DECISION

No. 3/28.03.2014

on approval of the Guideline on Good Pharmacovigilance Practices, Module XV – Safety communication

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 158/18.02.2013, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 28.03.2014, in accordance with Article 12(5) of Government Decision No. 734/2010 on establishment, organization and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following :

DECISION

Article 1. – The Guideline on Good Pharmacovigilance Practices, Module XV – Safety communication, is approved, in accordance with the Annexes which are integral parts of this Decision.

ARTICLE 2. – On this Decision coming into force, SCD no. 3/29.02.2008 on approval of the Guideline on Direct Healthcare Professional Communication is repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines
and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD no. 3/28.03.2014

Guideline on Good Pharmacovigilance Practices (GVP)

Module XV – SAFETY COMMUNICATION

Date of entry into force: 24 January 2013

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XV.A. Introduction

This Module provides guidance to marketing authorisation holders, competent authorities in Member States and the European Medicines Agency (EMA) on how to communicate and coordinate safety information in the EU. 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 benefit-risk 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.

The occurrence of new concerns is generally accompanied by a serious increase in public interest; it is thus 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 Module XI on public participation as well as the guidance on communication planning given in Module XII.

[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 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.

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.

Section XV.B. of this Module describes principles and means of safety communication. Section 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.

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:

- The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process, and should be part of risk assessment (see 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 benefit-risk balance may also be used.
- 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 (see Module XII).
- 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 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. 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 benefit-risk 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 [Law 95/2006[2], Article 818 (1)]. Safety information should not include any material or statement which might constitute advertising within the

[2] Law 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, hereinafter 'Law 95/2006'

scope of Law 95/2006 on healthcare reform – Title XVII – The medicinal product, as amended.

XV.B.5. Means of safety communication

Communication tools and channels[3] have become more numerous and varied over time, offering the public more information than was previously possible. The use of this increasing variety of 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 sections XV.B.5.1.-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 (see XV.B.4.) and the communication plan, including the intended recipients and the timetable for disseminating the DHPC (see Module XII).

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 Modules V and XV).

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;

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[3] In line with this Chapter, the tools and channels are equally described, since they frequently mix and there are no uniform opinions on their classification.

• 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 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. 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 [Article 26 of Regulation (EU) No 1235/2010]. 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 [Law 95/2006, Article 818]. 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, Articles 797(2) and 809(1) of Law 95/2006, as amended, 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 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 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 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 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 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[4]. 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 [Law 95/2006, as amended, Article 818[1](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 amendments [Law 95/2006, as amended, Article 818[1](3)].
For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between

[4] Competent authorities of Member States, EMA and the European Commission.

national competent authorities of safety announcements [Law 95/2006, as amended, Article 818[1]].
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 benefit-risk 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).

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 [Law 95/2006, Article 818[1](3)]. Whenever possible the safety announcement shall be sent to the network under embargo no less than 24 hours in advance of publication [Law 95/2006, Article 818[1](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 [Law 95/2006, Article 818[1](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 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.) which should be disseminated 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 Pharmacovigilance Risk Assessment Committee (PRAC) Lead Member State or the PRAC Rapporteur, as appropriate. The PRAC, as well as the Committee for Medicinal Products for Human Use (CHMP) or the Co-ordination group for Mutual recognition and Decentralised procedures – human (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 [Law 95/2006, Article 818[1](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 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 performed 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 (see 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 [Law 95/2006 Article 818[1]]. 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 [Law 95/2006, Article 818[1](1)].

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 benefit-risk 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) 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 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) 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 (see Module XII). The Agency may also request advice from the PRAC on issues related to other safety communications.
Once the content of a DHPC and communication plan from the MAH are agreed by national competent authorities or the Agency, the national competent authorities or the Agency should exchange 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 benefit-risk balance of a medicinal product [Regulation 1235/2010, Article 16(2) and Law 95/2006, Article 728(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 Annex I - Figure XV.I at the end of this Module.

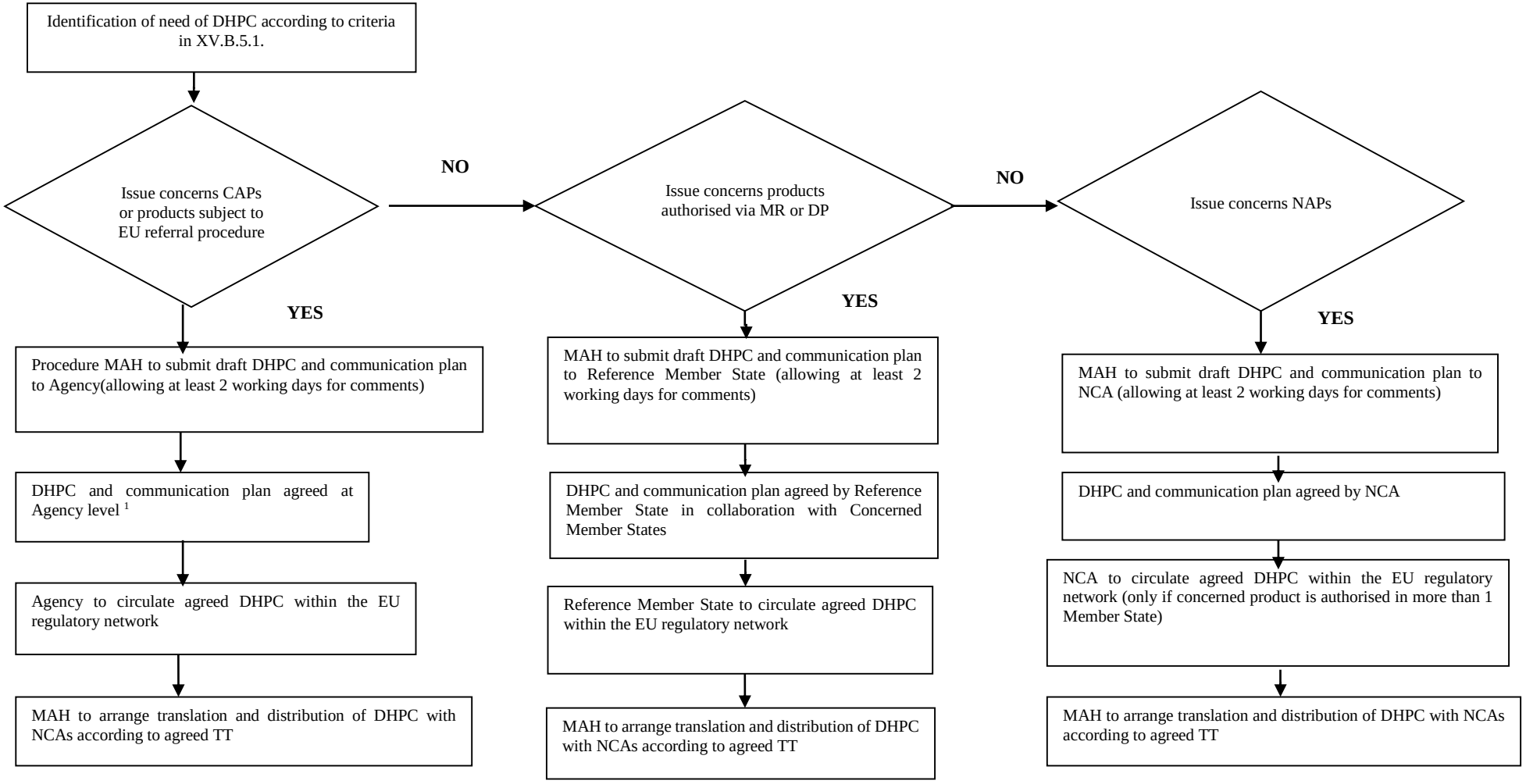
XV.C.2.2. Translation of DHPCs

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 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.

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



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

ANNEX II to GVP-Module XV
SCD no. 3/28.03.2014

TEMPLATE FOR DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

<Date>

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

Dear Healthcare Professional,

<Marketing Authorisation Holder> wishes to inform you about:

Summary*

- <A brief description of the safety concern, recommendations for risk minimisation (*e.g. contraindications, warnings, precautions*) and, if applicable, switch to alternative treatment>

- <Recall information, if applicable, level (pharmacy or patient level) and date of recall>

< A statement indicating that the information has been endorsed by a national Competent Authority/the Agency, if applicable >

Safety information on safety concern and recommendation

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, e.g. the pharmacodynamic mechanism, if known, temporal relationship, positive re-challenge or de-challenge, risk factors), also indicating the reason for disseminating the DHPC at this point in time.>

<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 needed, details on the recommendations for risk minimisation >

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

<A statement about newly submitted DHPCs, referring to the current safety issue>

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* ***Style guide: The Summary section should be in larger font size than the other sections of the DHPC and should preferably use markers.***

<A schedule for follow-up action(s) by the Marketing Authorisation Holder/Competent Authority, if applicable>

Further information

<Link/Reference to other available relevant information, e.g. information posted on the website of the competent authority>

<Therapeutic indications for the respective medicinal product, if not previously mentioned>

Call for reporting

<A reminder of the need to report adverse reactions in accordance with the national spontaneous reporting system>

"It is important to report any suspected adverse reaction associated with the administration of …… to the National Agency for Medicines and Medical Devices, in accordance with the national system for spontaneous reporting, using the "Adverse reaction reporting form".

<Please specify whether the medicinal product is subject to additional monitoring as well as the grounds for this decision>

<Details (name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

The "Adverse reaction reporting form" is available on the website of the National Agency for Medicines and Medical Devices (www.anm.ro), under section Medicinal products for human use/Report an adverse reaction. This may be submitted to the National Agency for Medicines and Medical Devices by post, fax or e-mail:

The National Agency for Medicines and Medical Devices
The National Pharmacovigilance Centre
48 Av. Sanatescu St.,
Sector 1, Bucharest, 011478 - RO
Romania
Telephone number: + 4 0757 117 259
Fax number: +40 213 163 497
E-mail address: adr@anm.ro
You can also report suspected adverse reactions to ..... – contact coordinates:

……."

Contact coordinates of the local representative of the Marketing Authorisation Holder

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

Annexes

<Text of the revised Product Information (with changes made visible)>

<Detailed scientific information, if necessary>

<List of literature references, if applicable>