communication, the scope of the evaluation may be broadened to include factors other than the performance of the individual tools used in the safety communication (see GVP Module XVI).

In the case of DHPCs, the marketing authorisation holder should ~~be responsible for evaluating the dissemination of the DHPCs they prepare and should~~ inform the competent authorities of encountered difficulties during the dissemination of the DHPCs ~~the outcome and of any difficulties identified~~ (e.g.

problems related to the list of recipients or the timing and mechanism of dissemination). Appropriate action should be taken as needed to correct the situation or prevent similar problems in the future.

XV.B.7. Quality system requirements for safety communication

In accordance with the quality system requirements in GVP Module I, procedures should be in place to ensure that safety communications comply with the principles in XV.B.2. as appropriate.

In particular, the communications should be subject to quality controls to ensure their accuracy and clarity. For this purpose review procedures with allocated responsibilities should be followed and documented.

XV.C. Operation of the EU regulatory network

XV.C.1. Coordination of safety announcements in the EU

In the EU, patients and healthcare professionals increasingly look at competent authorities as providers of important information on medicines. For safety communication to be effective, adequate coordination and cooperation is required within the EU regulatory network[3]. A good level of coordination of safety communication is of particular importance so that healthcare professionals and patients receive consistent information on regulatory decisions in the EU.

When issuing safety announcements, competent authorities may make use of the different tools and channels described in XV.B.5. Prior to the publication of a safety announcement, the Member States, the Agency or the European Commission shall inform each other not less than 24 hours in advance, unless urgent public announcements are required for the protection of public health [DIR Art 106a(2)].

For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements [DIR Art 106a(3)].

For practical reasons, ~~considering the potential for overlap between transparency measures and active communications and in order to focus on those topics of major health relevance,~~ not all safety information made public by a Member State or the Agency will be subject to systematic exchange and coordination. Only safety announcements that relate to the following and that pertain to active substances contained in medicinal products authorised in more than one Member State require coordination within the EU regulatory network:

- the suspension, withdrawal or revocation of a marketing authorisation due to changes to its risk-benefit balance;
- the start or finalisation of an EU referral procedure for safety reasons;
- restriction of indication or treatment population or the addition of a new contraindication;
- dissemination of a DHPC agreed by relevant competent authorities of a Member State or the Agency (see XV.C.2.1.);
- other emerging safety concerns judged by a national competent authority or the Agency to be likely to give rise to public or media interest in more than one Member State (e.g. a publication of important safety findings in a (scientific) journal, safety-related regulatory action taken in a Member State or in a country outside the EU).

[3] i.e. the competent authorities in the Member States, the Agency and the European Commission.

XV.C.1.1. Process for exchange and coordination of safety announcements

A competent authority of a Member State or the Agency shall inform the EU regulatory network prior to the publication of a safety announcement that pertains to active substances contained in medicinal products authorised in more than one Member State and that refer to any of the situations identified in XV.C.1. It shall include a timetable for the information being made public [DIR Art 106a(3)]. Whenever possible the safety announcement shall be sent to the network under embargo no less than 24 hours in advance of publication [DIR Art 106a (2)], in order to allow the members of the EU regulatory network to prepare or plan their own communication if necessary. Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message [DIR Art 106a(3)].

The Agency should decide for each case, on the basis of the public health relevance and urgency of the safety concern, the population and number of Members States affected and the potential for media attention, whether further communication action in addition to the dissemination of the safety announcement is needed, such as:

- the preparation of lines-to-take (see XV.B.5.7.) for dissemination to the EU regulatory network. The lines-to-take document should help the EU regulatory network to respond to any request for information which may follow the publication of the safety announcement;
- the preparation of an Agency safety announcement in addition to that of the Member State, which should also be disseminated under embargo to the EU regulatory network together with a timetable for its publication.

The Agency should prepare lines-to-take documents and any Agency safety announcement together with the Member State(s) who originated the process and the PRAC Lead Member State or the PRAC Rapporteur, as appropriate. The PRAC, as well as the CHMP or CMDh, should also be consulted as necessary.

Coordination of safety announcements should be done in cooperation with the concerned marketing authorisation holder(s). Whenever possible, the Agency and the competent authorities in Member States should provide any safety announcement prior to its publication to the concerned marketing authorisation holder(s), together with the timetable for the information being made public. Any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health [DIR Art 106a (4)].

The exchange and coordination of safety announcements within the EU regulatory network should make use of the EU Early Notification System (ENS). The ENS was developed for use by the Agency to provide advance notice to competent authorities in Member States and the European Commission of safety information on centrally authorised products. This system should also be used by competent authorities in Member States for the purpose of exchanging and coordinating safety announcements.

The ENS includes the Heads of Medicines Agencies (HMA), the members of the PRAC, CHMP, CMDh, the operational contact points for safety announcements at the competent authority in Member States, the European Commission and the Agency. Operational contact points should ensure that any information exchanged via the system reaches in a timely manner the relevant staff within each competent authority, including relevant staff working within the communications departments.

Safety announcements from the EU regulatory network should be shared with international partners ~~in accordance with the guidance provided in GVP Module XIV~~, subject to embargo and any specific confidentiality arrangements in place.

As a complement to the coordination of safety announcements within the EU regulatory network, competent authorities in Member States and the Agency should interact with concerned stakeholders in

the EU (mainly patients' and healthcare professionals' organisations), who can play a key role in reviewing and disseminating information to the end users (patients and healthcare professionals). It is recommended that national competent authorities and the Agency keep up-to-date contact details of relevant patients, and healthcare professionals' organisations.

XV.C.1.2. Exchange of safety information produced by third parties

There are situations where emerging safety information is to be published or has been published by a party other than a competent authority of a Member State or the Agency (e.g. scientific journals, learned societies). Competent authorities should bring to the attention of the EU regulatory network any such safety information that they become aware of, together with the timing of the publication if known. Where necessary and after evaluation of the information, the Agency should prepare and disseminate a lines-to-take document or an Agency safety announcement to address the information from the third party (see XV.C.1.1.).

In the context of collaboration with authorities outside the EU, the Agency or a competent authority of a Member State may become aware of safety announcements to be published by ~~these~~ authorities outside the EU ~~(see GVP Module XIV)~~. In these cases the Agency should, as necessary, prepare and disseminate lines-to-take or safety announcements within the EU regulatory network. In all cases, the terms of ~~any~~ relevant confidentiality agreements with non-EU regulatory authorities and the embargoes on the information received should be respected.

XV.C.1.3. Requirements for the marketing authorisation holder in the EU

As soon as a marketing authorisation holder in the EU intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, the marketing authorisation holder shall be required to inform the competent authorities in Member States, the Agency and the European Commission [DIR Art 106a]. This should apply to announcements intended for the EU as well as outside the EU (when they concern products authorised in the EU or those for which an opinion under Article 58 of Regulation (EC) 726/2004 has been given). Informing the authorities at the same time as the public (i.e. without advance notice to the authorities) should only occur exceptionally and under justified grounds. Whenever possible, the information should be provided under embargo at least 24 hours prior to its publication.

The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading [DIR Art 106a].

Whenever a marketing authorisation holder becomes aware that a third party (see XV.C.1.2.) intends to issue communication that could potentially impact the risk-benefit balance of a medicinal product authorised in the EU, the marketing authorisation holder should inform the relevant competent authorities in Member States and the Agency and make every effort to share the content of the communications with the relevant authorities.

XV.C.1.4. Consideration for third parties

Third parties (e.g. scientific journals, learned societies, patients' organisations) are encouraged to inform the Agency and the competent authorities in Member States of any relevant emerging information on the safety of medicines authorised in the EU and, if publication is planned, to share the information ahead of publication.

XV.C.1.5. Languages and translations

Consistent messages should reach the public across the EU in a timely manner and in the official languages of the Member States as specified by the Member States where the medicinal product is placed on the market.

For the purpose of coordination, the Agency shall use English to inform the EU regulatory network of any safety announcement. When informing the Agency, the competent authorities in Member States are encouraged to provide English translations of their safety announcements for the purpose of initiating the coordination process. In the absence of a full text translation, an English summary should be provided.

XV.C.2. Direct healthcare professional communications in the EU

In the EU, a direct healthcare professional communication (DHPC) (see XV.B.5.1.) is usually disseminated by one or a group of marketing authorisation holders for the respective medicinal product(s) or active substance(s), either at the request of a national competent authority or the Agency, or on the marketing authorisation holder's own initiative. The marketing authorisation holder should seek the agreement of the relevant national competent authorities or the Agency regarding the content of a DHPC (and communication plan) (see GVP Annex II) prior to dissemination.

XV.C.2.1. Processing of DHPCs

The situations when a DHPC is necessary or should be considered are provided in XV.B.5.1. When drafting a DHPC, the template (see GVP Annex II) and the guidance provided in the annotations in the template should be followed as appropriate.

The roles and responsibilities of the competent authorities in a Member State, the Agency and marketing authorisation holders in the preparation and processing of DHPCs depend on the route of authorisation of the medicinal products concerned:

- for centrally authorised products and for products subject to an EU ~~referral~~ procedure for safety reasons, the relevant marketing authorisation holders should submit the draft DHPC and communication plan (including the intended recipients and the timetable for disseminating the DHPC) (see GVP Annex II) to the Agency, which should coordinate the review process by its scientific committees (i.e. PRAC and CHMP) and CMDh.
- for products authorised through the mutual recognition or decentralised procedure, the marketing authorisation holder should submit the draft DHPC and communication plan to the Reference Member State, which should co-ordinate the process with the marketing authorisation holder, while keeping the Concerned Member States informed of any proposed action.
- for nationally authorised products not authorised through the mutual recognition or decentralised procedure, the marketing authorisation holder should submit the draft DHPC and any communication plan to the competent authorities of the Member States where the products are authorised.

The marketing authorisation holder should allow a minimum of two working days for comments. However, whenever possible more time should be allowed. The timing may be adapted according to the urgency of the situation.

The Agency will coordinate the review of DHPCs within its scientific committees/groups as appropriate (i.e. involvement of PRAC, and finalisation by CHMP or CMDh). The PRAC should always be involved in the review of DHPCs related to a safety concern being discussed at the PRAC and the DHPC should

form part of the PRAC ~~assessment~~ considerations of options for safety-related action ~~(see GVP Module XII)~~. The Agency may also request advice from the PRAC on issues related to other safety communications.

There might be situations where a single DHPC prepared at EU level may not be suitable as there may be differences in Member States (such as differences in available therapeutic alternatives) which cannot be addressed in a single DHPC. In such cases, it is proposed that a core EU DHPC is agreed at EU level setting out core EU messages. The core EU DHPC can then be complemented at national level with additional information to address the different national situations (for example in relation to availability and choice of alternative treatments).

Although there will be national tailoring of such DHPCs, any core messages agreed at EU level should be preserved (i.e. tailoring should not conflict with these core messages).

In each Member State, when several marketing authorisation holders are concerned (i.e. when the DHPC covers several products with the same active substance or products of the same therapeutic class), marketing authorisation holders are strongly encouraged to arrange for one marketing authorisation holder to act on behalf of all concerned marketing authorisation holders as the contact point for the national competent authority. Where generics are involved, the contact point should normally be the marketing authorisation holder of the originator product. If no originator product is marketed in a Member State, it is encouraged that one generic company acts as the contact point. Such coordination between concerned marketing authorisation holders aims to ensure that healthcare professionals in a given Member State receive a single DHPC covering all the products affected by a single safety concern (same active substance or a class review). The marketing authorisation holder acting as contact point for the national competent authority and on behalf of all others marketing authorisation holders should be included in the agreed communication plan (see GVP Annex II) to facilitate coordination.

Once the content of a DHPC and communication plan from the marketing authorisation holder are agreed by national competent authorities or the Agency, the national competent authorities or the Agency should ~~exchange~~ share the final DHPC and communication plan using the early notification system (see XV.C.1.1.), and the Agency should coordinate any subsequent safety announcement as appropriate using the process described in XV.C.1.1.. The early notification system is only used if the DHPC concerns an active substance authorised in more than one Member State.

In cases where an authority outside the EU requests the dissemination of a DHPC in their territory for a product also authorised in the EU, the marketing authorisation holder should notify the relevant competent authorities in the EU. This is part of the legal requirement under which the marketing authorisation holder shall notify the competent authorities of any new information which may impact the risk-benefit balance of a medicinal product [REG Art 16(2) and DIR 23(2)]. The need for any subsequent communication, e.g. a DHPC, in the EU should be considered and agreed on a case-by-case basis.

A flow chart describing the processing of DHPCs is provided in Figure XV.I. at the end of the Module.

XV.C.2.2. Translation and dissemination of DHPCs

For centrally authorised products, products subject to an EU ~~referral~~ procedure for safety reasons and, in most cases, for products authorised through the mutual recognition or decentralised procedure, the working language for preparing the DHPCs will normally be English.

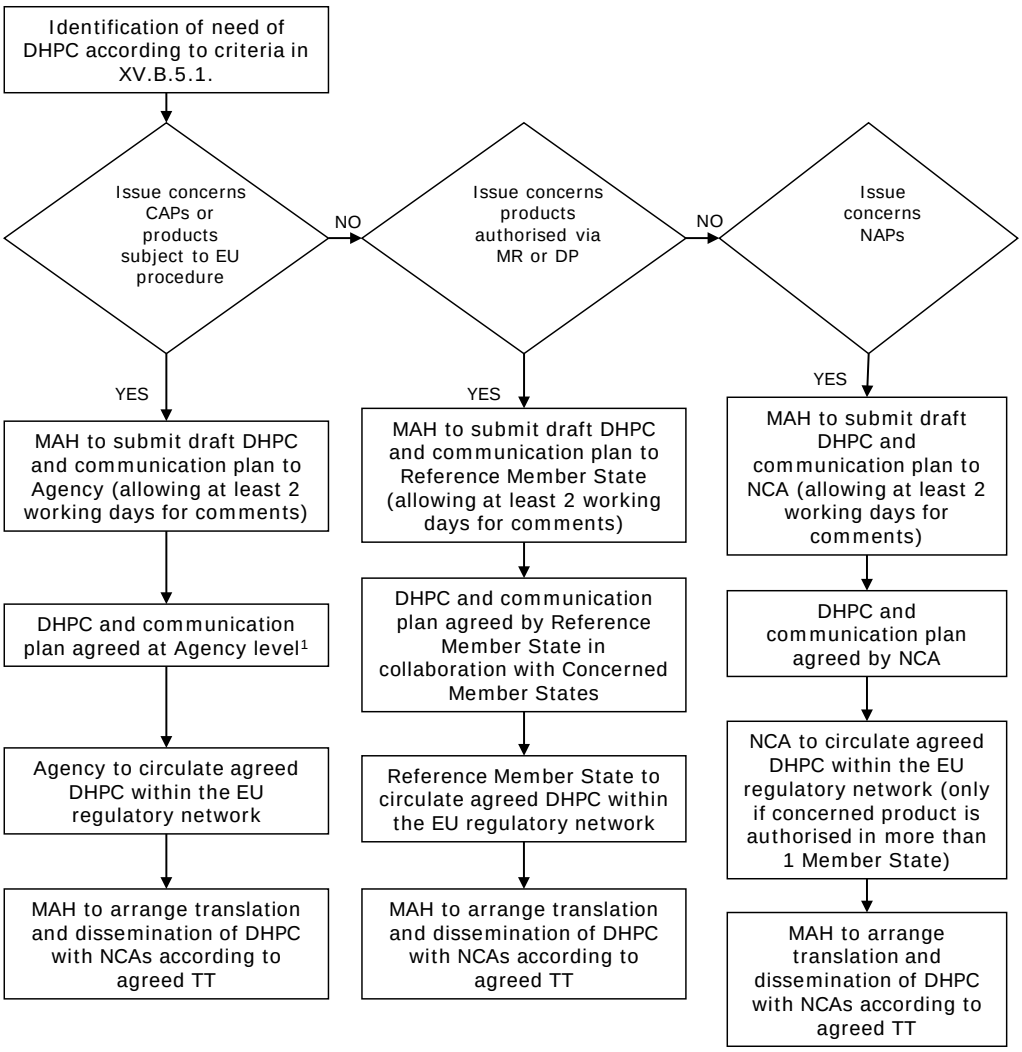
Once the text of the DHPC is agreed, the marketing authorisation holder should prepare translations in the official languages of the Member States, as specified by the Member States where the DHPC is to

be distributed. The draft translations should be submitted to the Member States for a language review within a reasonable timeframe (no more than ~~two~~ 4-5 working days).

For centrally authorised products and products subject to an EU ~~referral~~ procedure for safety reasons, the relevant marketing authorisation holder should provide the Agency with a complete set of all final EU official language versions as well as any additional related communication documents.

XV.C.2.3. Publication of DHPCs

The competent authorities may publish the final DHPC. The timing for such publication should be aligned to that of the dissemination of DHPC in the Member States. The competent authorities may also issue an additional safety announcement, and disseminate the DHPC to relevant healthcare professionals' organisations as appropriate.



[1] The Agency will coordinate the review of DHPC within its scientific committees (i.e. PRAC and CHMP) and CMDh.

562

563 ***Figure VX.1: Flow chart for the processing of Direct Healthcare Professional Communications***
564 ***(DHPCs) in the EU***

565

GVP Annex II – Templates: Direct Healthcare Professional Communication

Note: This is an identical replication of GVP Annex II – Templates: DHPC Rev 1 (EMA/36988/2013 Rev 1) in this Module for ease of reference.

<Date>

<Active substance, name of medicinal product and main message *(e.g. introduction of a warning or a contraindication)*>

Dear Healthcare professional,

<Name of marketing authorisation holder> in agreement with <the European Medicines Agency> and the <National Competent Authority > would like to inform you of the following:

Summary

Guidance: This section should be in bold/larger font size than the other sections of the DHPC and preferably in bullet points.

- <Brief description of the safety concern in the context of the therapeutic indication, recommendations for risk minimisation *(e.g. contraindications, warnings, precautions of use)* and, if applicable, switch to alternative treatment>
- <Recall information, if applicable, including level (pharmacy or patient) and date of recall>

Background on the safety concern

Guidance: This section may include the following information:

<Brief description of the therapeutic indication of the medicinal product>

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, and, if known, the pharmacodynamic mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors)>

<An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>

<A statement indicating any association between the adverse reaction and off-label use, if applicable>

<If applicable, details on the recommendations for risk minimisation>

<A statement if the product information is to be or has been revised, including a description of the changes made or proposed> *Guidance: No need however to include or attach the precise (translated) text of the product information which, at the time of dissemination of the DHPC may not be available as final approved translations)*

<Place of the risk in the context of the benefit>

<The reason for disseminating the DHPC at this point in time>

<Any evidence supporting the recommendation (e.g. include citation(s) of key study/ies)>

<A statement on any previous DHPCs related to the current safety concern that have recently been disseminated>

<Any schedule for follow-up action(s) by the marketing authorisation holder/competent authority, if applicable>

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system >

<Mention if product is subject to additional monitoring and the reason why>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes *(if applicable)*

<Link/reference to other available relevant information, such as information on the website of a competent authority>

<Additional scientific information, if applicable>

<List of literature references, if applicable>

GVP Annex II – Templates: Communication Plan for Direct Healthcare Professional Communication

Note: This is an identical replication of GVP Annex II – Templates: Communication Plan for DHPC (EMA/334164/2015) in this Module for ease of reference.

DHPC COMMUNICATION PLAN	
Medicinal product(s) / active substance(s)	
Marketing authorisation holder(s)	*In cases where the DHPC concerns several marketing authorisation holders of the same active substance or is part of a class review, it is strongly encouraged that a single consistent message is sent to healthcare professionals in each EU Member State.* *All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all active substance-containing products authorised in that Member State.* *It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority.*
Safety concern and purpose of the communication	*Consider using the title of the DHPC to describe the safety concern*
DHPC recipients	*List all recipients of the DHPC in this section, e.g. general practitioners, specialists, pharmacists, nurses, professional societies, national associations.*
Member States where the DHPC will be distributed	

Timetable *Delete steps which are not applicable*	**Date**
DHPC and communication plan (in English) agreed by PRAC	
DHPC and communication plan (in English) agreed by CHMP / CMDh	
Submission of translated DHPCs to the national competent authorities for review	
Agreement of translations by national competent authorities	
Dissemination of DHPC	