25 June 2012
EMA/428732/2012
Patient Health Protection

Comments received from public consultation on good pharmacovigilance practices (GVP)

GVP Annex I – Definitions

The first seven good-pharmacovigilance-practice (GVP) modules on prioritised topics were released for public consultation between 21 February and 18 April 2012. The modules have been revised, taking the comments received into account.

Those who participated in the public consultation were asked to submit comments using the specific templates for each module and the definition annex.

The comments received are published for each module, identifying the sender's organisation (but not name). Where a sender has submitted comments as an individual, the sender's name is published.

The European Medicines Agency thanks all those who participated in the public consultation for their contributions.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
AESGP

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment

	We suggest that all definitions be put in the definition annex and that cross-references to this annex be made in each GVP modules. Having the definition only once (in the annex) would ensure consistency.
	
	There is no definition of off label use and this term is used in several of the GVP modules e.g. PASS and PSUR modules. We propose that a definition of off label use is added to Annexe I Definitions as follows:
	
	Off Label Use
	
	Use of the product outside the terms of the marketing authorisation.
	
	The following four terms are also missing. For those four terms we would like to propose the following definitions:
	
	Additional Pharmacovigilance Activities:
	Where important identified risks, important potential risks, or important missing information are found, activities designed to collect additional information regarding these safety concerns which are not routine pharmacovigilance should be considered.
	
	Additional Risk Minimisation Activities:
	A risk minimisation activity put in place to reduce the probability of an adverse reaction from occurring or to reduce its severity should it still occur which is set up on top of routine risk minimisation activity – e.g. additional educational material.
	
	Routine Pharmacovigilance Activities:
	Routine pharmacovigilance should include the following:
	• Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
	• The preparation of reports for regulatory authorities:
	  ○ Expedited reports;
	  ○ Periodic Safety Update Reports (PSURs).

Stakeholder number *(To be completed by the Agency)*	General comment
	• Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities; • Other requirements, as defined by local regulations. **Routine Risk Minimisation Activities:** The warnings and information contained within the product labelling, and the careful use of labelling and packaging, which aim to reduce the probability of an adverse reaction occurring or its severity should it occur.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
105 - 106		Comment: **Closed signal** definition is defined as follows in the annex: "In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH-E2C(R2) Guideline)." This definition is too restrictive and confines the use of closed signal to the context of PSURs/PBRERs only. The language for signals at different stages in their review and analysis should be harmonised between the GVP modules for clarity (for example PSURs and signal detection). Proposed change: We recommend that "In periodic benefit risk evaluation reports" is deleted from the above definition to avoid confusion.
127 – 132		Comment: **Data Lock Point** is defined slightly differently between PSUR and PBRER as follows: "For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR. For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date (see Annex IV, ICH-E2C (R2) Guideline" . This is very confusing, because the overarching concept for a data lock point (Data until a given cut-off date) is regardless of the regulatory report documents. The underlying procedure how to arrive at defining a precise data for a particular active substance and a regulatory document type should not be part of the definition of the term data lock point. Proposed Change: Remove the second sentence so that the definition now reads as follows: **Data Lock Point** is defined as the date designated as the cut-off date for data to be included in a PSUR, RMP or other regulatory documents.
173-181		This definition is not consistent with the definitions given in the RMP module. The definition in the RMP module does not mandate the inclusion of all contraindications and warnings as important risks but merely suggests that they should be considered (reference is made to section 752 of the RMP module). The relevance between precautions and contraindications may vary, particularly in some medicines which have already been

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		introduced decades ago. Medical judgement may be required to determine whether an individual precaution or contraindication would need to be presented as important risk in the respective regulatory documents. Proposed change: We suggest that the clearer, more pragmatic, definition given in the RMP GVP module be used for this RMP module "Definitions".
189		Comment: The cross-reference provided under the definition of "important potential risk" is not accurate. It reads as follows: *See Important identified risk and Important potential risk* Proposed change: Instead it should read as follows: *See Important identified risk and ~~Important~~ ~~p~~Potential risk*
211-216		This definition is accurate with the directive but in order for some of the statements in the modules to be clear some additional clarification should be provided in this module. It would be useful to define active substance too. Proposed change: The term active substance alone should be defined in addition to "medicinal product". The definition of the Directive should be used. The definition of "medicinal product" may be enhanced to encompass that this term refers to an active substance as further qualified by any of the following: a form of administration, a strength and/or a tradename.
235 - 237		Comment: **Newly Identified Signal** again refers to the PBRER. This definition like the definition for a closed signal is too restrictive and confines its use to the context of PSURs/PBRERs only. The language for signals at different stages in their review and analysis should be harmonised between the GVP modules for clarity (for example PSURs and signal detection). Proposed change: We recommend that "In periodic benefit risk evaluation reports" is deleted to avoid confusion.
263 - 265		Comment: **Ongoing Signal** ...the definition quoted from ICH E2C is incorrect as it was an old one in ICH E2C which was subsequently revised.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change : Revise to be consistent with the current one in ICH E2C...namely, "a signal that is still under evaluation at the data lock point " This definition like the definition for a closed signal is too restrictive and confines its use to the context of PSURs/PBRERs only. The language for signals at different stages in their review and analysis should be harmonised between the GVP modules for clarity (for example PSURs and signal detection). Proposed change: We therefore recommend that "In periodic benefit risk evaluation reports" is deleted from the beginning of the definition text to avoid confusion.
297-299		Comment: The term "data" at the end of the definition should be deleted as this is not in the definition of the Directive referred to here. Proposed change: A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products ~~data~~ [DIR 2001/83/EC Art 1(28e)].
341		Comment: Reference Safety Information (RSI) is defined as "Information referred to as the company core safety information (CCSI) ". This definition would oblige MAHs to create a CCSI for each product, even for purely local ones where the RSI can reasonably be the approved SmPC (as currently accepted by authorities). Proposed change: Define the RSI as "Document used to assess listedness of adverse reactions in the frame of the PSUR. Usually this corresponds to the Company Core Safety Information (CCSI)".
377-379		Comment: In line with DIR 2001/83 (literal citation) and also the way other definitions are provided in this module the introductory words from the definition should be deleted. Proposed change: ~~Serious adverse reaction means~~ an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)].

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 APRIL 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
ALEXION Europe SAS

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Alexion recognises the high level quality and completeness of this module as compared to what was in Volume9A. It will be of great support for PV systems management and continuous improvement.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 202: listed adverse reaction definition and Line 432 unexpected adverse reaction definition		Comment: Among the criteria taken into account in the assessment of labelling there is one (specificity) that is not contained in the unexpectedness definition. Although specificity is to be considered in the process of labelling assessment, criteria to be taken into account in both systems (labelling assessment against CCDS and against local approved labelling) should not be different as it may lead to discrepancies between these assessments. Proposed change (if any): Best Suggestion would be to add the "specificity" criterion to the unexpectedness definition but as it is from the Directive it may not be possible to amend it. Alternative solution would be to align listedness definition criteria to those of unexpectedness definition.
Line 103 definition of "close signal"		Comment: In that definition a new notion of "periodic benefit-risk evaluation reports" is introduced: Alexion would like to know whether this corresponds to a stand-alone new document or part of the other defined periodic reports such as PSURs. Proposed change (if any):
Line 186 "important potential risk" definition.		Comment: This definition refers to the definition of "important identified risk" however they correspond to two different notions particularly as per GVP module on PSURs Proposed change (if any): create two distincts definitions: one for important identified risk" and one for "Important potential risk".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Bundesverband der Pharmazeutischen Industrie e. V. (BPI) - German Pharmaceutical Industry Association

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Definition of "Lack of efficacy" is missing. Proposed: insert definition for lack of efficacy including (see comment for Module VI): "in cancer therapy, stable disease or progression of disease should normally not be classified as lack of efficacy."

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 75-76		**Comment**: clinical-trial subject…have to have a causal relationship… – wording not exactly from 2001/20 **Proposed change (if any):** original wording from 2001/20: 'adverse event': any untoward medical occurrence in a patient or **clinical trial** subject administered a medicinal product and which **does not necessarily have a causal relationship** with this treatment;
Line 208 - 210		**Comment**: In our opinion, the term "medication error" is not practical enough as a criterion for deciding whether the side effect is a medication error or an adverse drug reaction. The definition uses the term "unintentional error" for defining "medication error". Therefore it is in our opinion a circular definition as it defines "error" with an "error". We welcome the fact that the term "unintentional" is used as an individual therapeutic attempt of a doctor aware of the responsibility is not a medication error. We suggest the following definition: **Proposed change (if any):** Medication error Any unintentional prescribing, dispense or administration of a medicinal product, which contradicts the product information or the current state of medical science, while under the control of a healthcare professional, patient or consumer.

<Date of submission>

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Celgene Europe Ltd.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Celgene welcomes the availability of an annex with definitions. This annex should be comprehensive and also include definitions included in each of the individual GVP modules.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
161		Reference: Definition of an identified risk Comment: Feedback has been received that a risk included in section .8 of the SmPC is by default an indentified risk. Proposed change (if any): Please include this in the definition if this is correct or clarify otherwise	
239		Reference: Definition of non-interventional studies Comment: It should also be mentioned here that non-interventional studies do not fall in the in the scope of Directive 2001/20/EC Proposed change (if any): Please include a sentence the like: 'Non-interventional studies do not fall in the scope of Directive 2001/20/EC.	
301		Reference: Definition of PASS	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: There is no definition of what constitutes a post-authorisation study as referred to in Article 107(1) of Directive 2010/84/EU. There is also not definition of post-authorisation efficacy studies repeatedly mentioned in Directive 2010/84/EU and Regulation (EU) 1235/2010 Proposed change (if any): Definition regarding what constitutes a post-authorisation study and a post-authorisation efficacy study should be included.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Council for International Organizations of Medical Sciences (CIOMS). c/o WHO, 20 Avenue Appia, CH-1211, Switzerland

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, non-profit organization (NGO) established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO). Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. Two major themes for CIOMS within the field of biomedicine have been bioethics and the development and use of drugs. In 1986, CIOMS set up its first pharmacovigilance working group to discuss international reporting of Adverse Drug Reactions (ADRs). Following that several different CIOMS Working Groups (WGs) have published consensus reports covering specific areas of drug development and drug safety such as terms and definitions for vaccine pharmacovigilance, SMQs, the Development Safety Update Report (DSUR), practical aspects of safety signal detection and management. The most recent report (vaccine pharmacovigilance) was published in collaboration with WHO January 2012. Working Groups are presently ongoing covering the area of a harmonized tool kit for risk management and meta-analysis of regulated biopharmaceutical safety data. Each WG has consisted of scientists invited to the group based on their recognized specific expertise and, if required, in consultation with their background institution. Regulatory agencies, health authorities, research-based biopharmaceutical companies and academia have been globally represented. As the CIOMS WGs have no legal jurisdiction or mandate to make binding decisions the goal have been to achieve harmonization and standardization across regulatory jurisdictions. Consequently the CIOMS' reports have served as internationally harmonized recommendations that could be implemented in regional/national legislation. It has also been used as educational material at various training institutes and seminars and in particular for new staff within the pharmaceutical industry and regulatory authorities. The overall collection and presented definitions are endorsed. It is also with great appreciation that CIOMS notes there is a very satisfactory overlap of many of the definitions also globally recommended to be used in this context in previous CIOMS' publications. It is noted that some important definitions used in the context of pharmacovigilance are missing. Examples are:

Stakeholder number *(To be completed by the Agency)*	General comment
	Adverse event of special interest and Designated medical event , Causality assessment, Cohort event monitoring or Prescription event monitoring, datamining, Proportional reporting ratio etc. Being fully aware of the fact that certain prioritisation and selection of definitions presented in this document have been necessary, some of the addressed definitions have been in practice previously and the rationale for the specific selection of terms in this document could therefore be further clarified.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 189		*"See Important identified risk and Important potential risk"* Proposed change (if any): Please clarify the reference
Line 393		Comment: The definition of a signal is greatly endorsed and similar to the definition adapted from Hauben & Aronson (Drug Safety 2009) and published in the CIOMS report "Practical Aspects of Signal Detection in Pharmacovigilance", 2010. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<18 April 2012>

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
EFPIA – European Federation of Pharmaceutical Industries & Associations

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Where the definitions are also quoted in the GVP modules a check should be made that these definitions are consistent with those in Annexe 1. Inconsistencies with this module will be pointed out in the commentary on the individual GVP modules. The definitions Annexe will be very useful and could be more user friendly if the definitions referenced to article 1 of the Directive are given in full in the definitions text followed by the reference. This would allow the definitions Annexe to be used as a standalone reference tool e.g definition of an "HCP"
	There is no definition of off label use and this term is used in several of the GVP modules e.g PASS and PSUR modules .We propose that a definition of off label use is added to Annexe I Definitions as follows: **Off Label Use** Where a product has been used in a non-approved indication, has been used in a non-approved population of patients, has been used in a higher dose than is approved or has been used where there is a contra-indication against using it. (N.B The assessment of "off label use" wherever possible will be against the prescribing information of the country in which the ADR occurred. However ,since determination of "off label use" will be influenced by the content of specific product labels worldwide, discussions of "off label use" in the PSUR or RMP should be based on the indications present in the Company Core Data Sheet)
	There is no definition of Emerging Safety Issue and this term is used in some of the modules (e.g. "emerging safety issues" in Module VI) . We propose that a definition of emerging safety issues is added to Annexe 1 definitions as follows: **Emerging Safety Issue:** Information on a new safety concern or another situation involving a medicinal product which could negatively impact the assessment of the risk-benefit balance and/or public health. Examples of emerging safety issues are major

Stakeholder number *(To be completed by the Agency)*	General comment
	safety findings arising from any source (animal or human studies, spontaneous reports...), major regulatory actions (marketing authorisation suspension, withdrawal...) taken in any country for safety reasons or quality defects potentially causing serious harm to patients.
	Three of the EFPIA comments (highlighted below) refer to the term periodic benefit-risk evaluation report (PBRER) not being adopted in Europe and therefore request removal of reference to it in the GVP Guidance. We would ask for confirmation of this, or whether the EU in fact plans to adopt the PBRER once ICH E2C is finalised and implemented.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 105 - 106	Comment: **Closed signal** definition is : In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH-E2C(R2) Guideline). Proposed change : As the term PBRER is not being adopted in Europe, recommend that " In periodic benefit risk evaluation reports" is deleted to avoid confusion. **Closed signal** Definition becomes: In periodic reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH-E2C(R2) Guideline). Additional comment **on "See Annex IV"**: does this refer to an Annex that will be released later, or to an Implementing Measures Annex? In IM, the PSUR content is described in Annex III, while in ICH E2C(R2), Glossary is in Appendix A
128 - 132	Comment: **Data Lock Point** is defined as **"**For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR. For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date (see Annex IV, ICH-E2C (R2) Guideline" . This is very confusing. Proposed Change: Remove the second sentence so that the definition now reads- **Data Lock Point** is defined as, the date designated as the cut-off date for data to be included in a PSUR.
175 - 178	Comment: The definition provided here for 'important identified risk' and 'important potential risk ' is not exactly the same as the one provided in GVP Module V (Lines 183-185), which seems more appropriate since it specifies that the impact on the risk-benefit balance must be

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	significant. Proposed change (if any): An identified risk or potential risk that could have ~~**an**~~ **a significant** impact on the risk-benefit balance of the product and/or have implications for public health'.
236 - 237	Comment: **Newly Identified Signal** again refers to the PBRER. Proposed change: As the term PBRER is not being adopted in Europe, recommend that " In periodic benefit risk evaluation reports" is deleted to avoid confusion. **Definition of Newly Identified Signal** : In periodic reports, a signal first identified during the reporting interval, prompting further action for evaluation (see Annex IV, ICH-E2C(R2) Guideline). Comment **on "See Annex IV"**: same as above for Closed signal
256-257	Comment: **Occupational exposure definition** should be extended to components of a medicinal product during manufacture or analysis **Proposed change (if any):** An exposure to a medicinal product for human use, or components of such a medicinal product; as a result of one's occupation.
263 - 265	Comment: **Ongoing Signal** ...the definition quoted from ICH E2C is incorrect as it was an old one in ICH E2C which was subsequently revised and again refers to PBRER Proposed change : Revise to be consistent with the current one in ICH E2C (now published on the ICH website)...namely, "a signal that is still under evaluation at the data lock point "

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Comment **on "See Annex IV"**: same as above for Closed signal
279-299(299)	Editorial comment: The term "data" at the end of the definition should be deleted, because it appears unnecessary
339	Comment: Reference Safety Information (RSI) is defined as "Information referred to as the company core safety information (CCSI) ". This definition would oblige MAHs to create a CCSI for each product, even for purely local ones where the RSI can reasonably be the approved SmPC (as currently accepted by HA). Proposed change: Define the RSI as **"**Document used to assess listedness of adverse reactions in the frame of the PSUR. Usually this corresponds to the Company Core Safety Information (CCSI)".
409 - 415	Comment: The definition of **Solicited Sources** is inconsistent with ICH E2D which it references. It should therefore be amended to be consistent. Proposed change : Definition of **Solicited Sources**-Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous. For the purposes of safety reporting, solicited reports should be classified as study reports, and therefore should have an appropriate causality assessment by a healthcare professional or an MAH. (see Annexe IV, 1CH - E2D)

Please add more rows if needed.

17 April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
EGA – European Generic Medicines Association

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Definition “lack of efficacy” is missing.
	Definition “unlisted adverse reaction” is missing.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 136-137		Comment: Data Lock Point. Date includes day and month. Do you consider the beginning or the end of a month? Do you consider 2 or 3 months after the IBD? Please specify.
Line 161-189 Line 350-357		Comment: Definitions in GVP Module V should be harmonised with this module.
Line 190		Proposed change (if any): Add safety report as a synonym of ICSR.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EUCOPE welcomes the availability of an annex with definitions. This annex should be comprehensive and also include definitions included in each of the individual GVP modules. For example, a definition of "Lack of efficacy" is missing here. This could be inserted including (see comment for Module VI): "in cancer therapy, stable disease or progression of disease should normally not be classified as lack of efficacy."

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 75-76		**Comment**: clinical-trial subject…have to have a causal relationship… – wording not exactly from Directive 2001/20/EC **Proposed change (if any):** original wording from Directive 2001/20/EC: 'adverse event': any untoward medical occurrence in a patient or **clinical trial** subject administered a medicinal product and which **does not necessarily have a causal relationship** with this treatment;
Line 161		**Reference:** Definition of an identified risk **Comment:** Feedback has been received that a risk included in section .8 of the SmPC is by default an indentified risk. **Proposed change (if any):** Please include this in the definition if this is correct or clarify otherwise

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 208 - 210		**Comment**: In our opinion, the term "medication error" is not practical enough as a criterion for deciding whether the side effect is a medication error or an adverse drug reaction. The definition uses the term "unintentional error" for defining "medication error". Therefore it is in our opinion a circular definition as it defines "error" with an "error". We welcome the fact that the term "unintentional" is used as an individual therapeutic attempt of a doctor aware of the responsibility is not a medication error. We suggest the following definition: **Proposed change (if any):** Medication error Any unintentional prescribing, dispense or administration of a medicinal product, which contradicts the product information or the current state of medical science, while under the control of a healthcare professional, patient or consumer.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 239		**Reference:** Definition of non-interventional studies **Comment:** It should also be mentioned here that non-interventional studies do not fall in the in the scope of Directive 2001/20/EC **Proposed change (if any):** Please include a sentence the like: 'Non-interventional studies do not fall in the scope of Directive 2001/20/EC.
Line 301		**Reference:** Definition of PASS **Comment:** There is no definition of what constitutes a post-authorization study as referred to in Article 107(1) of Directive 2010/84/EU. There is also not definition of post-authorization efficacy studies repeatedly mentioned in Directive 2010/84/EU and Regulation (EU) 1235/2010 **Proposed change (if any):** Definition regarding what constitutes a post-authorization study and a post-authorization efficacy study should be included.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
196		Comment: To avoid any confusion with Development International Birth Date, the International Birth Date (IBD) could be named "Market International Birth Date"
213-218		Comment: To the exclusion of cosmetic products and medical devices. Medical devices are supposed to be limited to a mechanical effect. Still, in the case of Alpha hydroxy acid for example, the manufacturer describes the mechanism of action as follows: "SCULPTRA works by initially filling with small particles of poly-L-lactic acid (PLLA) beads. As the particles are broken down by the body, beads biodegrade the body and may produce new collagen where SCULPTRA is injected." http://products.sanofi.us/sculptra/sculptra.html Other sources explain: "PLLA presumably creates a tissue response over the course of weeks to months characterized by a foreign body reaction and production of new collagen. The PLLA is eventually metabolized to lactic acid monomers that are then metabolized to carbon dioxide or incorporated into glucose. " http://www.skintherapyletter.com/2005/10.5/2.html This mechanism of action ("foreign body reaction") seems to correspond to the definition "modifying physiological functions" and still this product is not considered as a medicinal product, so the proposed definition of a medicinal product is unclear.
256-257		Comment: does occupation include e.g. leisure activity, or strictly professional activity? In this case, the definition could be clearer: Proposed change: An exposure to a medicinal product for human use as a result of one's occupation, including professional activity or leisure activity. Or An exposure to a medicinal product for human use as a result of ~~one's occupation~~ of one's professional

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		activity.
267-270		Comment: A patient may have taken the recommended dose, but due to his/her metabolism, or due to interaction, the drug accumulates above the desired concentrations. Overdose could include over-exposure, not due to too high dose taken compared to recommended dose, but due to a too high dose taken given the patient metabolism profile or interaction. Proposed change (if any): Adapt definition or revise the paragraph name to "over-exposure"
424-430		Comment: Patients' organisations can also stimulate spontaneous reporting by their members or other patients. Proposed change (if any): Stimulated reporting can occur in certain situations, such as direct healthcare professional communication (DHPC), a publication in the press or questioning of healthcare professionals by company representatives, an invitation by patients' or consumers' organisation to its members and adverse reaction reports arising from these situations are considered spontaneous reports (see Annex IV, ICH-E2D), provided the report meets the definition above.
435-436		Comment: an unexpected adverse reaction can also occur during a product development (clinical trials), before the SPC is validated. It can be defined as unexpected if it is not part of the investigational medicinal product information. Proposed changed: An adverse reaction, the nature, severity or outcome of which is not consistent with the product information in clinical trials or with the summary of product characteristics when the product is authorised.

Please add more rows if needed.

April 17th, 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

EVM
EVM welcomes the opportunity to comment on the public consultation of the first batch of modules on good pharmacovigilance practices (GVP).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The following critical definitions should be added to Annex I, taking into consideration "Definition & Application of Terms for Vaccine Pharmacovigilance, Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, CIOMS 2012": • Vaccine Failure • Low Responder
	Annex I is also missing the following definitions that should be included: - Off-label use - Lack of efficacy (see comments on module VI) - Incident

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/04/12

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Include a definition of expedited
	Include a definition of a stimulated report
	Include a definition of off-label use
	Include a definition of interventional study

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Comment: Proposed change (if any):

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
National Authority of Medicines and Health Products INFARMED, I.P. Portugal

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
195		Comment: Proposed change (if any): add the sentence "Contact details should be available for the reporter to be considered as identifiable."

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Alcon Inc. Novartis Consumer Health Novartis Pharma AG Novartis Vaccines & Diagnostics Sandoz Pharmaceuticals

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Declaration:
The author is signing to confirm that this document has been prepared in accordance with Novartis standards for commenting and impact analyses of regulatory guidelines. The review team has assessed that the operational aspects of this guideline are scientifically appropriate and achievable by the Drug Safety or Pharmacovigilance function. The team has confirmed that the Novartis Pharmacovigilance system will be modified appropriately to ensure that the guidance is met, according to a transition plan to be defined. The Global Head of Pharmacovigilance is signing to confirm sponsorship of process changes and that Novartis will meet the new requirements set-down in the final guideline, subject to approval and to the publication by EMA of a formal transition plan with timelines for Marketing Authorisation holders.

E-signature and date on file: [redacted] **Global Head of Pharmacovigilance**

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The definitions or use of the defined term in each individual GVP module must be identical to those in Annex 1. Proposed changes: Align all definitions

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
431-433		Comment: The definition for target population is not clear as to whether it is intended to include or exclude the population who are contraindicated. Proposed change (if any): Replace definition with "The patients who might be treated by the medicinal product according to the indication(s) subject to exclusions according to the contraindications in the authorised product information."

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Pfizer

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Annex I - Definitions) is well-organised and provides definitions for application across the pharmacovigilance activities that are described in the current draft GVP Modules I, II, V, VI, VII, VIII, and IX. We applaud the Agency for efforts to consolidate GVP definitions in a single Annex. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final definitions Annex. It is anticipated that an expanded and updated list of GVP terms and their definitions will have applicability to the remaining GVP modules, which have yet to issue in Wave 2 for public consultation.
	Many of the terms included in GVP Annex I and used in the Wave 1 draft GVP modules have already been defined by international consensus bodies and these definitions should be adopted in the GVP modules rather than modify or re-cast the definitions. International harmonisation is an important aspect of protecting patient safety and we note that the European Commission participates in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the European Medicines Agency, as well as several National Competent Authorities, participate in expert working groups of the Council for International Organisations of Medical Sciences (CIOMS). These organisations have many carefully developed definitions that can be adopted for GVP purposes.
	In addition to harmonisation of terms and definitions with those already established by international consensus, it is important that use of each defined term in the GVP modules conforms to its intended use. Where the definitions in Annex I are also quoted in the GVP modules, a check should be made that these definitions are consistent with those in Annex I.
	We reference the comments made by the European Federation of Pharmaceutical Industry Associations (EFPIA) and we also offer the following additional suggestions to improve the Guideline. We would be glad to meet with representatives of the Agency to provide clarification on our comments.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 105 - 106		**Comment**: A closed signal is defined as, "*In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH-E2C(R2) Guideline).*" **Proposed change**: As the term PBRER is not being adopted in Europe, revise lines 105-106 to read: " *In periodic* ***safety update reports (PSURs based on the ICH E2C(R2) guideline on*** *benefit-risk evaluation reports), a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH-E2C(R2) Guideline).*"
127 - 139		**Comment**: Data Lock Point is defined, in part, as: **"***For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR.* *"For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date (see Annex IV, ICH-E2C (R2) Guideline."* This is very confusing when the term PSUR transitions to mean PBRER in the EU. **Proposed Change**: Revise lines 127-132 to read: **"***For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR.* *"~~For a periodic benefit-risk evaluation report (PBRER), the date designated as the~~* ***The*** *cut-off date ~~for data to be included in a PBRER,~~* ***will ordinarily be*** *based on the international birth date (see Annex IV, ICH-E2C (R2) Guideline."*
235 - 238		**Comment**: Newly Identified Signal again refers to the PBRER.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Revise lines 235-237 to read: **"***Newly identified signal* *"In periodic **safety update reports (PSURs based on the ICH E2C(R2) guideline on** benefit-risk evaluation reports), a signal first identified during the reporting interval, prompting further actions for evaluation (see Annex IV, ICH-E2C(R2) Guideline).*
258		**Comment**: There is no definition of off-label use and this term is used in several of the GVP modules e.g., Modules VII (PSUR) and VIII (PASS). **Proposed change**: Insert, before line 258: "***Off-label use*** ***"Use of the product outside the terms of the marketing authorisation.*** ***"The assessment of "off-label use" wherever possible will be against the authorised prescribing information of the country in which the ADR occurred. However, since determination of "off-label use" will be influenced by the content of specific product labels worldwide, discussions of "off-label use" in the PSUR or RMP or in PASS should be based on the indications present in the Company Core Data Sheet.***"
263 - 266		**Comment**: Ongoing Signal ...the definition quoted from ICH E2C is incorrect as it was an old one in ICH E2C which has been revised. **Proposed change** : Revise lines 263-265 to be consistent with the current ICH definition: "*Ongoing signal* *"In periodic **safety update reports (PSURs based on the ICH E2C(R2) guideline on** benefit-risk evaluation reports), a signal that ~~had been identified before the reporting interval and~~ was*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		still under evaluation at the data lock point (see Annex IV, ICH-E2C(R2) Guideline).
341-344		**Comment**: Reference safety information (RSI) is defined as *"Information referred to as the company core safety information (CCSI) (see Annex IV, ICH-E2C(R2) Guideline)."* This definition would oblige MAHs to create a CCSI for each product, even for purely local ones where the RSI can reasonably be the approved SmPC (as currently accepted by HA). **Proposed change**: Revise lines 341-344 to read: "*Reference safety information* ***(RSI)*** "***Document used to assess listedness of adverse reactions in the frame of the periodic safety update report (PSUR based on the ICH E2C(R2) guideline on periodic benefit-risk evaluation reports).*** ~~*PSUR Information referred to as*~~ ***Usually this corresponds to*** *the company core safety information (CCSI) (see Annex IV, ICH-E2C(R2) Guideline).*
409 - 415		**Comment**: The definition of solicited sources is inconsistent with the ICH E2D guideline, which it references. The definition should, therefore, be amended for consistency. **Proposed change** : Revise lines 410-415 to read: "*Solicited sources of individual case safety reports* "***Solicited reports are those individual case safety reports derived from*** *organized data collection systems, which include clinical trials, registries, post-authorisation named patients~~,~~ use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance.* ***Adverse event reports obtained from any of these sources should not be considered spontaneous.*** *"For the purposes of safety reporting, solicited reports should be classified as individual case safety reports from studies, and therefore should have an appropriate causality assessment by a*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		healthcare professional or the marketing authorisation holder. (see Annex IV, 1CH-E2D)"

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
PHARMIG – association of the Austrian pharmaceutical industry

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on GVP Annex I – Definitions.
	In general we want to point out that the overall timeframe of the consultation was very short for an in-depth analysis and commenting on this comprehensive guidance documentation.
	The following terms are not defined: Compassionate use Off-label use

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
272		Comment: The term benefit-risk balance should be used throughout the whole document	
279		Comment: prevention of adverse effects Proposed change (if any): Please define adverse effects	

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Procter & Gamble

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Include a definition of expedited
	Include a definition of a stimulated report
	Include a definition of off-label use
	Include a definition of interventional study

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Comment: Proposed change (if any):

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
Teva Pharmaceuticals Europe B.V.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Consistency of the use of definitions should be checked through all modules and this annex.
	The following definitions are missing: drug diversion efficacy effectiveness off-label use lack of effect Quality assurance Quality control Expedited Valid case Emerging safety issue Registry (wrong definition mentioned in module V – line 1067)

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
127-139		Comment: data lock point of RMP is not mentioned/defined here, although it is mentioned in module V Proposed change (if any): Add definition of RMP DLP
223-224		Comment: The definition of misuse is not identical to the definition used in Module VI – lines 165-166.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<18 April 2012>

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
vfa (Association of Research-Based Pharmaceutical Companies), Germany

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Where the definitions are also quoted in the GVP modules a check should be made that these definitions are consistent with those in Annex 1. Inconsistencies with this module will be pointed out in the commentary on the individual GVP modules. However, duplication of definitions should be avoided wherever possible, and ideally definitions should exclusively be maintained in this GVP module. This module would be much more user friendly for the reader if the full text of definitions referenced to article 1 of the Directive are given in the definitions GVP text followed by the reference. This would allow this GVP definitions document to be used as a standalone lookup reference. One such example is the definition of an "HCP". The following terms are included in other GVP modules. However, their definitions are missing in this module: • Generic medicinal product • Well established use • Homeopathic medicinal product • Traditional herbal medicinal product • Risk • Risk-benefit balance • Therapeutic effect
	The following four terms are also missing. For those four terms we would like to propose the following definitions: ***Additional Pharmacovigilance Activities:*** Where important identified risks, important potential risks, or important missing information are found, activities designed to collect additional information regarding these safety concerns which are not routine pharmacovigilance should be considered. ***Additional Risk Minimisation Activities:*** A risk minimisation activity put in place to reduce the probability of an adverse reaction occurring or its severity should it occur

Stakeholder number *(To be completed by the Agency)*	General comment

	which is not a routine risk minimisation activity – e.g. additional educational material
	Routine Pharmacovigilance Activities:
	Routine pharmacovigilance should include the following:
	• Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
	• The preparation of reports for regulatory authorities:
	  ○ Expedited reports;
	  ○ Periodic Safety Update Reports (PSURs).
	• Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities;
	• Other requirements, as defined by local regulations.
	Routine Risk Minimisation Activities:
	The warnings and information contained within the product labelling, and the careful use of labelling and packaging, which aim to reduce the probability of an adverse reaction occurring or its severity should it occur.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 103 - 104		Comment: **Closed signal** definition: In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH-E2C(R2) Guideline). This definition is too restrictive and confines the use of closed signal to the context of PSURs/PBRERs only. The language for signals at different stages in their review and analysis should be harmonised between the GVP modules for clarity (for example PSURs and signal detection). Proposal: It is recommended that the words "In periodic benefit risk evaluation reports" is deleted from the above definition to avoid confusion.
128 – 132		Comment: **Data Lock Point** is defined slightly different between PSUR and PBRER as follows: **"**For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR. For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date (see Annex IV, ICH-E2C (R2) Guideline" . This is very confusing, because the overarching concept for a data lock point (Data until a given cut-off date) is regardless of the regulatory report documents. The underlying procedure how to arrive at defining a precise data for a particular active substance and a regulatory document type should not be part of the definition of the term data lock point. Proposed Change: Remove the second sentence so that the definition now reads as follows: **Data Lock Point** is defined as the date designated as the cut-off date for data to be included in a PSUR, RMP or other regulatory documents.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
173-181		This definition is not consistent with the definitions given in the RMP module. The definition in the RMP module does not mandate the inclusion of all contraindications and warnings as important risks but merely suggests that they should be considered (reference is made to lines 752ff of the RMP module). The relevance between precautions and occasionally also contraindications may vary, particularly in some which have already been introduced decades ago. Medical judgement may be required to determine whether an individual precaution or contraindication would need to be presented as important risk in the respective regulatory documents. Proposal: The clearer, more pragmatic, definition given in the RMP GVP module should be used for this GVP module "Definitions".
211-216		This definition is accurate with the directive but in order for some of the statements in the modules to be clear some additional clarification should be provided in this module. We understand that in some places the terms "medicinal product" or just "product" have been used when in fact "active substance" may have been meant. Therefore within this definitions module it is unclear whether this term (also) refers to an active moiety alone or alternatively to an active moiety in a particular indication or particular formulation or registered under a particular tradename. Proposal: The term active substance alone should be defined in addition to "medicinal product". This might read as follows: "Active substance stands for the international non-proprietary name. This term alone does not qualify a medicinal product". The definition of "medicinal product" may be enhanced to encompass that this term refers to an active substance as further qualified by any of the following: a form of administration, a strength and/or a tradename.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
236 - 237		Comment: **Newly Identified Signal** again refers to the PBRER. This definition like the definition for a closed signal is too restrictive and confines its use to the context of PSURs/PBRERs only. The language for signals at different stages in their review and analysis should be harmonised between the GVP modules for clarity (for example PSURs and signal detection). Proposed change: It is recommended to delete "In periodic benefit risk evaluation reports" to avoid confusion.
247-248		*Non-interventional studies include database research or review of records where all the events of interest have already happened (e.g. case-control, cross-sectional and cohort studies).* Comment: Although not explicitly mentioned, this statement could implicate that this sentence refers to retrospective studies. However, non-interventional studies (NIS) are actually prospective studies. Otherwise the requirements set out in lines 238 - 245 would make no sense. Proposed change: This statement (247–248) should be removed. A statement that NIS are prospective studies should be included instead.
261 - 263		Comment: **Ongoing Signal** ...the definition quoted from ICH E2C is incorrect as it was an old one in ICH E2C which was subsequently revised. Proposed change : Revise to be consistent with the current one in ICH E2C (now published on the ICH website)...namely, "a signal that is still under evaluation at the data lock point " This definition like the definition for a closed signal is too restrictive and confines its use to the context of PSURs/PBRERs only. The language for signals at different stages in their review and analysis should be harmonised between the GVP modules for clarity (for example PSURs and signal detection).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposal: It is therefore recommended that "In periodic benefit risk evaluation reports" is deleted from the beginning of the definition text to avoid confusion.
295-297 (297)		Editorial comment: The term "data" at the end of the definition should be deleted, because it appears unnecessary and slightly confusing. Proposal: A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products ~~data~~ [DIR 2001/83/EC Art 1(28e)].
343-347		Comment on the definition of Risk-benefit balance: It is acknowledged that significant off-label use will need to be addressed in the PSUR/PBRER. However, the overall assessment of benefits and the overall Risk-benefit balance is done based on the approved indications. To reflect that, the definition of Risk-benefit balance should focus on the *intended* therapeutic effects in the sense of per approved indications. Proposal: "Intended" should be added as follows: An evaluation of the intended positive therapeutic effects of the medicinal product in relation to the risks [DIR 346 2001/83/EC Art 1(28a)] (i.e. any risk relating to the quality, safety or efficacy of the medicinal product 347 as regards patients' health or public health [DIR 2001/83/EC Art 1(28)]).
375-377		Minor editorial comment: In line with DIR 2001/83 (literal citation) and also the way other definitions are provided in this module the introductory words from the definition should be deleted. Proposal: ~~Serious adverse reaction means~~ A~~a~~n adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)].

Please add more rows if needed.

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SCIENCE MEDICINES HEALTH

17 April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
341		Reference Safety Information (RSI) The CCSI is usually the RSI, in case of a Centralized Procedure. But for "old" products, authorized via national procedures, a CCSI is not always in place. MAH can use a local SmPC as RSI in such instances. For IMPs the RSI is the Investigator's Brochure. For single country products the RSI may be the SmPC.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Annex I – Definitions' (EMA/876333/2011)

Comments from:

Name of organisation or individual
ZEINCRO Hellas S.A.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We agree with the definitions given in Annex I. Nevertheless, we propose a clarification to be made in the definition of the Development International Birth Date (please see comment below)

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 141 - 142		Comment: The definition of DIBD does not clearly state that the DIBD remains the same for all Clinical Trials for a specific investigational drug. Even though this definition is referenced from ICH E2F and CIOMS VII, we believe that a clarification could be made in GVP Annex I. Proposed change (if any): Date of first approval (or authorisation) for conducting an interventional clinical trial in any country, for a specific investigational product.